NICE advice

CytoSorb for reducing risk of bleeding during cardiac surgery

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is CytoSorb. It is used for the removal of the blood thinning medication, ticagrelor, from blood during on-pump urgent or emergency cardiac surgery.
- The **innovative aspects** are that it is the first medical device that can be used to remove ticagrelor from the blood during urgent or emergency cardiac surgery. Using CytoSorb in emergency cardiac surgery could reduce resource use for management of bleeding complications, and in urgent cardiac surgery could reduce length of hospital stay before the procedure and the use of adjunctive bridging treatments.
- The intended **place in therapy** would be as an alternative to surgical management of bleeding in emergency surgeries (when ticagrelor is not removed) or as an alternative to a 5- to 7-day delay in urgent surgeries for natural ticagrelor washout.

- The **main points from the evidence** summarised in this briefing are from 6 studies (4 observational studies, 1 bootstrap analysis based on a retrospective case series and 1 case study) including a total of 209 people. They show that CytoSorb may be more effective than no CytoSorb adsorption in people having cardiac surgery.
- **Key uncertainties** around the evidence or technology are that 3 small comparative observational studies focusing on emergency cardiac surgery were included. In most studies people were given ticagrelor or rivaroxaban. No comparative studies were included for people having urgent cardiac surgery. None of the studies were done in the UK.
- The **cost** of CytoSorb is £1,500 per unit (excluding VAT). The **resource impact** would be less than standard care for emergency cardiac surgery (a UK cost-utility analysis reported a cost saving of £3,941 for CytoSorb compared with no removal of ticagrelor), and less than standard care for urgent surgery (about £1,575).

The technology

CytoSorb (CytoSorbents Corporation) is a technology for purifying the blood outside of the body. The technology is designed to remove ticagrelor (a blood thinner) from the blood during on-pump cardiac surgery to prevent bleeding complications. CytoSorb consists of a 300 ml cartridge containing small absorbent polymer beads that permit the removal of hydrophobic substances. The sorbent cartridge can be stored for up to 36 months.

CytoSorb is used for multiple indications. More details are available in:

- NICE's medtech innovation briefing on CytoSorb therapy for sepsis
- NICE's medtech innovation briefing on cytokine adsorption devices for treating respiratory failure in people with COVID-19.

Innovations

The company claims that CytoSorb is the first of its kind and the only option available to remove ticagrelor from the blood during cardiopulmonary bypass surgery. There are no other medical devices or drugs approved for the removal of ticagrelor or the inhibition of ticagrelor activity. The company also claims that compared with standard care, CytoSorb

allows cardiac surgery to be done immediately in people who have been taking ticagrelor, without the need for a washout period. This can reduce perioperative and postoperative morbidity by reducing ticagrelor-associated bleeding complications.

Current care pathway

People with acute coronary syndrome (ACS) who have ischaemic electrocardiogram changes or elevation of cardiac troponin should have immediate treatment with both aspirin (300 mg loading dose) and ticagrelor (180 mg loading dose). Ticagrelor is an oral antagonist of the P2Y12 adenosine diphosphate receptor that inhibits platelet aggregation and thrombus formation in atherosclerotic disease. Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS with:

- ST-elevation myocardial infarction that cardiologists intend to treat with primary percutaneous coronary intervention (PCI), or
- non-ST-elevation myocardial infarction, or
- admission to hospital with unstable angina.

Current standard care for emergency cardiac surgery is no ticagrelor removal and medical management of expected bleeding complications. These include surgical management of bleeding, blood product transfusions, and prolonged hospital care after operation.

Current standard care for urgent cardiac surgery is delaying surgery for 5 to 7 days for natural ticagrelor clearance. This requires hospitalisation and potentially adjunctive bridging treatments such as short-acting drugs or low molecular weight heparin.

