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This presentation contains “forward-looking statements” pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include, without limitation, any statement that may predict, forecast, indicate, or imply future results, performance or achievements, and may contain the words "estimate," "intend," "target," "will," "is likely," "would," "may," or, in each case, their negative, or words or expressions of similar meaning. These forward-looking statements are found at various places throughout this presentation and include information concerning possible or assumed future results of our operations; business strategies; future cash flows; financing plans; plans and objectives of management; any other statements regarding future operations, future cash needs, business plans and future financial results, and any other statements that are not historical facts. Unless otherwise indicated, the terms “CytoSorbents,” “Company,” “we,” “us” and “our” refer to CytoSorbents Corporation. Any or all of the forward-looking statements included in this presentation are not guarantees of future performance and may turn out to be inaccurate. These forward-looking statements represent our intentions, plans, expectations, assumptions and beliefs about future events and are subject to risks, uncertainties and other factors. Many of those factors are outside of our control and could cause actual results to differ materially from the results expressed or implied by those forward-looking statements. Although these expectations may change, we are under no obligation to inform you if they do. Actual events or results may differ materially from those contained in the forward-looking statements. The following factors, among others, could cause our actual results to differ materially from those described in a forward-looking statement: our history of losses; potential fluctuations in our quarterly and annual results; competition, inability to achieve regulatory approval for our device, technology systems beyond our control and technology-related defects that could affect the companies’ products or reputation; risks related to adverse business conditions; our dependence on key employees; competition for qualified personnel; the possible unavailability of financing as and if needed; and risks related to protecting our intellectual property rights or potential infringement of the intellectual property rights of third parties. This list is intended to identify only certain of the principal factors that could cause actual results to differ from those discussed in the forward-looking statements. In light of these risks, uncertainties and assumptions, the events described in the forward-looking statements might not occur or might occur to a different extent or at a different time than we have described. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of the applicable presentation. You are referred to a discussion of important risk factors detailed in the Company’s Form 10-K filed with the Securities and Exchange Commission on March 5, 2020 and other reports and documents filed from time to time by us, which are available online at www.sec.gov.
Opening Remarks
Dr. Phillip Chan, MD, PhD
Chief Executive Officer
CytoSorbents Corporation
CytoSorbents At a Glance (NASDAQ: CTSO)

- CytoSorbents is a U.S. NASDAQ-traded medical device company that specializes in treating life-threatening conditions with its blood purification technology.

- CytoSorb® is E.U. approved, manufactured in the U.S. by CytoSorbents, and commercialized in 65 countries as an extracorporeal cytokine adsorber to help treat hyperinflammatory conditions where cytokines are elevated (e.g. “cytokine storm”) with more than 88,000 cumulative treatments to date.

- CytoSorb is also E.U. approved to remove ticagrelor (Brilinta®) or rivaroxaban (Xarelto®) in cardiac surgery, bilirubin (liver disease) and myoglobin (trauma).

- CytoSorb is not yet FDA-approved but on a dual path for U.S. approval:
  - FDA Breakthrough Designation to remove ticagrelor during CPB in urgent & emergent cardiothoracic surgery
  - U.S. REFRESH 2-AKI Trial – Pivotal study at 25 U.S. centers using CytoSorb intraoperatively to reduce risk of post-op AKI

- Received U.S. FDA Emergency Use Authorization for use in critically-ill adult COVID-19+ patients with respiratory failure and has been used ~1,000 COVID-19 patients in 20+ countries, including the U.S.

- 156 employees with international footprint across two wholly-owned subsidiaries:
  - CytoSorbents Medical, Inc: Headquarters - New Jersey, USA (ISO 13485 certified manufacturing, R&D, Management)
  - CytoSorbents Europe GmbH: International sales office - Berlin, Germany (Sales and Marketing)

- Strong government support with ~$33M in grants, contracts, other non-dilutive funds.
CytoSorb is “Plug and Play” Compatible

Compatible with Existing Blood Pump Infrastructure In Hospitals Today

Dialysis or CRRT
(Continuous Renal Replacement Therapy)

ECMO
(Extracorporeal Membrane Oxygenation)

Hemoperfusion
(Standalone Treatment)

CPB
(Cardiopulmonary Bypass)
CytoSorb Commercialization Focus

**By Market**
- Critical Care: 67%
- Cardiac Surgery: 33%
- Sepsis and Septic Shock: 50%
- Other Critical Care: 17%
  - ARDS
  - Reversal of Shock
  - Trauma
  - Acute Liver / Pancreatic
  - Many Others

**By Geography**
- 20 – 30%: Distributor / Partner
- 10 – 15%: Other Direct
- 60 – 65%: Germany – Direct
  - Austria
  - Switzerland
  - 7 other countries

**World Class Partners**
- FRESENIUS MEDICAL CARE (Critical Care)
- TERUMO (Cardiac Surgery)
- Biocon (India – Cardiac / Critical Care)
CytoSorb Adoption Continues to Grow

Product Sales (ttm) and Blended Product Gross Margin Growth

<table>
<thead>
<tr>
<th></th>
<th>Q1 2015</th>
<th>Q1 2016</th>
<th>Q1 2017</th>
<th>Q1 2018</th>
<th>Q1 2019</th>
<th>Q1 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>CytoSorb Sales (ttm)</td>
<td>$3,269,802</td>
<td>$4,937,610</td>
<td>$9,204,720</td>
<td>$15,219,016</td>
<td>$20,395,666</td>
<td>$26,345,244</td>
</tr>
<tr>
<td>Blended Product Gross Margin</td>
<td>59%</td>
<td>61%</td>
<td>63%</td>
<td>65%</td>
<td>67%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Growth Driven By Many Macro Trends in Healthcare
Introduction of Agenda & Speakers

Efthymios N. Deliargyris, MD, FACC, FESC, FSCAI
Chief Medical Officer
CytoSorbents Corporation
Antithrombotic Removal
CytoSorb Drug Adsorption: Mechanism of Action

**Device:**
- favors hydrophobic binding
- pore size = selective access to $\leq 60$ kDa
- dependent on drug concentration
- dependent on time of blood exposure

**Drug:**
- Hydrophobic molecular functional groups (aromatic, alkyl, etc.) increase binding affinity
- Free fraction vs. protein-bound: free fraction adsorbed and shifting free-bound ratio
- Active metabolites: generation rate and compartmentalization factor into removal rates
- $T_{1/2}$: very short $T_{1/2}$ limits availability for adsorption vs. longer $T_{1/2}$
- Volume of distribution ($V_D$): more adsorption with smaller $V_D$
- Chronicity of dosing: higher adsorption early before steady-state $V_D$
CytoSorb Integrates Easily Into Cardiopulmonary Bypass

