CytoSorbents™

WORKING TO SAVE LIVES

CytoSorb Antithrombotic Removal
July 13, 2020

Safe Harbor Statement

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.

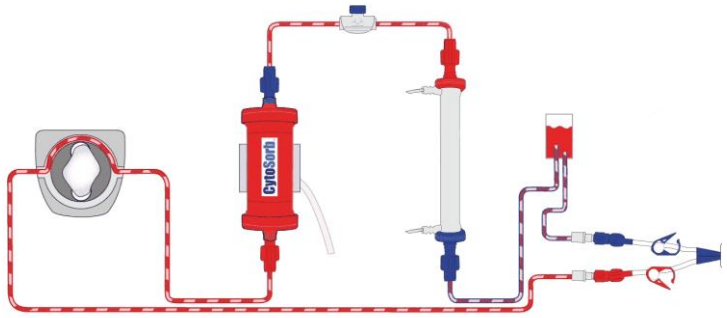
- 156 employees with international footprint across two wholly-owned subsidiaries
  - CytoSorbents Medical, Inc: Headquarters - New Jersey, USA (ISO 13485 certified manufacturing, R&D, Management)
  - CytoSorbents Europe GmbH: International sales office - Berlin, Germany (Sales and Marketing)

- Strong government support with ~$33M in grants, contracts, other non-dilutive funds

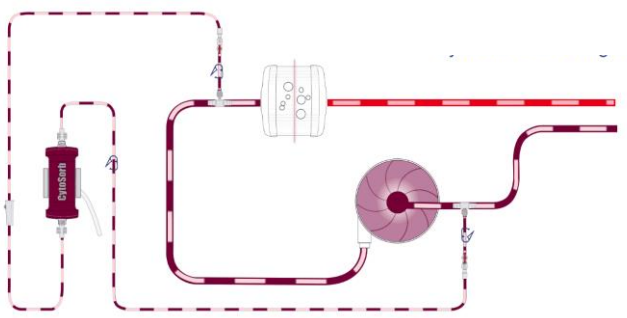
CytoSorb is “Plug and Play” Compatible

Compatible with Existing Blood Pump Infrastructure In Hospitals Today

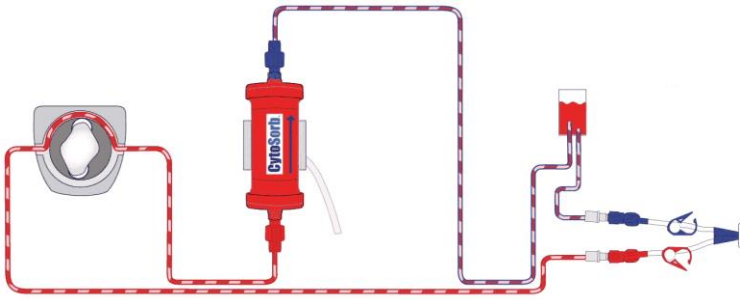
Dialysis or CRRT
(Continuous Renal Replacement Therapy)



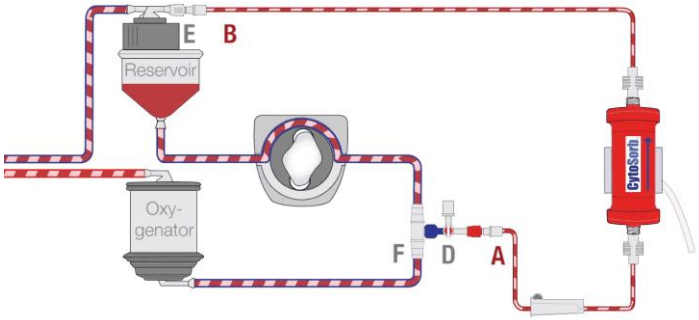
ECMO
(Extracorporeal Membrane Oxygenation)



Hemoperfusion
(Standalone Treatment)



CPB
(Cardiopulmonary Bypass)



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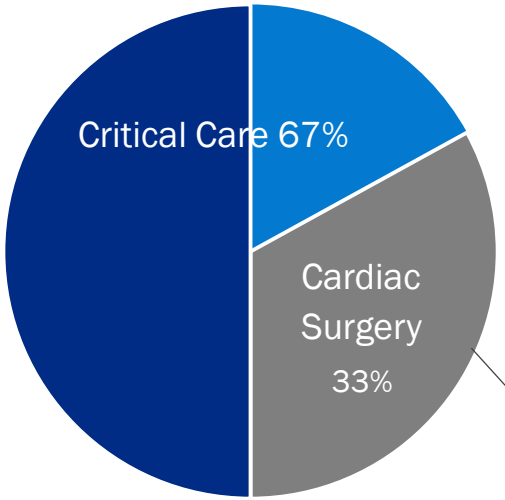
CytoSorb Commercialization Focus

By Market



Sepsis and Septic Shock 50%

Other Critical Care – 17%

- ARDS
- Reversal of Shock
- Trauma
- Acute Liver / Pancreatic
- Many Others

Cardiac Surgery – 33%

- Infective Endocarditis
- Reversal of Vasoplegia
- Removal of Antithrombotics
- Complex Procedures

By Geography

20 – 30% Distributor / Partner

10 – 15% Other Direct

- Austria
- Switzerland
- 7 other countries

60 – 65% Germany – Direct

World Class Partners

FRESENIUS MEDICAL CARE (Critical Care)

TERUMO (Cardiac Surgery)

Biocon (India – Cardiac / Critical Care)

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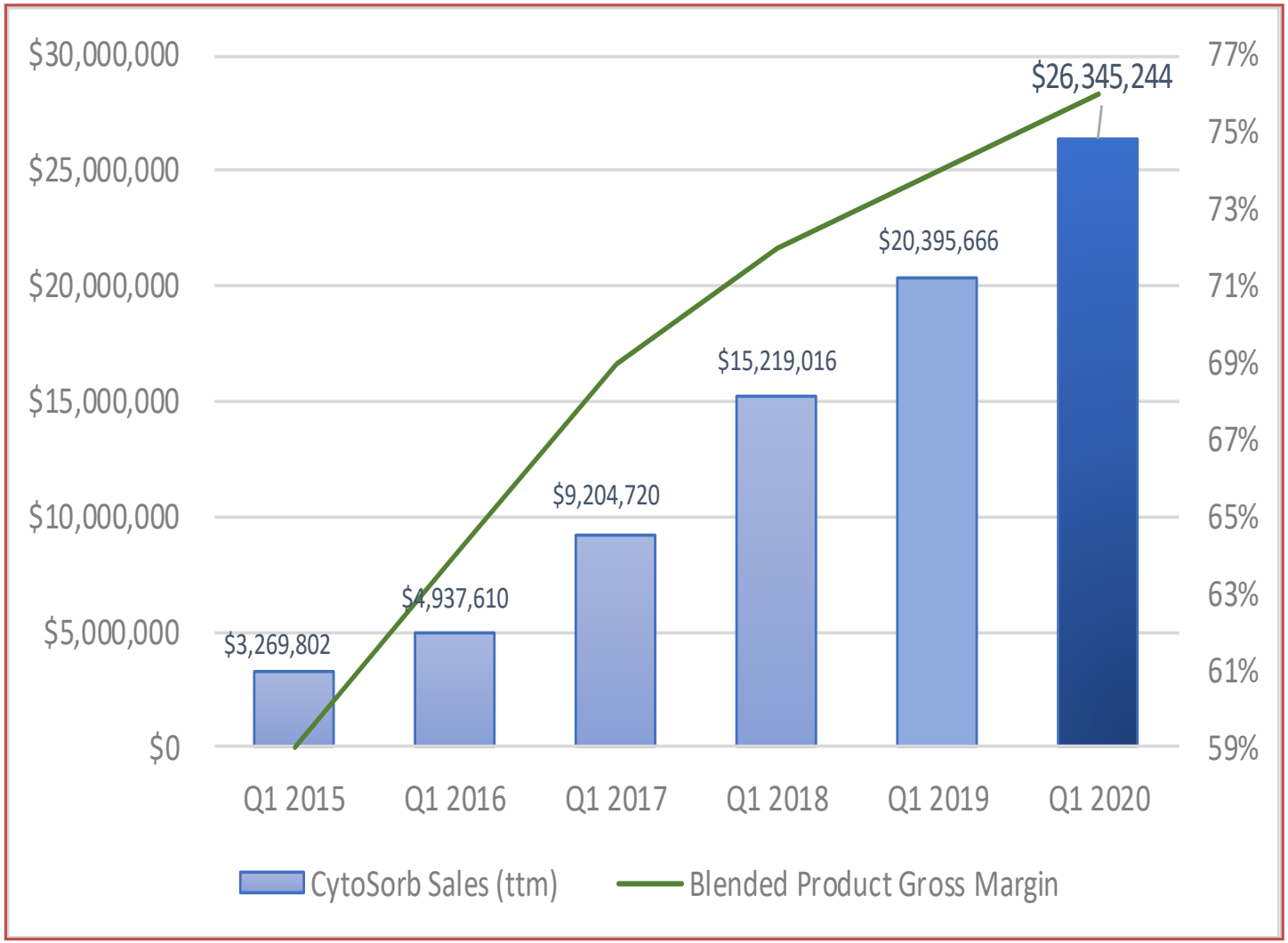
CytoSorb Adoption Continues to Grow