The following publications have been identified as relevant to this care pathway:

- NICE's technology appraisal guidance on ticagrelor for preventing atherothrombotic events after myocardial infarction
- NICE's technology appraisal guidance on ticagrelor for the treatment of acute coronary syndromes
- NICE's guideline on acute coronary syndromes

- NICE's technology appraisal guidance on ticagrelor for preventing stroke after previous ischaemic stroke or high-risk transient ischaemic attack. Publication expected June 2022.
- NICE's technology appraisal guidance on ticagrelor for preventing cardiovascular events in people with type 2 diabetes and coronary artery disease. Publication to be confirmed.

Population, setting and intended user

CytoSorb is used for people who need urgent or emergency cardiac surgery, including for acute cardiovascular events, acute deterioration, or a failed PCI.

The technology is used by cardiothoracic surgeons, cardiac anaesthesiologists, perfusionists and specialised nurses. It is used in tertiary care during cardiac surgery.

The company states that CytoSorb can be integrated into the extracorporeal circuit by a perfusionist or specialised nurse, and only minimal training is needed. The company offers free-of-charge training on-site or by video conferencing, depending on the preference of the hospital.

Costs

Technology costs

CytoSorb costs £1,500 per device.

Cost of cardiac surgery was calculated based on the average theatre time and the length of stay in hospital. For surgery with CytoSorb, the average theatre time costs £5,760 and length of stay in hospital costs around £6,254, which included 2 days in an intensive care unit (ICU) and 11 days of hospital stay (Javanbakht et al. 2020).

Costs of standard care

For standard care, costs of cardiac surgery were £7,060 for average theatre time and around £8,620 for average length of stay in hospital, which included 3 days for ICU stay and 14 days of hospital stay (Javanbakht et al. 2020).

Among people who need emergency cardiac surgery, results from a de novo cost-utility analysis indicate that over a 30-day time period, removal of ticagrelor using CytoSorb during surgery is less costly (£12,933 versus £16,874) and more effective (0.06201 quality-adjusted life years [QALYs] versus 0.06091 QALYs) than standard care.

Among people who need urgent cardiac surgery, results indicate that over a 30-day time period, removal of ticagrelor using CytoSorb during surgery was less costly than delaying surgery for natural ticagrelor washout without adjunctive therapy (£12,912 versus £12,959), or with adjunctive therapy using short-acting antiplatelet agents (£12,939 versus £13,200) or low molecular weight heparin (£12,959 versus £13,030; Javanbakht et al. 2020).

Resource consequences

CytoSorb is used in 8 NHS centres as part of the TISORB study. The company estimates that it is also used in 6 additional hospitals across the UK.

The company claims that using CytoSorb to remove ticagrelor during cardiac surgery is a cost-saving strategy because it improves outcomes during and after surgery and decreases health resource use.

The company states CytoSorb is compatible with virtually all heart-lung machines that are already present in NHS cardiac surgery operating theatres.

Regulatory information

CytoSorb is a CE-marked class IIb medical device.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

CytoSorb is intended for use in people having urgent or emergency cardiac surgery. Older people, people who are male, and people with diabetes, high blood pressure or obesity are

more likely to develop coronary heart disease. People of South Asian family origin are more likely to develop coronary heart disease. People of African or African Caribbean family origin are at higher risk of developing high blood pressure and having a stroke. People of African, African Caribbean and South Asian family origin are more likely to develop type 2 diabetes. CytoSorb is contraindicated in some health states that may, next to acute critical care scenarios, also occur in chronic conditions. This may include, for example, people with a very low platelet count, people having immunosuppressive therapy (except for corticosteroids), people with acute sickle cell crisis, or people who have severely suppressed immune systems in the context of chronic diseases. People with chronic conditions may be considered disabled. CytoSorb is partially contraindicated for people who are, or may be, pregnant. Age, disability, sex, race, and pregnancy and maternity are protected characteristics under the Equality Act (2010).

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with NICE's interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

There are 6 studies summarised in this briefing, including a total of 209 people.

The evidence includes 4 observational studies, of which 3 had a comparator group, 1 bootstrap analysis based on a retrospective case series and 1 case study. The studies investigated the effect of CytoSorb on ticagrelor removal and subsequent risk of bleeding.