- CytoSorb installs within minutes and is placed in a parallel circuit: post-pump, back to the venous reservoir
- High blood flow, low resistance up to 700 mL/min
- Fully-compatible with heparin anti-coagulation
- Used safely in thousands of cardiopulmonary bypass procedures to date
## Antithrombotic Removal - Overview

<table>
<thead>
<tr>
<th>Evidence</th>
<th>TICAGRELOR</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
<th>DABIGATRAN</th>
<th>EDOXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Benchtop</td>
<td>In vitro**</td>
<td>&gt;90%</td>
<td>&gt;90%</td>
<td>--</td>
<td>&gt;90%</td>
</tr>
<tr>
<td><strong>Human PK/PD</strong></td>
<td>+</td>
<td>+</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td><strong>Clinical Evidence</strong></td>
<td>√</td>
<td>√</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td>**EU</td>
<td>US**</td>
<td>√</td>
<td>BD</td>
<td>√</td>
<td>--</td>
</tr>
</tbody>
</table>
## Today’s Agenda & Speakers

<table>
<thead>
<tr>
<th>Speaker</th>
<th>Title</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phillip Chan</td>
<td>Welcome &amp; Opening Remarks</td>
<td>5 min</td>
</tr>
<tr>
<td>Makis Deliargyris</td>
<td>Introduction of Agenda &amp; Speakers</td>
<td>5 min</td>
</tr>
<tr>
<td>Robert Storey</td>
<td>Ticagrelor and CytoSorb</td>
<td>15 min</td>
</tr>
<tr>
<td>Michael Schmoeckel</td>
<td>Intraoperative removal of Ticagrelor and Rivaroxaban during Emergency Cardiac Operations</td>
<td>15 min</td>
</tr>
<tr>
<td>Michael Gibson</td>
<td>NOACs and CytoSorb</td>
<td>15 min</td>
</tr>
<tr>
<td>Makis Deliargyris</td>
<td>Closing Remarks – Size of the opportunity</td>
<td>5 min</td>
</tr>
<tr>
<td>All</td>
<td>Q &amp; A Session</td>
<td>30 min</td>
</tr>
</tbody>
</table>
Antithrombotic Removal

- Unmet clinical need
- Clinical evidence with CytoSorb
- Size of the addressable market
Ticagrelor and CytoSorb

Professor Robert Storey, BSc, BM, DM, FRCP, FESC

Professor of Cardiology and Cardiovascular Disease Theme Lead, Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield and

Academic Director and Honorary Consultant Cardiologist, Cardiology and Cardiothoracic Surgery Directorate, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom
Ticagrelor: the first oral reversibly-binding P2Y$_{12}$ receptor antagonist belonging to the class CPTP (cyclo-pentyl-triazolo-pyrimididine)

ONSET/OFFSET Study: inhibition of platelet aggregation

Gurbel PA, Storey RF et al. Circulation 2009

Ticagrelor 180mg LD / 90 mg bd (n=54)
Clopidogrel 600mg LD / 75 mg od (n=50)
PLATO PLATELET: VerifyNow P2Y$_{12}$ Assay

Comparing Maintenance Therapy with Clopidogrel vs Ticagrelor in ACS

![Graph showing platelet reaction units for Clopidogrel and Ticagrelor at trough and peak levels.]

**P<0.0001; PRU = Platelet reaction units.**

Storey RF, et al. J Am Coll Cardiol 2010
### PLATO Secondary efficacy endpoints

#### Myocardial infarction
- **Clopidogrel**: 6.9%
- **Ticagrelor 90mg bd**: 5.8%

**Cumulative incidence (%)**
- **HR**: 0.84 (95% CI 0.75–0.95), *p*=0.005

#### Cardiovascular death
- **Clopidogrel**: 5.1%
- **Ticagrelor 90mg bd**: 4.0%

**Cumulative incidence (%)**
- **HR**: 0.79 (95% CI 0.69–0.91), *p*=0.001

<table>
<thead>
<tr>
<th>Days after randomization</th>
<th>Clopidogrel</th>
<th>Ticagrelor 90mg bd</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9291</td>
<td>8626</td>
</tr>
<tr>
<td>60</td>
<td>8560</td>
<td>8780</td>
</tr>
<tr>
<td>120</td>
<td>8405</td>
<td>8589</td>
</tr>
<tr>
<td>180</td>
<td>8520</td>
<td>7079</td>
</tr>
<tr>
<td>240</td>
<td>8177</td>
<td>5441</td>
</tr>
<tr>
<td>300</td>
<td>7079</td>
<td>4364</td>
</tr>
<tr>
<td>360</td>
<td>8626</td>
<td>4419</td>
</tr>
</tbody>
</table>

### No. at risk
- **Ticagrelor**: 9333, 8678, 8520, 8279, 6796, 5210, 4191
- **Clopidogrel**: 9291, 8560, 8405, 8177, 6703, 5136, 4109

UK networks for ACS and revascularisation

South Yorkshire Cardiothoracic Centre

Provides a PCI and CABG surgery service including 24/7 primary PCI to the South Yorkshire and North Derbyshire regions of England – a population of 1.8 million people.
Sheffield observational study
10,793 consecutive invasively-managed ACS patients

Iqbal J et al. Presented at AHA 2014; Gosling R et al. Platelets 2017 online
Sheffield observational study
Adjusted definite stent thrombosis rates

Gosling R et al. Platelets 2017
BCIS National Audit
Adult Interventional Procedures

1st April 2018 to 31st March 2019
Ticagrelor
Use by Indication for PCI

![Image of Ticagrelor pill]

% of Procedures

Stable | NSTEMI / UA | PCI for STEMI

2012: 10.8
2013: 40.9
2014: 49.1
2015: 2016
2017-18
2018-19

(BCIS 2018-19 data)
Mean time waiting for **urgent** CABG in 2017/18 was **10 days** in the UK (no change from 2016/17)

Proportion treated within 7 days = **34%**

Only 4 hospitals managed to treat >50% within 7 days
PLATO: chest tube drainage according to time after drug intake

Held C et al. J Am Coll Cardiol 2011
PLATO: fall in hemoglobin >50g/L according to time after drug intake

Held C et al. J Am Coll Cardiol 2011
Offset of ticagrelor’s effects in ACS patients

Ow K, Storey RF et al. Platelets 2020
Expert position paper on the management of antiplatelet therapy in patients undergoing coronary artery bypass graft surgery