Product Sales(ttm) and Blended Product Gross Margin Growth



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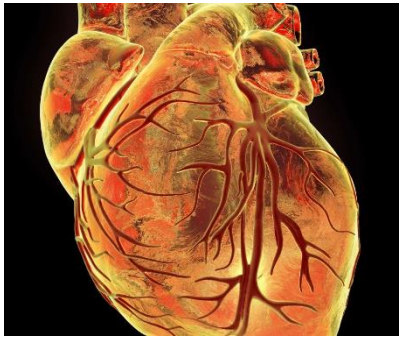
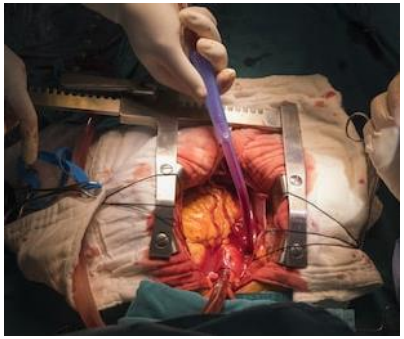
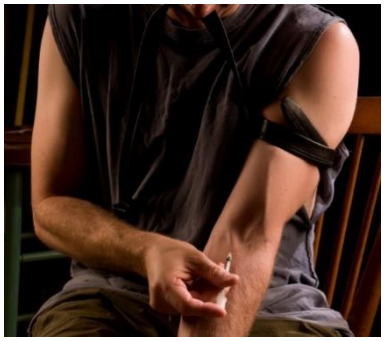
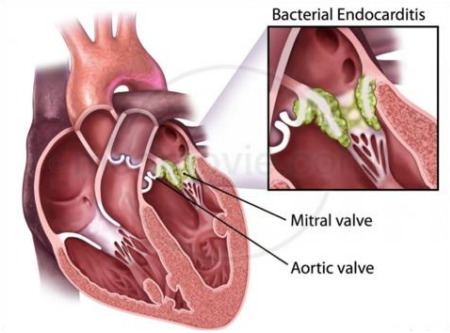
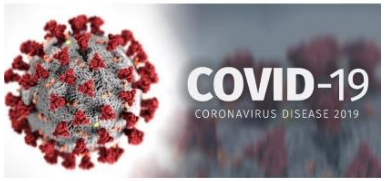
Growth Driven By Many Macro Trends in Healthcare

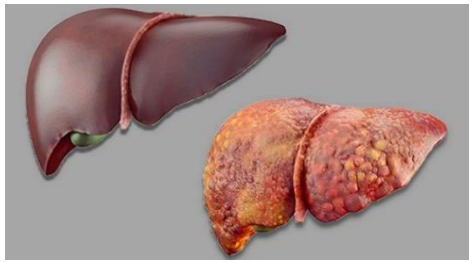


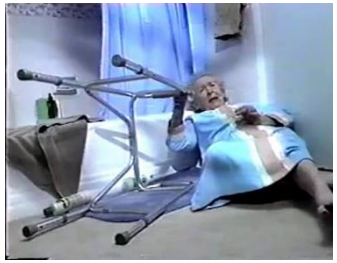












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Introduction of Agenda & Speakers

Efthymios N. Deliargyris, MD, FACC, FESC, FSCAI
Chief Medical Officer
CytoSorbents Corporation

Antithrombotic Removal

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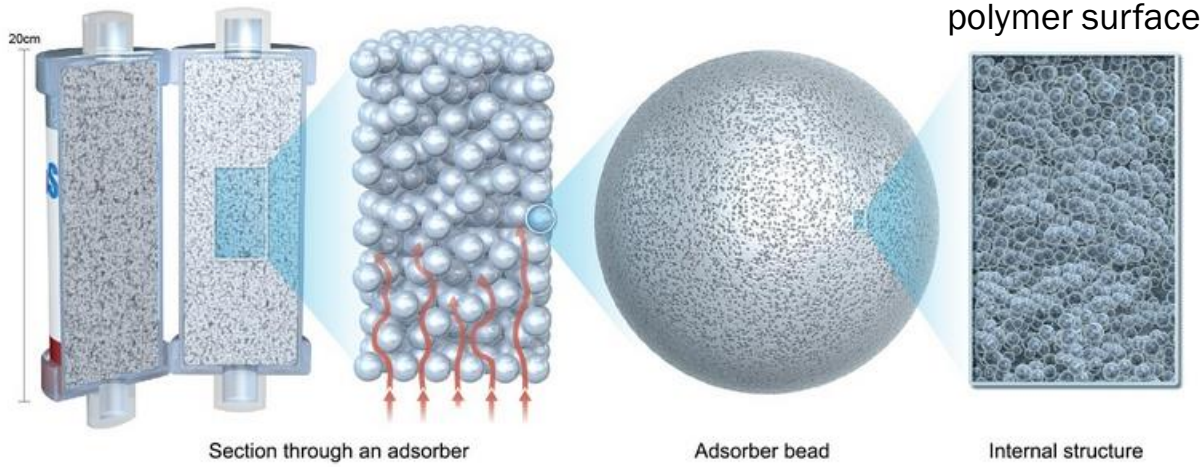
CytoSorb Drug Adsorption: Mechanism of Action

Device :