There is an in vitro study that is not presented below (Angheloiu et al. 2017). This study showed that CytoSorb can remove ticagrelor from bovine serum albumin solution and human blood samples.

Overall assessment of the evidence

The evidence for the technology is of low methodological quality, and all the studies are small in terms of patient numbers. All studies were done in Germany, apart from 1 that was

done in Croatia. Three studies had a comparator, looking at emergency cardiac surgery without adsorption. The studies suggest that using CytoSorb to remove ticagrelor during surgery is a safe and effective method to reduce bleeding complications. Further evidence is needed comparing CytoSorb with standard care for people having urgent or emergency cardiac surgery, with a large sample size.

Hassan et al. (2019)

Study size, design and location

Non-randomised observational study in 55 people at high risk of bleeding having open heart surgery in Germany.

Intervention and comparator

CytoSorb and no adsorption (control).

Key outcomes

All people in the study had therapy with either ticagrelor (n=43) or rivaroxaban (n=12). Standardised CytoSorb adsorption was installed into the heart-lung machine for 39 patients. In the Cytosorb ticagrelor adsorption group, no re-thoracotomies had to be done, compared with 4 in the control group. Mean drainage volume over 24 hours was 350 ml in the CytoSorb ticagrelor adsorption group compared with 890 ml in the ticagrelor control group (p=0.0037). Compared with the CytoSorb adsorption group, multiple bleeding complications occurred in the control group that were associated with more transfusions of red blood cells (p=0.0119) and platelets (p=0.0475). CytoSorb adsorption significantly influenced the length of hospital stay in the intensive care unit (ICU; p=0.0141) and total length of hospital stay (p=0.0244).

Strengths and limitations

This study suggests that using CytoSorb to remove ticagrelor and rivaroxaban during surgery is a safe and effective method to reduce bleeding complications. The authors noted that it was unclear how much adsorption time is needed to fully clear ticagrelor from the body. This was the first study to report on the use of CytoSorb and the authors recommended further randomised prospective studies to confirm their findings.

Hassan et al. (2020a)

Study size, design and location

Observational study in 55 people with acute coronary syndrome having isolated emergency coronary artery bypass graft (CABG) surgery in Germany.

Intervention and comparator

CytoSorb adsorption.

Key outcomes

All procedures were done as isolated CABG surgery with the use of both thoracic arteries in 65.5% of people for complete arterial revascularisations (n=36). Ticagrelor adsorption was done during cardiopulmonary bypass over 103 minutes (plus or minus 35 minutes). Mean drainage volume over 24 hours was 480 ml (plus or minus 211 ml). Only 1 re-thoracotomy (1.8%) for surgical bleeding was done. Mean length of stay in the ICU was 2 days (plus or minus 3 days) and total length of hospital stay was 12 days (plus or minus 5 days). Most people in the study did not need transfusion of blood products. Red blood cell transfusion was done in 20% (n=11) and platelet transfusion in 30.9% (n=17). The 30-day mortality rate was 1.8%.

Strengths and limitations

This study suggests that using CytoSorb adsorption for people taking ticagrelor having emergency CABG for acute coronary syndrome is a safe and effective method, providing low rates of bleeding complications. It is unclear whether the sample from this study is independent from the sample in the Hassan et al. 2019 study. This study is reported in conference abstract form only, so is limited in detail.

Hassan et al. (2020b)

Study size, design and location

Bootstrap analysis based on a retrospective single-centre case series of 43 people having emergency open heart surgery in Germany.

Intervention and comparator

CytoSorb adsorption and control group (no adsorption).

Key outcomes

Compared with the control group, CytoSorb patients had 72% fewer transfusions of red blood cells or platelets, 33% fewer days in ICU, and 18% shorter operation times. A significantly higher re-thoracotomy rate in the control group was also associated with prolonged ICU stay and use of more blood products. Cost of ICU stay had the highest impact on the level of cost savings. CytoSorb was less costly regardless of differences in cost-driving variables. The economic benefit was calculated as €3.656 per person without reimbursement.