Miguel Sousa-Uva\textsuperscript{1,2}, Robert Storey\textsuperscript{3}, Kurt Huber\textsuperscript{4}, Volkmar Falk\textsuperscript{5}, Adeline Leite-Moreira\textsuperscript{6,7}, Julien Amour\textsuperscript{6}, Nawwar Al-Attar\textsuperscript{9}, Raimondo Ascione\textsuperscript{10}, David Taggart\textsuperscript{11}, and Jean-Philippe Collet\textsuperscript{8*}, on behalf of ESC Working Group on Cardiovascular Surgery and ESC Working Group on Thrombosis

Table 3  Proposed strategies for discontinuation of P2Y\textsubscript{12} inhibitors prior to coronary artery bypass grafting surgery

<table>
<thead>
<tr>
<th>Thrombotic risk</th>
<th>High\textsuperscript{b}</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS or recent stent PCI</td>
<td>Ticagrelor/clopidogrel: stop 5 days before and bridge for 4 days. Prasugrel: stop 7 days and bridge for 5 days</td>
<td>Clopidogrel/ticagrelor: stop 5 days before or less if indicated by platelet function test. Prasugrel: stop 7 days before or less if indicated by platelet function test.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bleeding risk</th>
<th>High\textsuperscript{a}</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>High\textsuperscript{a}</td>
<td>Early Heart Team Consultation</td>
<td>Early Heart Team Consultation</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Examples of high-bleeding risk: renal or hepatic insufficiency, advanced age, anaemia, small body surface area, cardiac failure, and redoes operation.

\textsuperscript{b} Examples of high-thrombotic risk: haemodynamic instability, ongoing ischaemia, complex coronary anatomy, stenting < 1 month for BMS, and < 6 months for DES.

CABG, coronary artery bypass grafting.
Ticagrelor Removal From Human Blood

George O. Angheloiu, MD, a,b,c Gabriel B. Gugiu, PhD, d Cristian Ruse, PhD, e Rishikesh Pandey, PhD, a Ramachandra R. Dasari, PhD, a Carl Whatling, PhD f

![Diagram of blood management system with a CytoSorb column for ticagrelor removal.](image)

**Removal of Ticagrelor on a CytoSorb 300 cc column**

<table>
<thead>
<tr>
<th>Time of Blood Sampling</th>
<th>Percent Ticagrelor Removal from Whole Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hrs</td>
<td>100%</td>
</tr>
<tr>
<td>7 hrs</td>
<td>98%</td>
</tr>
<tr>
<td>10 hrs</td>
<td>96%</td>
</tr>
</tbody>
</table>

*Angheloiu GO et al. JACC Basic Trans Sci 2017*
Ticagrelor removal by CytoSorb® is associated with reduced morbidity in patients who require emergent or urgent cardiac surgery:
An economic model with implications for hospital resource utilisation in the UK

M. Javanbakht¹, K. Rahimi², F. Degener³, D. Adam³, F. Preissing³, J. Scheier⁴, SF. Cook⁵, E. Mortensen⁶*

¹. Optimax Access UK Ltd, Market Access Consultancy, Southampton, United Kingdom; ². The George Institute for Global Health, University of Oxford, Oxford, United Kingdom; ³. Reimbursement & Health Economics, CytoSorbents Europe GmbH, Berlin, Germany; ⁴. Medical Affairs, CytoSorbents Europe GmbH, Berlin, Germany; ⁵. CERobs Consulting LLC, Chapel Hill, United States of America; ⁶. Medical Affairs, CytoSorbents Corporation, Monmouth Junction, United States of America

*Presenting author
Methods

- A de novo decision analytic model was developed to estimate resource utilisation in each strategy (CytoSorb vs. usual care) over a 30-day time horizon.

- Primary clinical inputs were those that might have significant impact on hospital care resource utilisation, including:
  - bleeding complications
  - re-thoracotomies
  - number of transfused units of red blood cells (RBC) and platelets
  - hospital/intensive care unit length of stay and total operating time
  - incidence of myocardial infarction while waiting for physiologic clearance of ticagrelor before an urgent cardiac surgery

- A wide range of parametric and structural sensitivity analyses were performed to explore the uncertainty surrounding the model results.
Results: Emergent Cardiac Surgery (Cohort 1)

- CytoSorb use resulted in fewer blood product transfusions, fewer re-thoracotomies, shorter operation time, and shorter ICU/hospital length of stay.
- Patients treated with CytoSorb incurred lower total cost (£3,982) and had better health-related quality of life (+0.00125 quality-adjusted life years (QALYs)).
- CytoSorb remained dominant in all sensitivity analyses.

<table>
<thead>
<tr>
<th>Outcome (30-day time horizon; Comparator: No physiologic clearance)</th>
<th>Without CytoSorb</th>
<th>With CytoSorb</th>
<th>Δ incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs transfusions (units) per patient</td>
<td>0.91</td>
<td>0.44</td>
<td>-0.47</td>
</tr>
<tr>
<td>Platelet transfusions (units) per patient</td>
<td>1.55</td>
<td>0.38</td>
<td>-1.16</td>
</tr>
<tr>
<td>Operation time (in minutes)</td>
<td>353</td>
<td>288</td>
<td>-65</td>
</tr>
<tr>
<td>Re-thoracotomy rate</td>
<td>36%</td>
<td>0%</td>
<td>-100%</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>3</td>
<td>2</td>
<td>-1</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>14</td>
<td>11</td>
<td>-3</td>
</tr>
</tbody>
</table>

Javanbakht M et al. Presented at EACTS 2019 meeting, Lisbon, Portugal, October 2019
Results: Urgent Cardiac Surgery (Cohort 2)

- In urgent CABG, CytoSorb was less costly (-£55) and more effective when compared to waiting for 5 days to allow for physiological washout of ticagrelor to reduce bleeding risk.
- In all 3 comparators, waiting alone, waiting plus short acting antiplatelet agent, and waiting plus low molecular weight heparin:
  - As expected, transfusion of blood and platelet are similar with or without CytoSorb treatment, as bleeding risk is reduced in both cases.
  - Hospital length of stay was reduced by 5 days as surgery could proceed earlier.