adsorption on **divinylbenzene** polymer surface

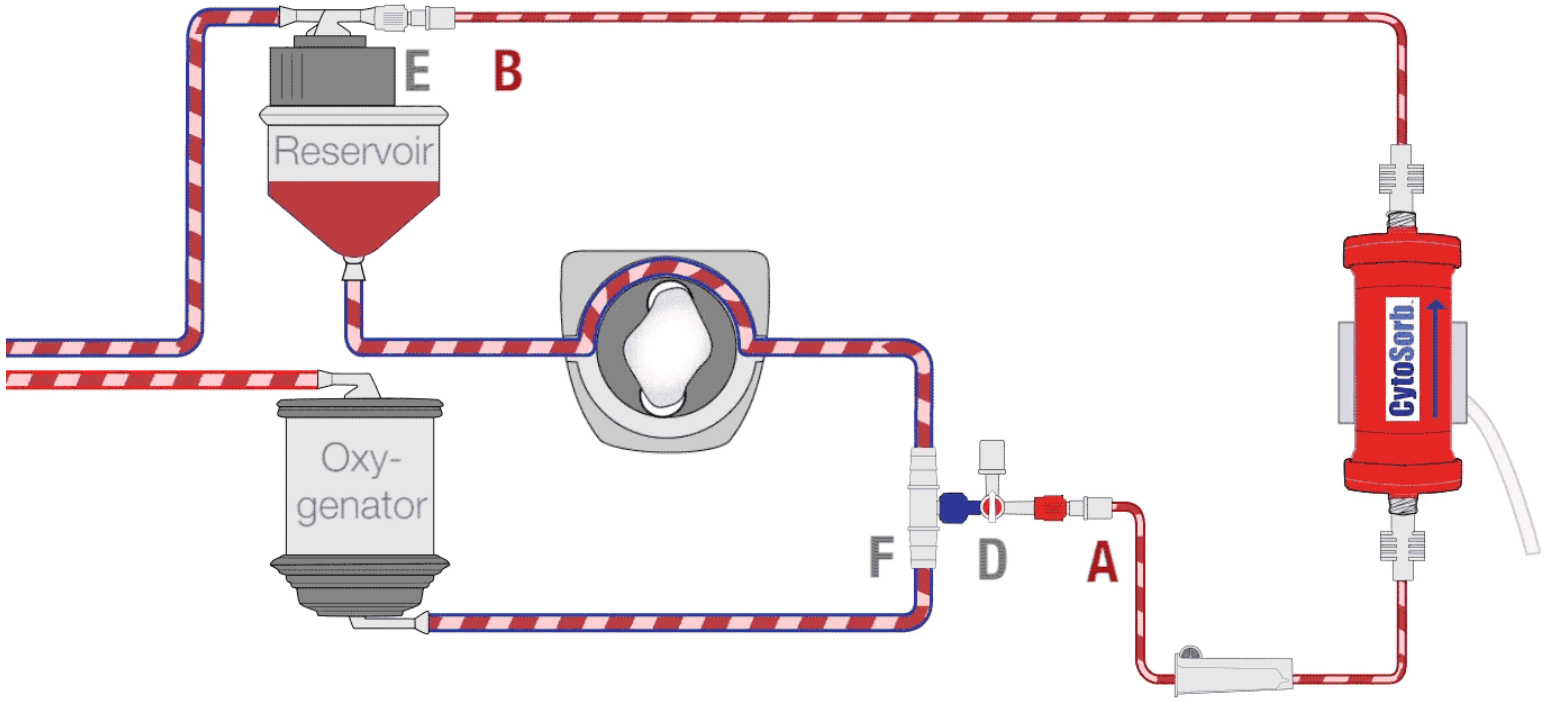
- favors hydrophobic binding
- pore size = selective access to ≤ 60 kDa
- dependent on drug concentration
- dependent on time of blood exposure

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



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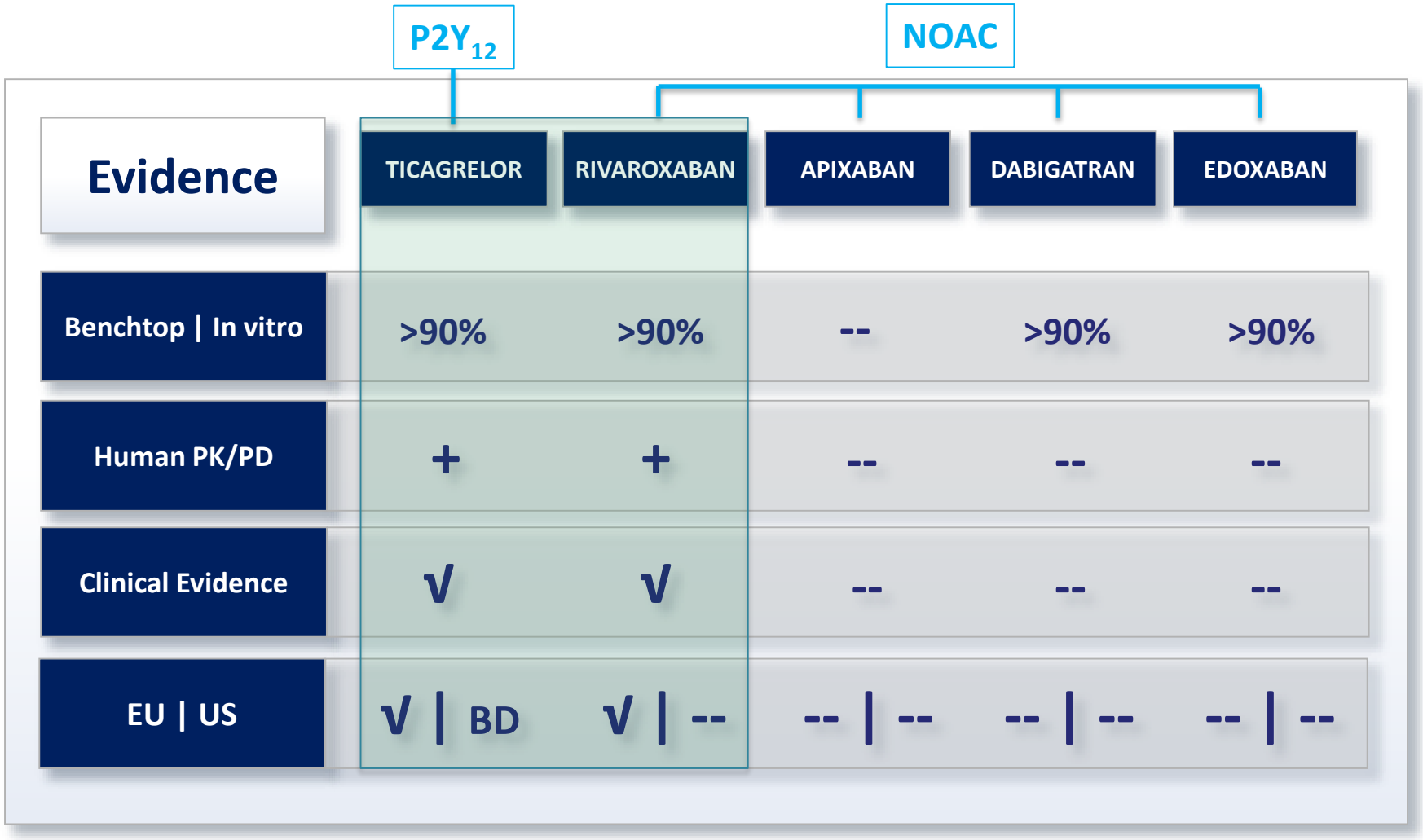
Antithrombotic Removal - Overview



Today's Agenda & Speakers

Speaker	Title	Time
Phillip Chan	Welcome & Opening Remarks	5 min
Makis Deliargyris	Introduction of Agenda & Speakers	5 min
Robert Storey	Ticagrelor and CytoSorb	15 min
Michael Schmoeckel	Intraoperative removal of Ticagrelor and Rivaroxaban during Emergency Cardiac Operations	15 min
Michael Gibson	NOACs and CytoSorb	15 min
Makis Deliargyris	Closing Remarks – Size of the opportunity	5 min
All	Q & A Session	30 min