Strengths and limitations

This study suggests that CytoSorb leads to cost savings because of reductions in length of ICU stay, use of blood products, and operation times. This study is reported in conference abstract form only, so is limited in detail.

Hassan et al. (2020c)

Study size, design and location

Observational study in 21 people with acute type A aortic dissection having emergency cardiac surgery in Germany.

Intervention and comparator

CytoSorb adsorption and control group (no adsorption).

Key outcomes

All people in the study were taking either ticagrelor (n=12) or rivaroxaban (n=9). In 10 out of 21 cases, the standardised adsorber was installed into the heart-lung machine (AD group) and compared with 11 patients without adsorption (WAD group). In the AD group drainage volumes over 24 hours were 500 ml (interquartile range [IQR] 450 to 675) after ticagrelor administration, and 450 ml (IQR 310 to 430) after rivaroxaban therapy.

There were multiple bleeding complications in the WAD group. These were associated with longer total operation time, higher drainage volumes ($p<0.05$), and more transfusions ($p<0.05$). In the AD group no re-thoracotomies had to be done compared with a significantly higher re-thoracotomy rate in the WAD group.

Strengths and limitations

This study suggests that CytoSorb is safe and effective in preventing major bleeding complications in people with acute type A aortic dissection needing emergency cardiac surgery. This study is reported in conference presentation form only, so is limited in detail. The abstract is not available to access online.

Mair et al. (2020)

Study size, design and location

Case study of 1 person having urgent off-pump coronary artery bypass surgery in Germany.

Intervention and comparator

CytoSorb adsorption.

Key outcomes

CytoSorb adsorption was started 1 hour before the operation and was continued for 1.5 hours during the operation. The patient was extubated on the same day of the surgery. By the first day after the operation, low-dose norepinephrine was stopped. The chest tubes delivered 570 ml in 24 hours and were removed on the second day after the operation. Haemoglobin dropped from 14.0 g/dl before the operation to 8.5 g/dl after the operation. This was treated with 1 unit of red blood cells. After the operation, maximum creatine kinase levels were 380 U/l (normal range, 40 U/l to 310 U/l), and the creatine kinase myocardial band remained in normal range. The patient made a good recovery, and at discharge received a renewed prescription for dual antiplatelet therapy and rivaroxaban. At 6-month follow up the patient had good pump function, sinus rhythm, and no cardiac symptoms.

Strengths and limitations

This single case suggests that using CytoSorb haemoadsorption appears to be safe and effective to reduce bleeding in people taking ticagrelor or rivaroxaban. This case study has several limitations, including the use of a haemodialysis device as an extracorporeal circuit because no appropriate blood pump was available as a power unit, and the lack of generalisability of the findings.

Bradic et al. (2020)

Study size, design and location

Observational study in 34 people having emergency cardiac surgery who were taking preoperative direct oral anticoagulants in Croatia.

Intervention and comparator

CytoSorb adsorption and control group (no adsorption).

Key outcomes

All people in the study were having therapy with either ticagrelor (n=19), rivaroxaban (n=12) or dabigatran (n=3). CytoSorb was used in 22 of 34 people, compared with 12 people without adsorption. People without CytoSorb had a longer total surgery time (310 minutes versus 240 minutes), higher average draining volumes in the first 24 hours (1,200 ml versus 320 ml), more transfusions of red blood cells (950 ml versus 250 ml), platelets (800 ml versus 150 ml), and fresh frozen plasma (1,180 ml versus 620 ml). People without CytoSorb also had higher re-sternotomy rates (58% versus 18%) and longer ICU stays (5.3 days versus 2.4 days).

Strengths and limitations

This study suggests a favourable effect of CytoSorb in people who were taking preoperative direct oral anticoagulants. The patient numbers have not been reported consistently. This study is reported in conference poster abstract form only, so is limited in detail.

Sustainability

None.