<table>
<thead>
<tr>
<th>Outcome per patient (Deterministic)</th>
<th>Without CytoSorb</th>
<th>With CytoSorb</th>
<th>Δ Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusions of red blood cells and platelets and (units) per patient</td>
<td>0.82</td>
<td>0.82</td>
<td>0</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>16</td>
<td>11</td>
<td>-5</td>
</tr>
</tbody>
</table>

Javanbakht M et al. Presented at EACTS 2019 meeting, Lisbon, Portugal, October 2019
Ticagrelor CytoSorb Hemoadsorption (TISORB) study

UK prospective, multi-center study in patients undergoing cardiac surgery <48 hours since last dose of ticagrelor

8 Sites
TISORB patient journey:
Surgery $\leq$ 48 hrs after last ticagrelor dose

- **Screening Phase**: Informed consent, etc.
- **Pre-CPB Phase**: Pre-op MEA testing
- **Operation Phase**: CytoSorb hemo-adsorption of ticagrelor
- **Post-CBP Phase**: Post-op MEA testing
- **Post-Operation Phase**: Post-op study assessments
- **Follow up Visit**: Day 30 post-op

**PD substudy**: multiple aspects of platelet function, inflammatory markers, bleeding time
TISORB primary effectiveness endpoint

**HYPOTHESIS**

\[ [\text{ticagrelor}]_{\text{Blood pre-op}} > 22 \text{ U} \]

intra-op ticagrelor removal from blood by CytoSorb

\[ [\text{ticagrelor}]_{\text{Blood post-op}} < 22 \text{ U} \]
Summary

- Acute coronary syndromes (ACS) have become the dominant reason for revascularization over the last decade.

- Dual antiplatelet therapy with aspirin and ticagrelor is first-line therapy for ACS patients and has dramatically cut stent thrombosis rates in PCI patients.

- Level of platelet P2Y$_{12}$ inhibition has a critical effect on surgical blood loss and the risks of urgent CABG surgery.

- Ticagrelor has the advantage over irreversible P2Y$_{12}$ inhibitors of reversibility and can be removed from the blood by the CytoSorb system.

- CytoSorb has the potential to transform the safety, timeliness, simplicity and cost-effectiveness of CABG surgery in the ACS population.
Intraoperative removal of Ticagrelor and Rivaroxaban during Emergency Cardiac Operations

Prof. Dr. med. Michael Schmoeckel
Head
Dept. of Cardiac Surgery
AK St. Georg, Hamburg, Germany
Perioperative management of NOACs

• **Apixaban (Eliquis)**: discontinue apixaban 24 to 48 hours prior to surgery depending on the bleeding risk.

• **Dabigatran (Pradaxa)**: high bleeding risk procedures or surgeries: to be discontinued 48–72 hours before. in renal impairment: 72–96 hours before.

• **Rivaroxaban (Xarelto)**: to be discontinued 48 hours prior to high bleeding risk procedures.

• **Edoxaban (Savaysa)**: in high bleeding risk procedures, edoxaban should be discontinued 72 hours before.
who underwent open-heart operations at our institution between July 2014 and June 2016. All patients presented for surgery while on NOAC therapy: 37 received rivaroxaban (45.7%), 35 apixaban (43.2%), and 9 dabigatran (11.1%). The calculated risk using the European System for Cardiac Operative Risk Evaluation II was 3.5% (IQR: 2.0% to 8.1%).

**Results.** Surgery was performed at a median 4 days (IQR: 3 to 6) after NOAC withdrawal. Reduced renal function was predictive for length of intensive care unit stay and administration of red blood cells ($p < 0.0001$ and $p = 0.0291$, respectively). The NOAC withdrawal interval significantly influenced postoperative drainage volume ($p = 0.047$). Intensive care unit stay was 4 days after NOAC withdrawal of 10 days, compared with 4.2 days without termination. Thirty-day mortality was 3.7%.

**Conclusions.** A lengthy NOAC withdrawal period, particularly for patients with reduced renal function, is essential for safe open-heart surgery. We conclude that despite official recommendations, patients should whenever possible not be considered for elective cardiac surgery within 10 days of terminating NOAC treatment.

Evolution of PCI in Germany
Evolution of antiplatelet therapy after PCI
2017 ESC Guidelines for STEMI patients

---

**Antiplatelet therapy**

A potent P2Y₁₂ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at least at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.¹⁸⁶,¹⁸⁷
Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study

Emma C. Hansson¹, Lena Jidéus², Bengt Åberg³, Henrik Bjursten⁴, Mats Dreifaldt⁵, Anders Holmgren⁶, Torbjörn Ivert⁷, Shahab Nozohoor⁸, Mikael Barbu³, Rolf Svedjeholm⁹, and Anders Jeppsson¹,⁹

38% major bleeding!
Ticagrelor Removal From Human Blood

George O. Angheloiu, MD, Gabriel B. Gugiu, PhD, Cristian Ruse, PhD, Rishikesh Pandey, PhD, Ramachandra R. Dasari, PhD, Carl Whatling, PhD

VISUAL ABSTRACT

HIGHLIGHTS

• Ticagrelor is reversibly bound to albumin.
• CytoSorb and Porapak Q 50-80 mesh remove ticagrelor from bovine serum albumin solution with >99% efficiency.
• CytoSorb removes ticagrelor from human blood and human plasma with >99% efficiency.

...after 10 hours, and 94% after 3-4 hours recirculation


MIT Cambridge, MA, USA & Astra Zeneca
Platelet transfusion is not a definitive solution because of circulating Ticagrelor binding to transfused platelets.

Using adsorber technology may reduce bleeding complications in patients treated with Ticagrelor.

Similar effects may be expected in patients treated with NOACs.
Study design (n = 55)

- Single centre prospective cohort study

- Patients who underwent emergency cardiac surgery at our institution between June 2016 and June 2018 with preoperative treatment of ticagrelor (n = 43) or rivaroxaban (n = 12).

- Since April 2017 (JACC paper) we routinely installed standardized Cytosorb adsorption into the extracorporeal circulation.
Intraoperative setting
Emergency open-heart surgery
June 2016 – June 2018; n=217

Operations under **Ticagrelor** (n=43) or **Rivaroxaban** (n=12)

- Cytosorb adsorption of **Ticagrelor** (n=32)
- Cytosorb adsorption of **Rivaroxaban** (n=7)

Operations without previous Ticagrelor or Rivaroxaban therapy

- No Cytosorb adsorption of **Ticagrelor** (n=11)
- No Cytosorb adsorption of **Rivaroxaban** (n=5)

n=55 (25.3%)

n=162 (74.7%)

Single center prospective cohort study since 04/2017 until 04/2017

## Preoperative data I

<table>
<thead>
<tr>
<th>Demography</th>
<th>Cytosorb Ticagrelor (n=32)</th>
<th>Cytosorb Rivaroxaban (n=7)</th>
<th>Control Ticagrelor (n=11)</th>
<th>Control Rivaroxaban (n=5)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>age (y)</td>
<td>66</td>
<td>77</td>
<td>69</td>
<td>72</td>
<td>.33</td>
</tr>
<tr>
<td>female (%)</td>
<td>19</td>
<td>57</td>
<td>18</td>
<td>20</td>
<td>.22</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27</td>
<td>26</td>
<td>27</td>
<td>27</td>
<td>.79</td>
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</table>