Antithrombotic Removal

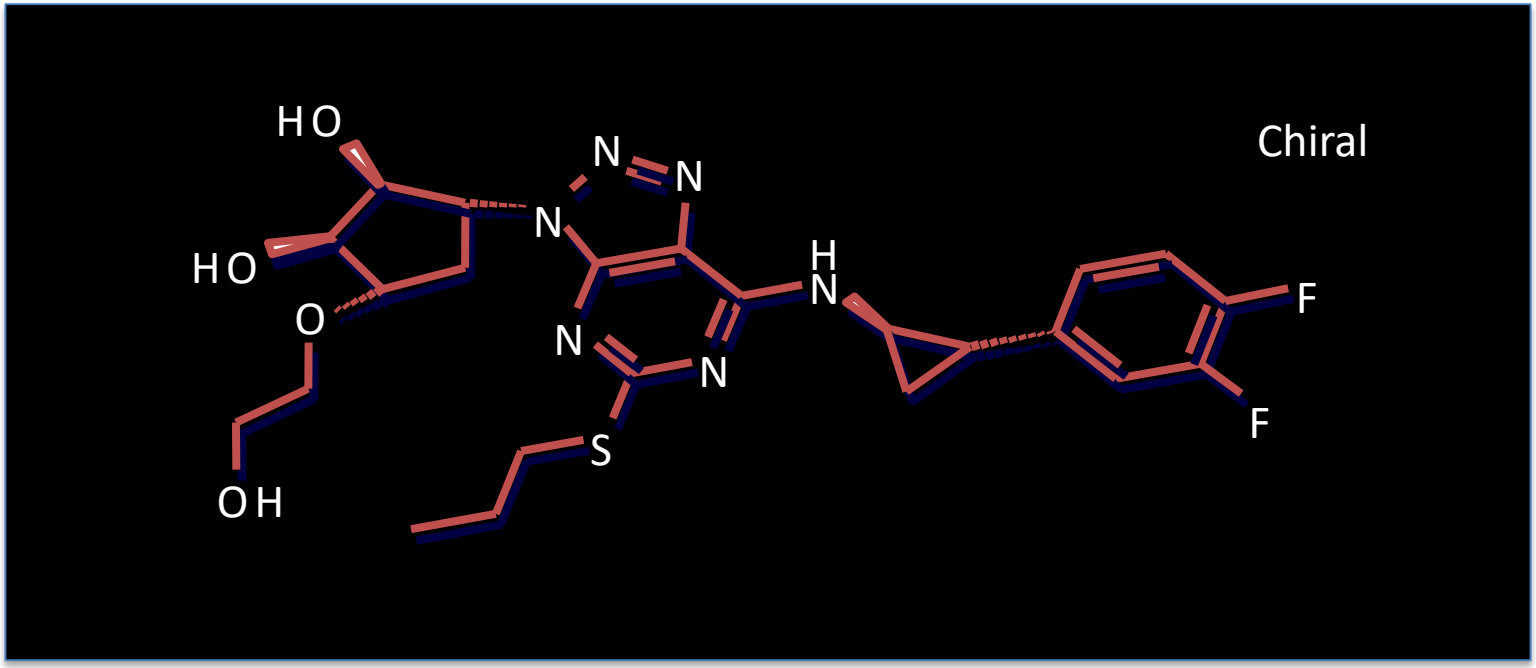
- Unmet clinical need
- Clinical evidence with CytoSorb
- Size of the addressable market

Ticagrelor and CytoSorb

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

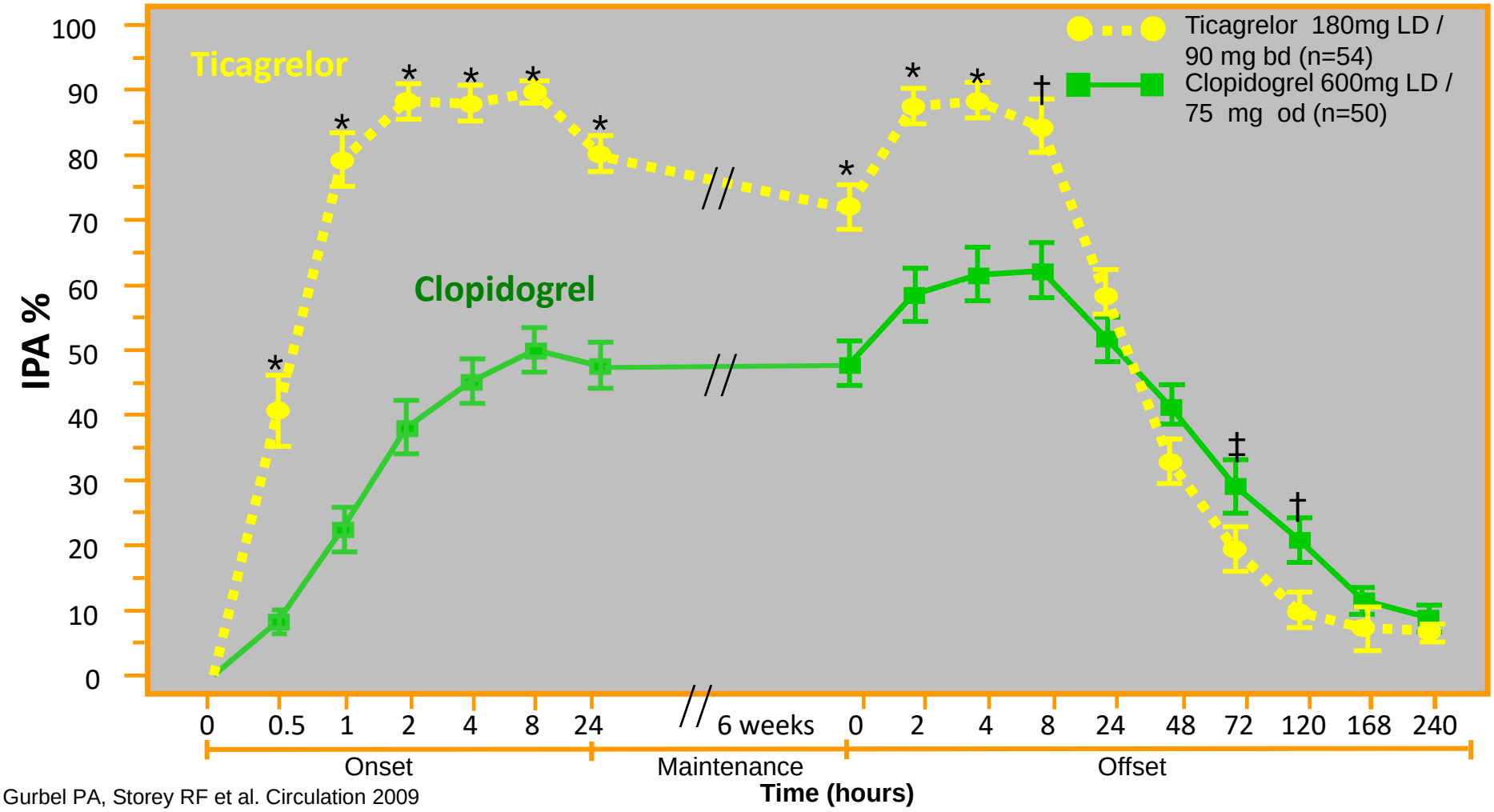
Professor of Cardiology and Cardiovascular Disease Theme Lead, Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield
and
Academic Director and Honorary Consultant Cardiologist, Cardiology and Cardiothoracic Surgery Directorate, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom

Ticagrelor: the first oral reversibly-binding $P2Y_{12}$ receptor antagonist belonging to the class CPTP (cyclo-pentyl-triazolo-pyrimidine)



van Giezen JJJ, Humphries RG. *Semin Thromb Hemost.* 2005;31:195-204.

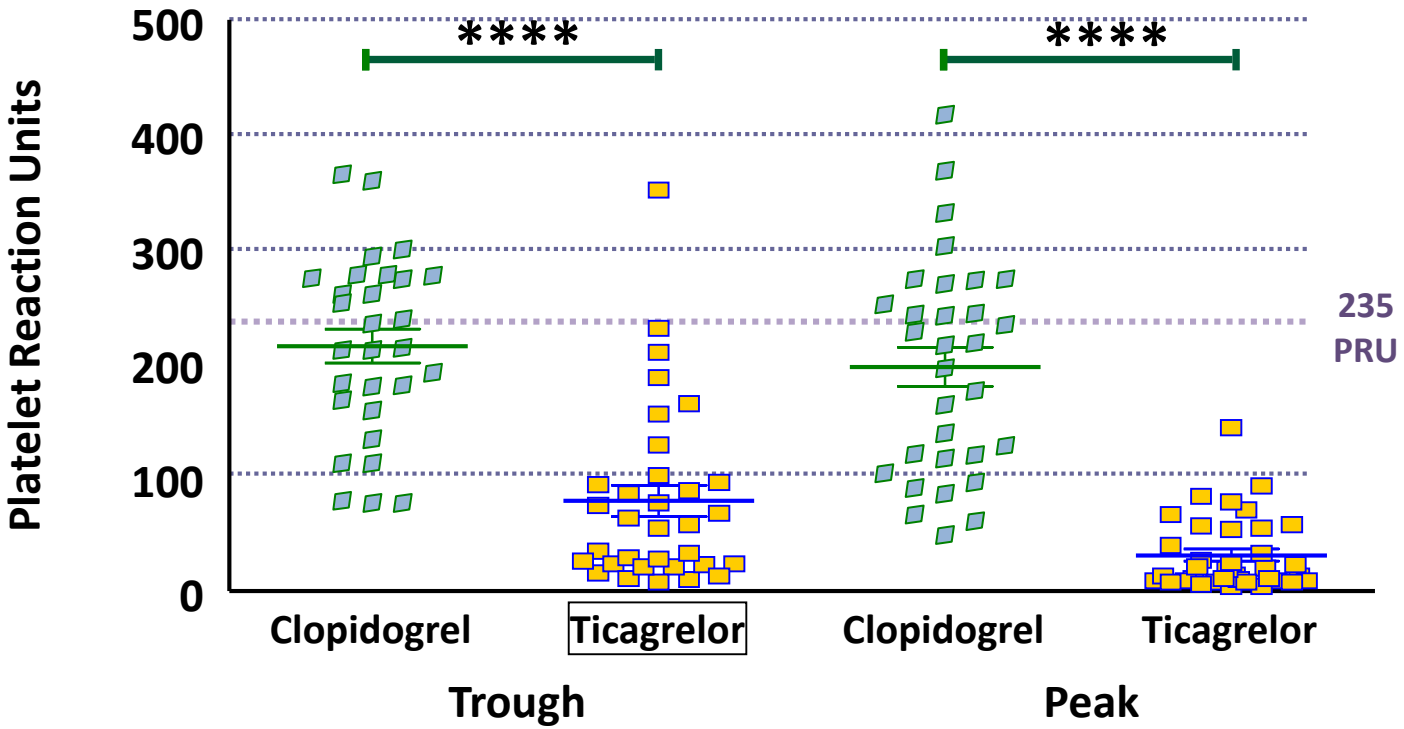
ONSET/OFFSET Study: inhibition of platelet aggregation