Recent and ongoing studies

- Ticagrelor CytoSorb hemoadsorption (TISORB). ClinicalTrials.gov Identifier: NCT04131959. Status: recruiting. Indication: cardiothoracic surgery, bleeding. Devices: CytoSorb. Estimated completion date: August 2021. Country: UK.
- Ticagrelor removal study using CytoSorb® 300 ml device during cardiopulmonary bypass in patients undergoing emergent cardiothoracic surgery (CyTation). ClinicalTrials.gov Identifier: NCT04625764. Status: recruiting. Indication: acute coronary syndrome. Devices: CytoSorb. Estimated completion date: January 2022. Country: Germany.

Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All 3 experts were familiar with and had used this technology before.

Level of innovation

All experts said that CytoSorb is innovative because it actively removes ticagrelor from blood. One expert said that CytoSorb is the first in a new class of procedure, while the other 2 experts said that CytoSorb is definitely novel and has uncertain safety and efficacy. However, 1 expert noted that the TISORB trial is addressing these issues. Experts were unaware of any other competing or alternative technologies available to the NHS. However, 1 expert noted that there is a monoclonal antibody entering into clinical trials as an antidote for ticagrelor.

Potential patient impact

Experts said that potential benefits to patients included less bleeding with reduced need for the use of blood products and to prevent reopening- and transfusion-related complications. Two experts said that this technology would particularly benefit patients having emergency or urgent cardiac surgery, who are loaded with ticagrelor. One expert said that this can benefit older people or people with suboptimal organ function.

One expert said that 20% of the patients referred for cardiac surgery would be eligible for this technology.

Potential system impact

All experts agreed that CytoSorb has the potential to change the current pathway. It can reduce operating theatre occupancy time, and lengths of intensive care unit and hospital stays. Furthermore, there is less need to return to the theatre for re-exploration for bleeding and cardiac tamponade, and reduced need for blood products. Two experts said that no changes to clinical facilities were needed. One expert said that changes need to be made to the perfusion department to do this procedure safely. All experts agreed that despite the cost of the technology, overall CytoSorb is likely to cost less compared with standard care.

All experts agreed that training for staff is needed. Experts were not aware of any safety issues. However, 1 expert noted some potential side effects including removal of antibiotics and other beneficial molecules, and potential thrombocytopenia and leukopenia. The expert said that this will need close monitoring. Another expert said that there are theoretical risks of allergic reactions and clotting with the device because of inadequate anticoagulation or device priming. Furthermore, there is possibility of a small blood leak from the connectors, but the expert also said that there is no evidence that CytoSorb would carry a higher risk to patients than bypass or haemofiltration alone.

General comments

All experts said that CytoSorb has the potential to replace current standard care, subject to supportive evidence from large prospective trials. Two experts said that this procedure will be done in a minority of hospitals, about 10 in the UK, in specialist cardiothoracic centres. One expert could not predict in how many hospitals this could be done. One

expert identified the need for cardiopulmonary bypass or haemofiltration as a potential issue with the usability of the technology. All experts agreed that the cost could be a barrier to adoption in the NHS.

One expert noted some uncertainty around CytoSorb, such as the timing and duration. For example, whether CytoSorb is used preoperatively as a standalone application or if there is need for postoperative application in addition to intraoperative use.

All experts agreed that randomised clinical trials are needed to address the uncertainty in the evidence base. One expert said that these trials should ideally include a multi-ethnic population. Another expert said that TISORB will address most of these issues. However, the expert said that this study has important exclusion criteria such as age, comorbidities and comedication, that should be included as these patients could benefit more from ticagrelor removal.

Expert commentators

The following clinicians contributed to this briefing:

- Shahzad G Raja, consultant cardiac surgeon, Royal Brompton & Harefield NHS Foundation Trust. Did not declare any interests.
- Ulrich A Stock, consultant cardiothoracic and transplant surgeon, Royal Brompton & Harefield NHS Foundation Trust. Did not declare any interests.
- Nandor Marczin, consultant cardiothoracic anaesthetist, Royal Brompton & Harefield NHS Foundation Trust. Received financial reimbursement for advisory board meeting, user meeting attendance, conference attendance and lectures.

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This briefing was developed by NICE. NICE's interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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