<table>
<thead>
<tr>
<th>NYHA class (%)</th>
<th>Cytosorb Ticagrelor (n=32)</th>
<th>Cytosorb Rivaroxaban (n=7)</th>
<th>Control Ticagrelor (n=11)</th>
<th>Control Rivaroxaban (n=5)</th>
<th>p value</th>
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<tbody>
<tr>
<td>II</td>
<td>56</td>
<td>57</td>
<td>36</td>
<td>60</td>
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<tr>
<td>III</td>
<td>38</td>
<td>43</td>
<td>64</td>
<td>40</td>
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<td>IV</td>
<td>6</td>
<td>0</td>
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<table>
<thead>
<tr>
<th>Comorbidities (%)</th>
<th>Cytosorb Ticagrelor (n=32)</th>
<th>Cytosorb Rivaroxaban (n=7)</th>
<th>Control Ticagrelor (n=11)</th>
<th>Control Rivaroxaban (n=5)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypertension</td>
<td>91</td>
<td>86</td>
<td>100</td>
<td>100</td>
<td>.99</td>
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<tr>
<td>periph. vasc. disease</td>
<td>28</td>
<td>29</td>
<td>18</td>
<td>40</td>
<td>.68</td>
</tr>
<tr>
<td>COLD</td>
<td>38</td>
<td>57</td>
<td>46</td>
<td>60</td>
<td>.92</td>
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</table>

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Cytosorb Ticagrelor (n=32)</th>
<th>Cytosorb Rivaroxaban (n=7)</th>
<th>Control Ticagrelor (n=11)</th>
<th>Control Rivaroxaban (n=5)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>28</td>
<td>0</td>
<td>27</td>
<td>0</td>
<td>.95</td>
</tr>
<tr>
<td>moderate</td>
<td>41</td>
<td>71</td>
<td>55</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>31</td>
<td>29</td>
<td>18</td>
<td>20</td>
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</tbody>
</table>
# Preoperative data II

<table>
<thead>
<tr>
<th></th>
<th>Cytosorb Ticagrelor (n=32)</th>
<th>Cytosorb Rivaroxaban (n=7)</th>
<th>Control Ticagrelor (n=11)</th>
<th>Control Rivaroxaban (n=5)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td><strong>LVEF (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>good (&gt;50%)</td>
<td>47</td>
<td>57</td>
<td>36</td>
<td>40</td>
<td>.73</td>
</tr>
<tr>
<td>moderate (31-50%)</td>
<td>47</td>
<td>14</td>
<td>64</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>poor (&lt;30%)</td>
<td>6</td>
<td>29</td>
<td>0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Pathology (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>coronary artery dis.</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>aortic valve disease</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>mitral valve disease</td>
<td>9</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>aortic dissection</td>
<td>3</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>atrial fibrillation</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>EuroSCORE II (%)</strong></td>
<td>3.1</td>
<td>3.9</td>
<td>3.1</td>
<td>3.3</td>
<td>.56</td>
</tr>
<tr>
<td><strong>Emergency (%)</strong></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Cytosorb Ticagrelor (n=32)</th>
<th>Cytosorb Rivaroxaban (n=7)</th>
<th>Control Ticagrelor (n=11)</th>
<th>Control Rivaroxaban (n=5)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>84</td>
<td>100</td>
<td>91</td>
<td>100</td>
<td>.41</td>
</tr>
<tr>
<td>CABG + AVR</td>
<td>9</td>
<td>9</td>
<td></td>
<td></td>
<td>.9</td>
</tr>
<tr>
<td>CABG + MVR</td>
<td>3</td>
<td>9</td>
<td></td>
<td></td>
<td>.9</td>
</tr>
<tr>
<td>Aortic replacement</td>
<td>3</td>
<td>9</td>
<td></td>
<td></td>
<td>.9</td>
</tr>
<tr>
<td>Concomitant surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afib ablation</td>
<td>9</td>
<td>43</td>
<td>9</td>
<td>40</td>
<td>.41</td>
</tr>
<tr>
<td>LAA occlusion</td>
<td>6</td>
<td>14</td>
<td>9</td>
<td>40</td>
<td>.41</td>
</tr>
<tr>
<td>Time-related outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPB time</td>
<td>115</td>
<td>80</td>
<td>108</td>
<td>97</td>
<td>.41</td>
</tr>
<tr>
<td>X clamp time</td>
<td>77</td>
<td>81</td>
<td>64</td>
<td>70</td>
<td>.54</td>
</tr>
<tr>
<td>Total duration</td>
<td>288</td>
<td>184</td>
<td>353</td>
<td>309</td>
<td>.004</td>
</tr>
</tbody>
</table>

## Bleeding / Length of stay

<table>
<thead>
<tr>
<th></th>
<th>Cytosorb Ticagrelor (n=32)</th>
<th>Cytosorb Rivaroxaban (n=7)</th>
<th>Control Ticagrelor (n=11)</th>
<th>Control Rivaroxaban (n=5)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rethoracotomy</td>
<td>0</td>
<td>0</td>
<td>36</td>
<td>40</td>
<td>.0003</td>
</tr>
<tr>
<td>Drainage volume (24hrs)</td>
<td>350</td>
<td>390</td>
<td>890</td>
<td>600</td>
<td>.004</td>
</tr>
<tr>
<td>Days in ICU</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>.01</td>
</tr>
<tr>
<td>Total length of stay (days)</td>
<td>11</td>
<td>11</td>
<td>14</td>
<td>18</td>
<td>.02</td>
</tr>
</tbody>
</table>
Postoperative drainage volume

![Graph showing drainage volume for Rivaroxaban and Ticagrelor with and without adsorbers, with p = 0.004]
Conclusions: CytoSorb adsorption is a safe and effective method to reduce bleeding complications during emergency open-heart surgery in patients with Ticagrelor or Rivaroxaban medication.
Conclusions

Both medical and economic benefits of using Cytosorb in Ticagrelor- and Rivaroxaban-loaded patients:

- reduced operation time
- decreased use of blood products
- saves costs by faster discharge of patients from ICU

The data show that the strategy is a safe and effective method to

- reduce bleeding complications
- improve surgical outcome significantly.
The story continues...