Gurbel PA, Storey RF et al. Circulation 2009

PLATO PLATELET: VerifyNow $P2Y_{12}$ Assay

Comparing Maintenance Therapy with Clopidogrel vs Ticagrelor in ACS

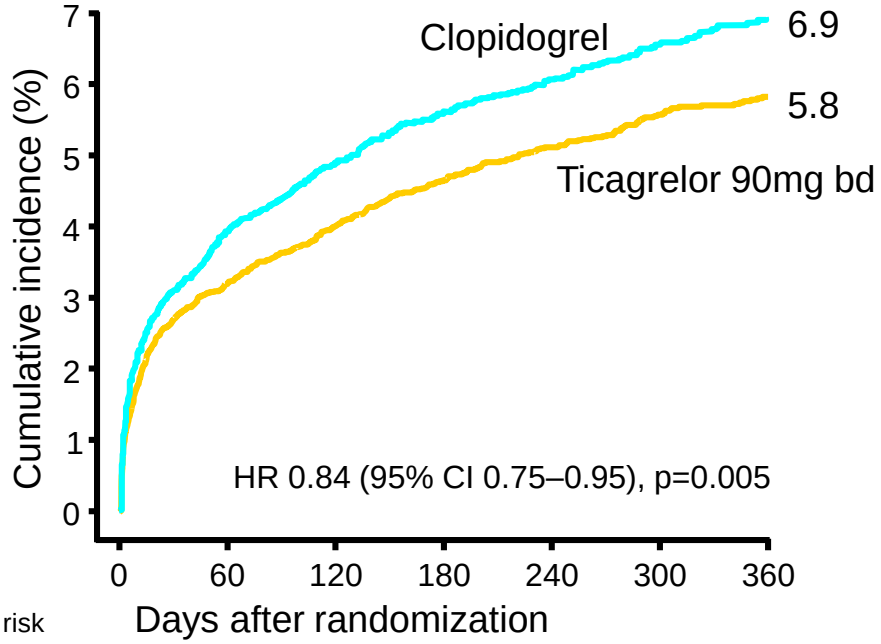


***P<0.0001; PRU = Platelet reaction units.

Storey RF, et al. J Am Coll Cardiol 2010

PLATO Secondary efficacy endpoints

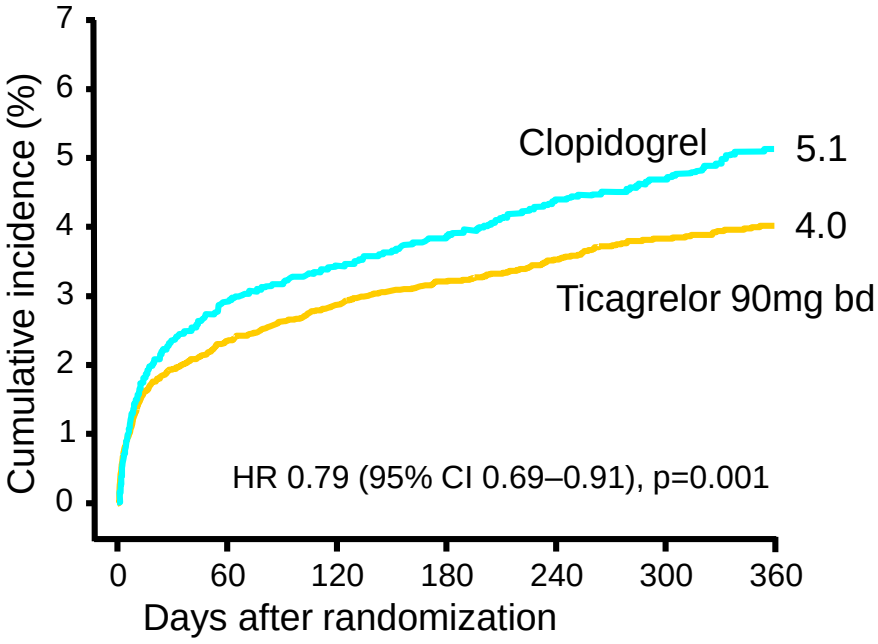
Myocardial infarction



No. at risk

Ticagrelor	9333	8678	8520	8279	6796	5210	4191
Clopidogrel	9291	8560	8405	8177	6703	5136	4109