<table>
<thead>
<tr>
<th></th>
<th>Cytosorb Ticagrelor (n=32)</th>
<th>Cytosorb Ticagrelor (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rethoracotomy</td>
<td>0</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Drainage volume/ 24hrs</td>
<td>420 ± 246</td>
<td>487 ± 222</td>
</tr>
<tr>
<td>Days in intensive care</td>
<td>3 ± 2</td>
<td>2 ± 3</td>
</tr>
<tr>
<td>Total length of stay</td>
<td>12 ± 7</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>30-days-mortality, n (%)</td>
<td>0</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Transfusion of platelets</td>
<td>11 (34.4%)</td>
<td>20 (32.8%)</td>
</tr>
<tr>
<td>Transfusion of red blood cells</td>
<td>7 (21.9%)</td>
<td>13 (21.3%)</td>
</tr>
</tbody>
</table>

From 01/2020-05/2020 cytosorb adsorption in 18% of all pats.
## Alternatives: Ticagrelor / NOAC antidots

<table>
<thead>
<tr>
<th>Drug</th>
<th>Purpose</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PB2452</strong> (PhaseBio Pharma. Inc.)</td>
<td>for Ticagrelor monoclonal ab, phase I (2019)</td>
<td></td>
</tr>
<tr>
<td><strong>Idarucizumab (Praxbind)</strong></td>
<td>for Dabigatran</td>
<td><strong>5g (100ml)</strong> US$ 8,385.20</td>
</tr>
<tr>
<td><strong>Andexanet alfa (Ondexxya)</strong></td>
<td>for Apixaban, Rivaroxaban</td>
<td><strong>US$ 2,873.38/ 100 mg vial</strong> low dose: 400 mg bolus + 480 mg iv total US$ 25,850.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>US$ 5,744.38/ 200 mg vial</strong> high dose: 800 mg bolus + 960 mg iv total US$ 48,828.42</td>
</tr>
</tbody>
</table>
Clinical perspective

Standard procedure:

Cytosorb adsorption in all ticagrelor and/or NOAC-loaded patients during emergency cardiac surgery
Thank you for your attention!
NOACs and CytoSorb

C. Michael Gibson, M.S., M.D.

Interventional Cardiologist
Professor of Medicine Harvard Medical School
President & CEO of Non-Profit Baim Institute
Founder, Editor-In-Chief www.wikidoc.org
Disclosure

• Dr. Gibson has received research grant support and consulting fees in the past from all major manufacturers of antiplatelets and antithrombins

• This is an educational lecture and is not intended to be an inducement to use any drug or drug in a fashion that is inconsistent with the drug or device label. Rivaroxaban is not approved for use in acute coronary syndromes in the US, but is so in many other countries

• The slides were prepared by C. Michael Gibson, M.S., M.D. and/or were under the editorial control of C. Michael Gibson, M.S., M.D.
### Present Research/Grant Funding
- Angel Medical Corporation
- Janssen/Johnson & Johnson
- CSL Behring
- SCAD Alliance
- Baim Institute

### Consultant
(with monies paid to hospital)
- Bayer Corporation
- Janssen Pharmaceuticals

### Spouse: Employee of Boston Clinical Research Institute in which she has equity position
- Amarin
- Amgen
- AstraZeneca
- Bayer/Janssen/ J&J
- Boehringer Ingelheim
- Boston Scientific
- Cardiovascular Research Foundation
- Caladrius Biosciences
- Cardiovascular Research Foundation
- CeleCor Therapeutics
- Chiesi
- CSL Behring
- DCRI
- Eidos Therapeutics
- Eli Lilly
- GE Healthcare
- Gilead Sciences, Inc.
- Gilead Sciences, Inc.
- Impact Bio, LTD
- Kiniksa Pharmaceuticals
- MD Magazine
- The Medicines Company

### Patents and Stocks: None

### Equity: nference, Inc.

---

Check the label in your country. Rivaroxaban is not FDA approved in the ACS setting or in patients with atrial fibrillation undergoing stent placement. It is in many other countries. Check your local label. The use of Rivaroxaban in chronic CAD is under regulatory review and is off label at present.

*Slide by C. Michael Gibson, M.S., M.D.*
Indications for NOAC

• Atrial fibrillation
• Surgical VTE prophylaxis (knee and hip surgery)
• Medically ill VTE prophylaxis
• VTE treatment (DVT and PE)
• Acute coronary syndrome (Ex US)
Atrial Fibrillation Prevalence Continues to Grow

- Atrial fibrillation prevalence is substantial and expected to grow.

![Graph showing the increase in prevalence of atrial fibrillation from 2000 to 2050, with predictions for continued increase in incidence and no further increase in incidence.](image-url)
Atrial fibrillation prevalence increases with age.

- Atrial fibrillation prevalence increases with age.
NOAC in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Stroke</td>
<td>0.92 (0.83 - 1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.49 (0.38 - 0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.97 (0.78 - 1.20)</td>
<td>0.77</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>0.90 (0.85 - 0.95)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Heterogeneity p=NS for all outcomes

NOAC in Atrial Fibrillation
Major Bleeding

**Risk Ratio (95% CI)**

- **RE-LY** [150 mg]
  - 0.94 (0.82 - 1.07)

- **ROCKET AF**
  - 1.03 (0.90 - 1.18)

- **ARISTOTLE**
  - 0.71 (0.61 - 0.81)

- **ENGAGE AF-TIMI 48** [60 mg]
  - 0.80 (0.71 - 0.90)

- **Combined** [Random Effects Model]
  - 0.86 (0.73 - 1.00)
  - p=0.06

*N=58,498*  
Heterogeneity p=0.001

NOAC Are the Standard of Care For Venous Thromboembolism and Atrial Fibrillation

Anticoagulants Market to be Worth US$ 40,158.4 Million by 2026, Says TMR

ALBANY, New York, May 3, 2019 /PRNewswire/ -- TMR's analysts estimate that the global anticoagulants market is expected to touch US$ 40,158.4 mn by the end of the forecast period. The market was valued US$ 21,759.3 mn in 2018. The growth of the market is anticipated to occur at a promising 8.0% CAGR during 2018-2026.

From the perspective of drug class, factor Xa inhibitors segment is gaining traction in the global anticoagulants market due to its high usage in various indications such as stroke, heart attack, pulmonary embolism (PE), angina, surgery, and deep venous thrombosis (DVT). On the regional front, North America showcases the highest share in the global anticoagulants market with growing number of several surgical procedures such as knee and hip replacements, and rising healthcare expenditures.
## ED Visits for ADEs
### By Drug Class (2005-2014)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>19.2 (17.7-20.7)</td>
<td>18.6 (16.8-20.4)</td>
<td>18.6 (16.7-20.6)</td>
<td>17.9 (16.6-19.3)</td>
<td>16.1 (14.4-17.8)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>7.3 (4.6-9.9)</td>
<td>9.9 (7.6-12.2)</td>
<td>11.2 (8.2-14.1)</td>
<td>13.3 (11.1-15.4)</td>
<td>17.6 (14.2-21.0)</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>1.8 (0.8-2.8)</td>
<td>1.6 (0.8-2.4)</td>
<td>2.5 (1.2-3.9)</td>
<td>2.4 (1.3-3.4)</td>
<td>3.0 (1.6-4.3)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>3.7 (2.1-5.2)</td>
<td>4.6 (2.7-6.5)</td>
<td>4.6 (2.9-6.2)</td>
<td>4.8 (3.2-6.4)</td>
<td>6.6 (4.7-8.5)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>2.8 (2.2-3.4)</td>
<td>3.0 (2.5-3.5)</td>
<td>3.0 (2.6-3.4)</td>
<td>3.1 (2.5-3.7)</td>
<td>2.7 (2.1-3.2)</td>
</tr>
<tr>
<td>Diabetes agents</td>
<td>10.9 (7.3-14.5)</td>
<td>12.8 (9.1-16.6)</td>
<td>12.0 (9.1-14.9)</td>
<td>12.0 (9.1-14.8)</td>
<td>13.3 (10.8-15.8)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>4.1 (3.4-4.8)</td>
<td>3.5 (3.0-3.9)</td>
<td>3.2 (2.8-3.6)</td>
<td>3.2 (2.7-3.7)</td>
<td>2.8 (2.4-3.2)</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>7.7 (6.9-8.6)</td>
<td>7.9 (7.1-8.8)</td>
<td>7.2 (6.6-7.8)</td>
<td>7.9 (7.2-8.5)</td>
<td>6.8 (6.3-7.4)</td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>2.4 (1.9-2.9)</td>
<td>2.5 (1.9-3.0)</td>
<td>2.9 (2.2-3.7)</td>
<td>3.2 (2.4-4.0)</td>
<td>3.5 (2.6-4.4)</td>
</tr>
<tr>
<td>Sedative/hypnotic agents</td>
<td>3.2 (2.7-3.7)</td>
<td>3.2 (2.8-3.6)</td>
<td>3.6 (3.1-4.2)</td>
<td>3.4 (2.8-3.9)</td>
<td>3.0 (2.4-3.5)</td>
</tr>
</tbody>
</table>

*Slide by C. Michael Gibson, M.S., M.D.*
Increased Morbidity and Mortality in Patients Admitted on a NOAC As Compared to Non-Anticoagulated Patients

Cost of Major Bleeding:
- Top 15% > $100K to treat
- Mean ~$50,000

1. Truven, MarketScan Commercial, Medicare Supplemental, last 12 months ending April 30, 2015. Medicaid accounts for ~5% of the total bleed related admissions.
2. LOS = The LOS in the Truven report varies by payor. In the YTD 10/2014 report the LOS were 8.0 (12.0), 7.1 (9.3) for Commercial, Medicare respectively.
3. The data for mortality from major bleeds ranges from 5.1% (DRESDEN Registry) to 33% (RIETE Registry). Other data such as the ARISTOTLE trial (Granger et al, NEJM 2011) suggest 11–15%.
## Management for Patients on NOAC Today

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Treatment for Life-Threatening Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pradaxa®</strong></td>
<td><strong>Praxbind</strong> (idarucizumab)</td>
</tr>
<tr>
<td>(dabigatran)</td>
<td></td>
</tr>
<tr>
<td><strong>Xarelto®</strong></td>
<td><strong>Andexxa</strong> (andexanet alfa)</td>
</tr>
<tr>
<td>(rivaroxaban)</td>
<td></td>
</tr>
<tr>
<td><strong>Eliquis®</strong></td>
<td></td>
</tr>
<tr>
<td>(apixaban)</td>
<td></td>
</tr>
<tr>
<td><strong>Savaysa®</strong></td>
<td></td>
</tr>
<tr>
<td>(edoxaban)</td>
<td></td>
</tr>
</tbody>
</table>

3. Cytosorb. Instructions for use.


Andexanet Limitations

• Approved for reversal of ongoing life threatening bleeding

• NOT approved for reversal in a patient with no bleeding who is to undergo surgery

• Numeric excess of thrombotic events following reversal

• Cost
# Management for Patients on NOAC in the Future

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Prevention of Bleeding</th>
<th>Treatment for Life-Threatening Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pradaxa® (dabigatran)</td>
<td>CytoSorb®</td>
<td>Praxbind (idarucizumab)</td>
</tr>
<tr>
<td>Xarelto® (rivaroxaban)</td>
<td>CytoSorb®</td>
<td>Andexxa (andexanet alfa)</td>
</tr>
<tr>
<td>Eliquis® (apixaban)</td>
<td>CytoSorb®</td>
<td></td>
</tr>
<tr>
<td>Savaysa® (edoxaban)</td>
<td>CytoSorb®</td>
<td></td>
</tr>
</tbody>
</table>
# Preventing Bleeding in Cardiac Surgery


## Comparison of Techniques

<table>
<thead>
<tr>
<th>Table</th>
<th>CPB + CytoSorb (n=32)</th>
<th>CPB alone (n=11)</th>
<th>CPB + CytoSorb (n=7)</th>
<th>CPB alone (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>43 patients emergency surgery with ticoagrelor</strong></td>
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<tr>
<td><strong>55 patients</strong></td>
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<td><strong>12 patients emergency surgery with rivaroxaban</strong></td>
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<td><strong>32 patients with intra-operative CytoSorb</strong></td>
<td><strong>288 ± 63</strong></td>
<td><strong>353 ± 84</strong></td>
<td><strong>184 ± 97</strong></td>
<td><strong>309 ± 50</strong></td>
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<td><strong>11 patients control without CytoSorb</strong></td>
<td><strong>21.9% (n=7)</strong></td>
<td><strong>45.5% (n=5)</strong></td>
<td><strong>14.3% (n=1)</strong></td>
<td><strong>100% (n=5)</strong></td>
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<td><strong>Procedure duration</strong> (min; mean ± SD)</td>
<td><strong>34.4% (n=11)</strong></td>
<td><strong>100% (n=11)</strong></td>
<td><strong>28.6% (n=2)</strong></td>
<td><strong>100% (n=5)</strong></td>
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<td><strong>Red blood cell transfusion</strong></td>
<td><strong>350 [300 - 450]</strong></td>
<td><strong>890 [630 - 1025]</strong></td>
<td><strong>390 [310 - 430]</strong></td>
<td><strong>600 [590 - 1000]</strong></td>
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<td><strong>Platelet transfusion</strong></td>
<td><strong>0% (n=0)</strong></td>
<td><strong>36.4% (n=4)</strong></td>
<td><strong>0% (n=0)</strong></td>
<td><strong>40% (n=2)</strong></td>
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<tr>
<td><strong>Chest tube drainage remove volume/24hrs (ml; median [IQR])</strong></td>
<td><strong>2 [1 - 3]</strong></td>
<td><strong>3 [2 - 4]</strong></td>
<td><strong>2 [2 - 3]</strong></td>
<td><strong>6 [5 - 6]</strong></td>
</tr>
<tr>
<td><strong>Re-thoracotomy</strong></td>
<td><strong>11 [9 - 12]</strong></td>
<td><strong>14 [10 - 16]</strong></td>
<td><strong>11 [10 - 13]</strong></td>
<td><strong>18 [18 - 20]</strong></td>
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</tbody>
</table>