Cardiovascular death



	9333	8294	8822	8626	7119	5482	4419
	9291	8865	8780	8589	7079	5441	4364

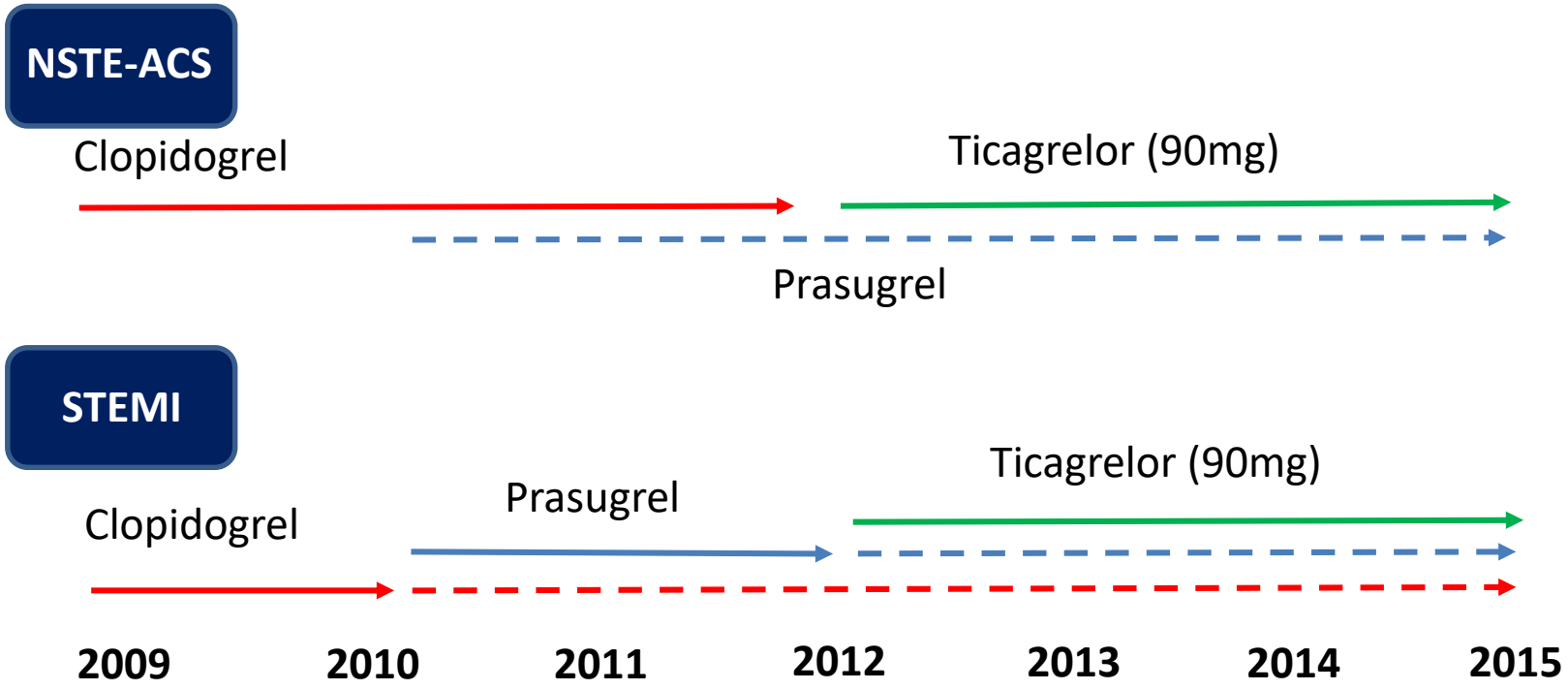
Wallentin L et al. *N Eng J Med.* 2009

UK networks for ACS and revascularisation

South Yorkshire Cardiothoracic Centre

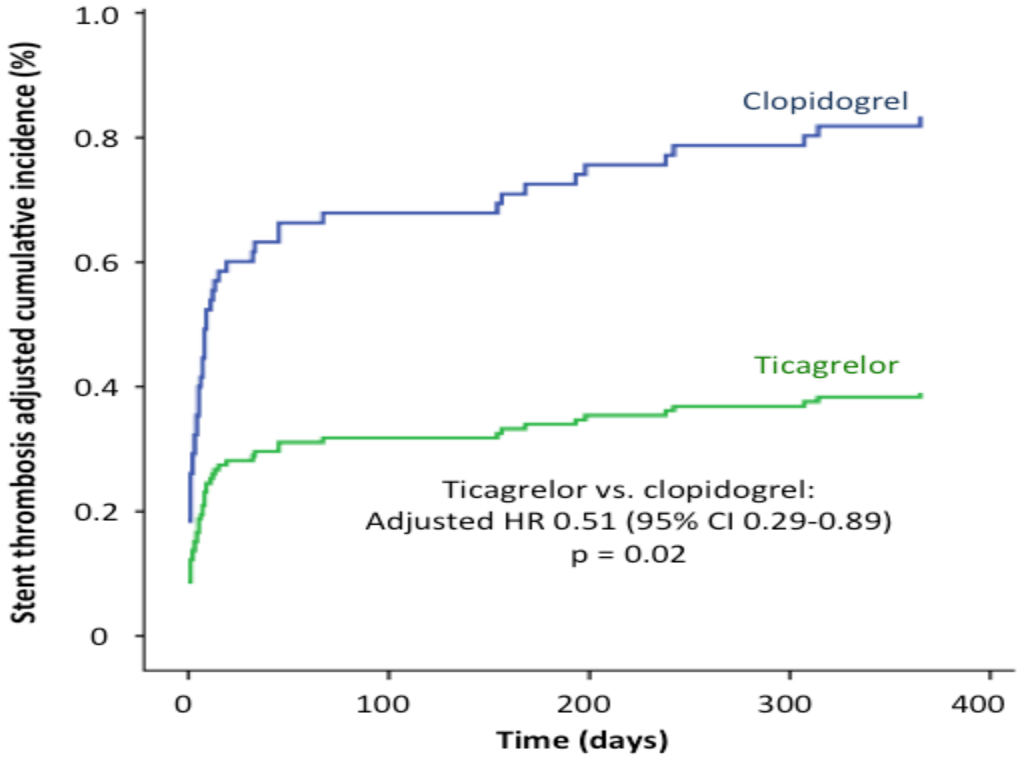
Provides a PCI and CABG surgery service including 24/7 primary PCI to the South Yorkshire and North Derbyshire regions of England –
a population of 1.8 million people

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

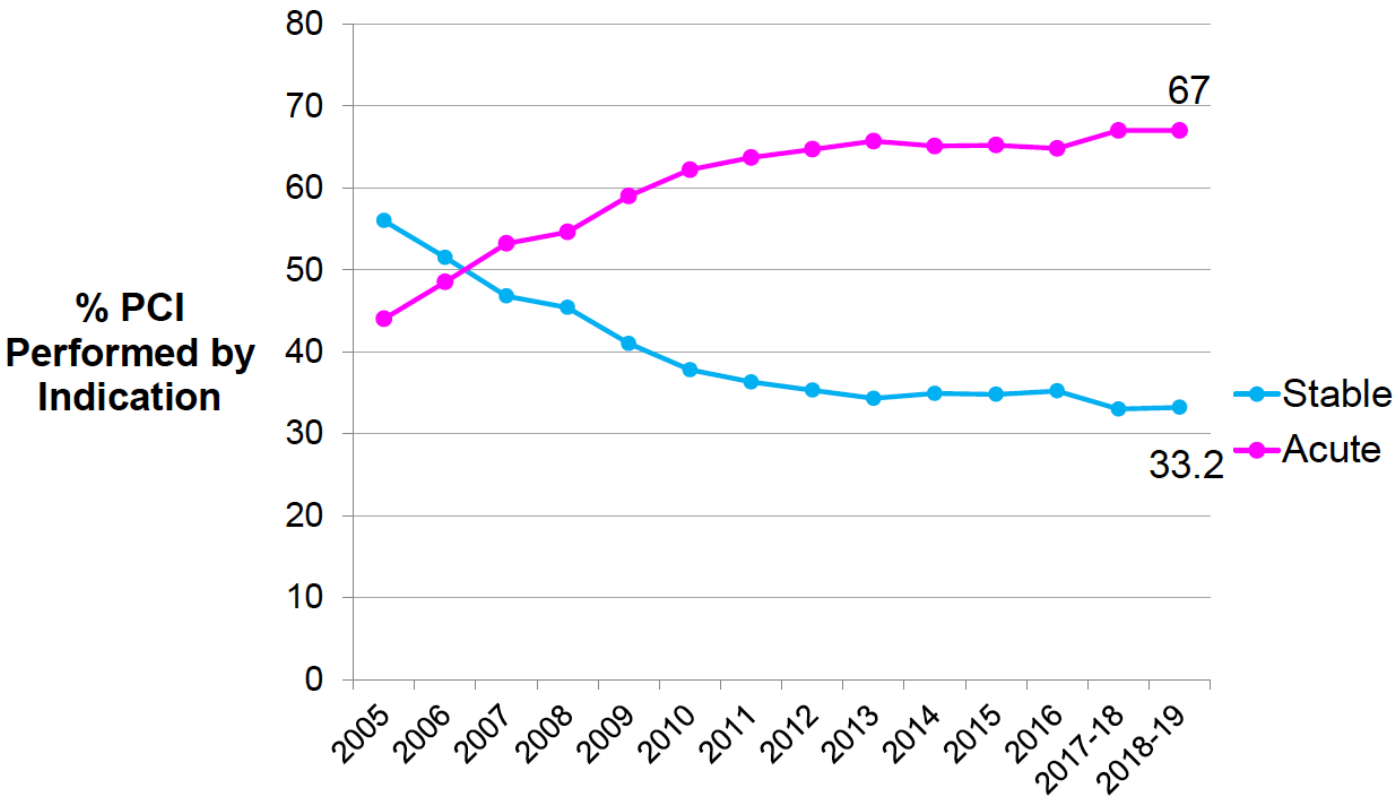
BCIS National Audit
Adult Interventional Procedures

1st April 2018 to 31st March 2019

NICOR
Data extract
25-10-2019

BCIS
2018-19 data

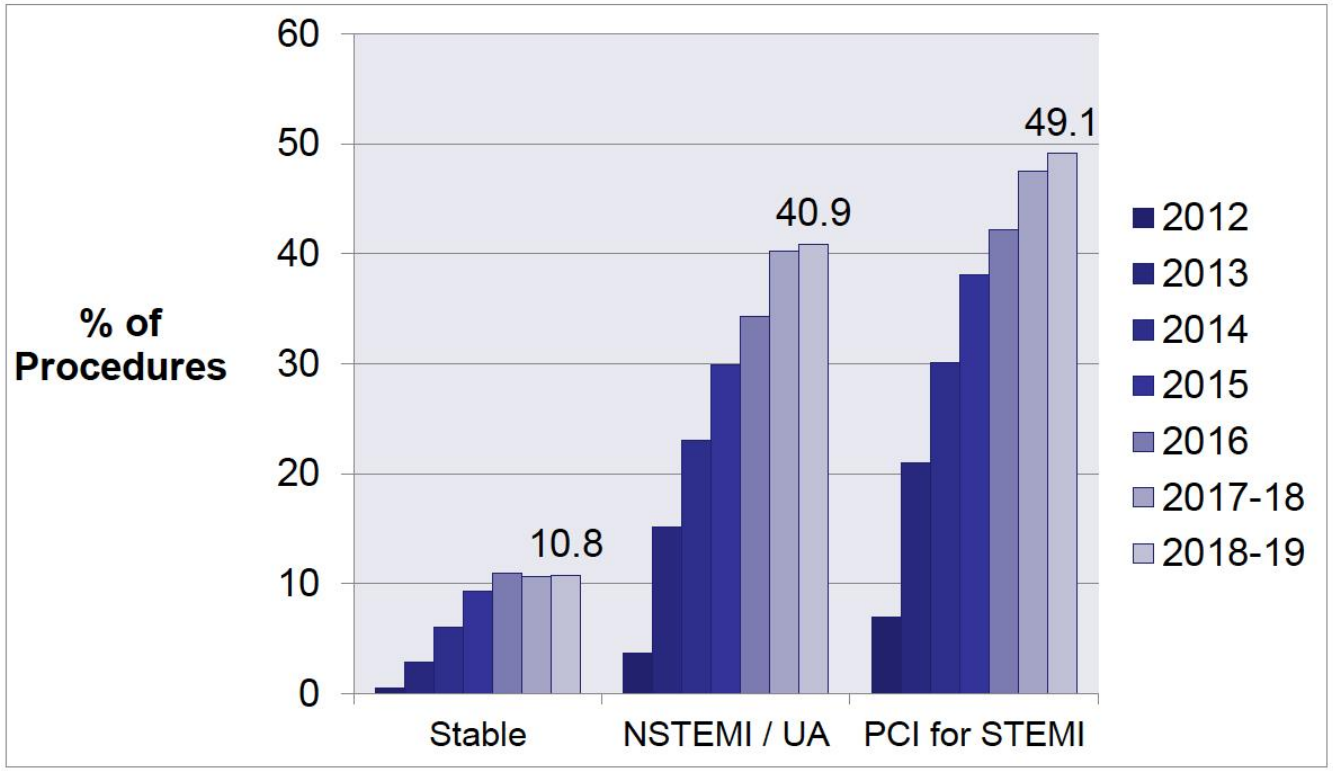
Clinical Syndrome



Ticagrelor

Use by Indication for PCI

BCIS 2018-19 data

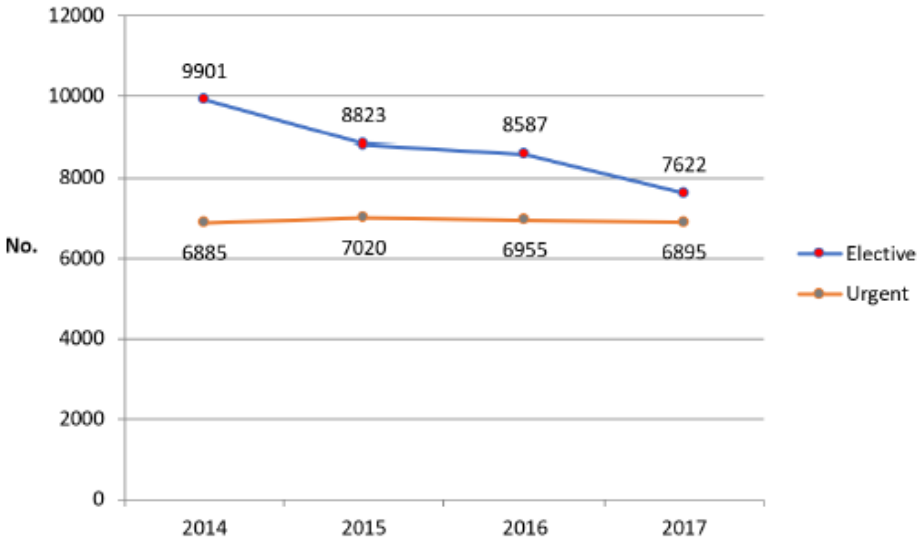


NATIONAL ADULT CARDIAC SURGERY AUDIT

2019 SUMMARY REPORT
(2015/16-2017/18 DATA)

NICOR

Isolated CABG surgery: elective vs. urgent

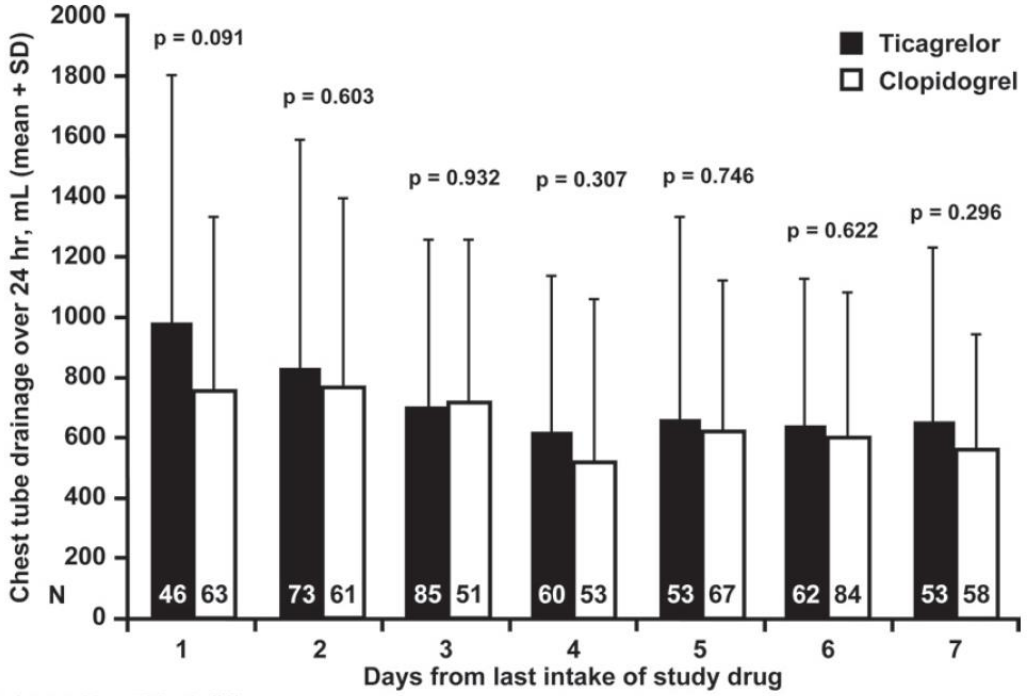


Mean time waiting for **urgent** CABG in 2017/18 was **10 days** in the UK (no change from 2016/17)