For Cytokine Removal
Cardiac Surgery vs. Non-Cardiac Surgery

In-vitro Removal of Rivaroxaban by CytoSorb

“Within 1 hour 91.6% of circulating rivaroxaban was removed.”

“For normal therapeutic concentrations below 300 μg/L, we expect plasma concentration to be reduced below the critical threshold in 30 to 60 minutes.”

58 y/o male, high bleeding risk, undergoing urgent OPCAB

- PCI - dissected LAD. On aspirin, ticagrelor, rivaroxaban (Afib)
- Ongoing chest pain, (+) TnI
- Urgent OPCAB recommended
- Cytosorb started 1 hour prior to surgery and continued for 1.5 h into CABG
- Cytosorb integrated in hemoperfusion mode
- Operative course uneventful without excess bleeding
- Patient well at 6 months f/u

**Ticagrelor + Rivaroxaban Removal off-pump**

Dual antithrombotic removal (TIC + RIV) without CPB

“Dabigatran is robustly removed by a sorbent hemadsorption method already proven successful for ticagrelor. Dabigatran removal restores the aPTT, suggesting reversal of the anticoagulant effect of this drug.”

In-vitro Removal of Edoxaban by CytoSorb

“Sorbent-mediated technology may represent a viable pathway for edoxaban removal from human plasma.”

Hospital-wide Applications

- Off-pump cardiac surgery
- Cardiac electrophysiology procedures
- Neurosurgical procedures
  - Reduce risk of life-threatening bleeding
  - Avoid surgery (subdural hematomas)
- Acute stroke  (NOAC = contraindication for t-PA)
- Urgent orthopedic procedures
- Urgent GI or oncological procedures
- Trauma
Summary: NOAC and CytoSorb

- NOAC are the standard of care for chronic anticoagulation (Afib, VTE, etc.)
- Aging of the population will only increase use
- Patients on NOAC present unique challenges in the hospital setting due to bleeding risk
- CytoSorb® is the only strategy that can prevent bleeding in these patients
- Clinical evidence supports its use for on pump cardiac surgery
- Future studies can establish its use throughout the hospital (any OR, ED, etc.)
Closing Remarks
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Chief Medical Officer
CytoSorbents Corporation
Regulatory Status & Clinical Activities

European Union
• CytoSorb is CE Mark label approved for ticagrelor and rivaroxaban removal

USA
• Ticagrelor removal granted
FDA Breakthrough Designation
• Ongoing discussions with FDA to set regulatory pathway

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Study | Design | Region | Start
---|---|---|---
TISORB Ticagrelor CytoSorb Hemoadsorption | Prospective, open label trial | United Kingdom | Q3 ’20
CYTATION The CytoSorb® Ticagrelor HemoAdsortion Study | Prospective, open label trial | Germany | Q3 ‘20
STAR Safe and Timely Antithrombotic Removal | Prospective, international registry | Phase 1: EU Phase 2: US + ROW | Q4 ‘20

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CytoSorb is indicated for use in conditions where elevated levels of cytokines and/or bilirubin and/or myoglobin exist. CytoSorb is indicated for use intraoperatively during cardio-pulmonary bypass surgery for the removal of P2Y₁₂-Inhibitor Ticagrelor and/or Factor Xa-Inhibitor Rivaroxaban.
### Total Addressable Market For Ticagrelor Removal

#### United States

- **~154,000 Surgeries**
  - (142,000 CABG and 12,000 AA)
- **~100,000 Surgeries**
  - ($500M TAM)*
  - (92,000 CABG and 8,000 AA)
- **~50,000 Surgeries**
  - ($250M TAM)*
- **~384,000 Surgeries**
  - (355,000 CABG and 29,000 AA)

*CytoSorb price = $5,000*

- **CABG**: Coronary Artery Bypass Graft surgery
- **AA**: Aortic Aneurysm Repair

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- Urgent/Emergent Surgeries (~40%)
- P2Y$_{12}$ Pre-treated Patients (~65%)
- Ticagrelor Pre-treated Patients (~50%)
- Total Addressable Cardiac Surgeries

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* US Addressable Market Today
  - ~50,000 Surgeries
    - ($250M TAM)*
  - ~100,000 Surgeries
    - ($500M TAM)*
    - (92,000 CABG and 8,000 AA)
  - ~154,000 Surgeries
    - (142,000 CABG and 12,000 AA)
  - ~384,000 Surgeries
    - (355,000 CABG and 29,000 AA)
US Market – Sequential Growth

- **TICAGRELOR + NOAC**
  - Cardiac surgery: $250M (Today)
  - All surgery: $1.5B

- **TICAGRELOR + NOAC**
  - Cardiac surgery: $500M
Final Thoughts

- Antithrombotic drug removal with CytoSorb is a novel solution to a very large unmet hospital need
- Currently no available therapies to prevent bleeding
  - Andexxa® or PB2452 (not yet approved) intended only for use after life-threatening bleeding
- CytoSorb antithrombotic removal in cardiac surgery is safe, effective, easy to implement and is expected to lead to substantial cost savings (dominant value proposition)
- Already approved in E.U. for cardiac surgery (ticagrelor + rivaroxaban) and Breakthrough Designation granted by FDA (ticagrelor)
- Ongoing clinical projects to establish removal of additional NOACs and hospital-wide clinical use
- Market opportunity for all "at-risk" surgeries exceeds $1.5 Billion annually in the U.S. alone

THANK YOU FOR YOUR ATTENTION