Proportion treated within 7 days = 34%

Only 4 hospitals managed to treat >50% within 7 days

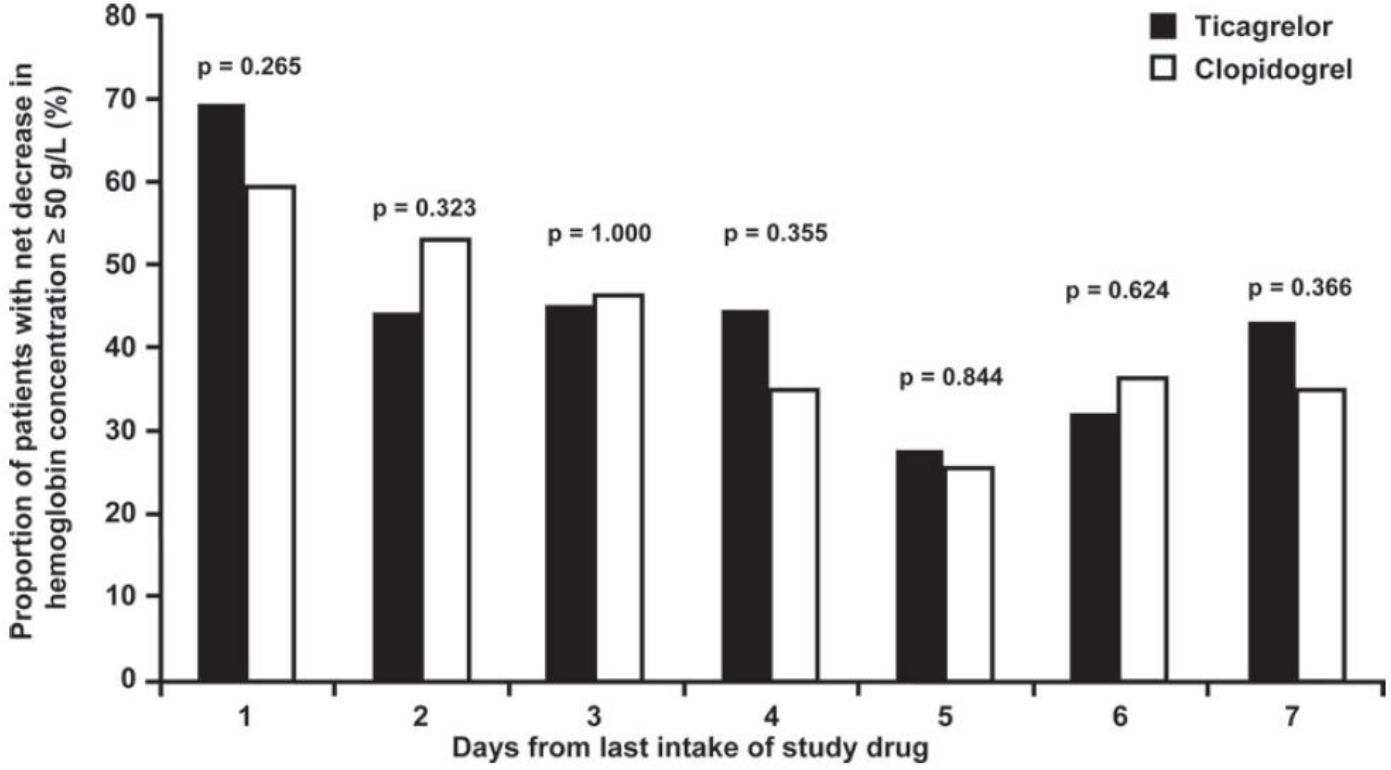
PLATO: chest tube drainage according to time after drug intake



Patients with > 500 mL (%)							
Ticagrelor	72	60	56	52	57	56	51
Clopidogrel	67	64	53	43	52	54	47

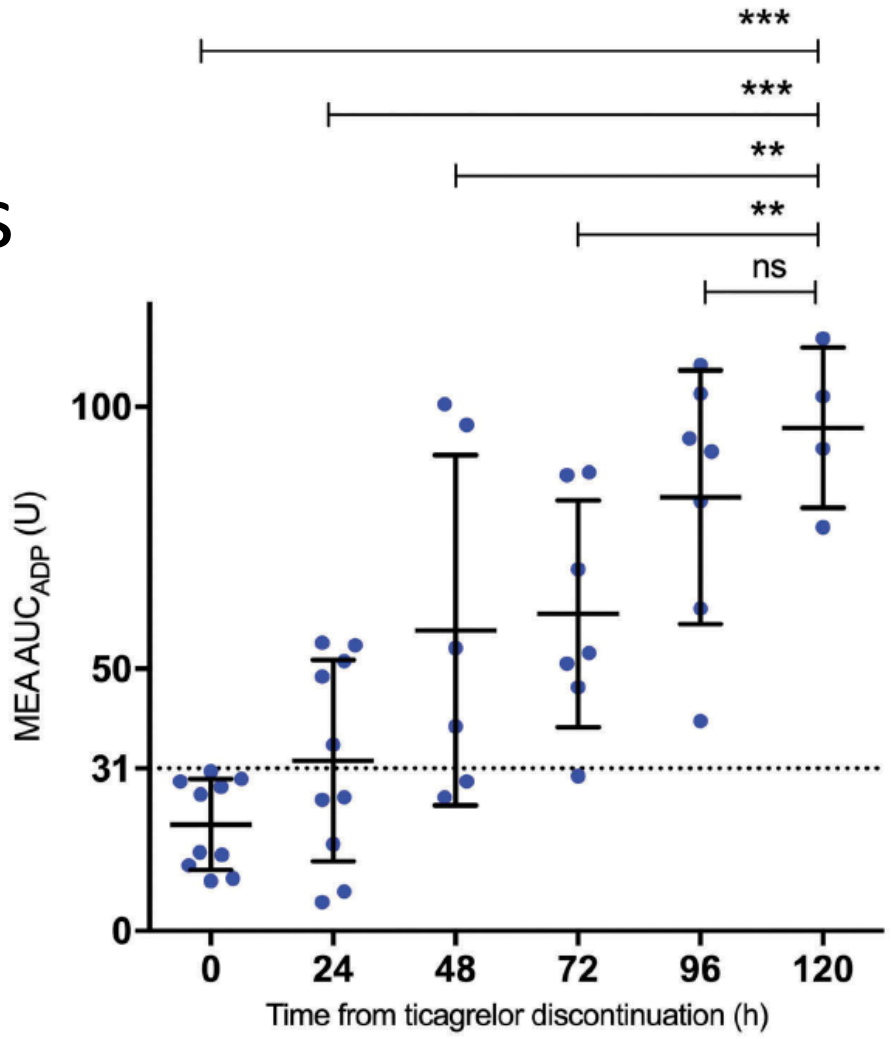
Held C et al. J Am Coll Cardiol 2011

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

European Heart Journal
doi:10.1093/eurheartj/ehu158

CURRENT OPINION

Expert position paper on the management of antiplatelet therapy in patients undergoing coronary artery bypass graft surgery

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

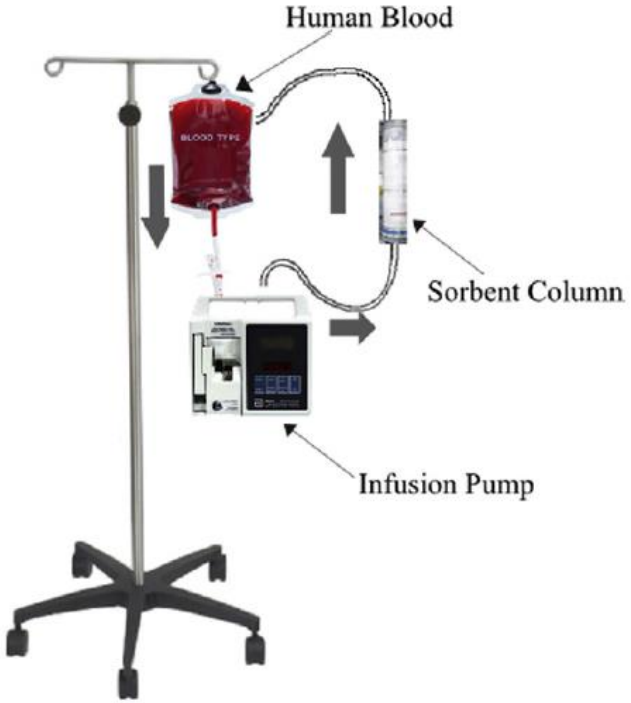
Table 3 Proposed strategies for discontinuation of $P2Y_{12}$ inhibitors prior to coronary artery bypass grafting surgery

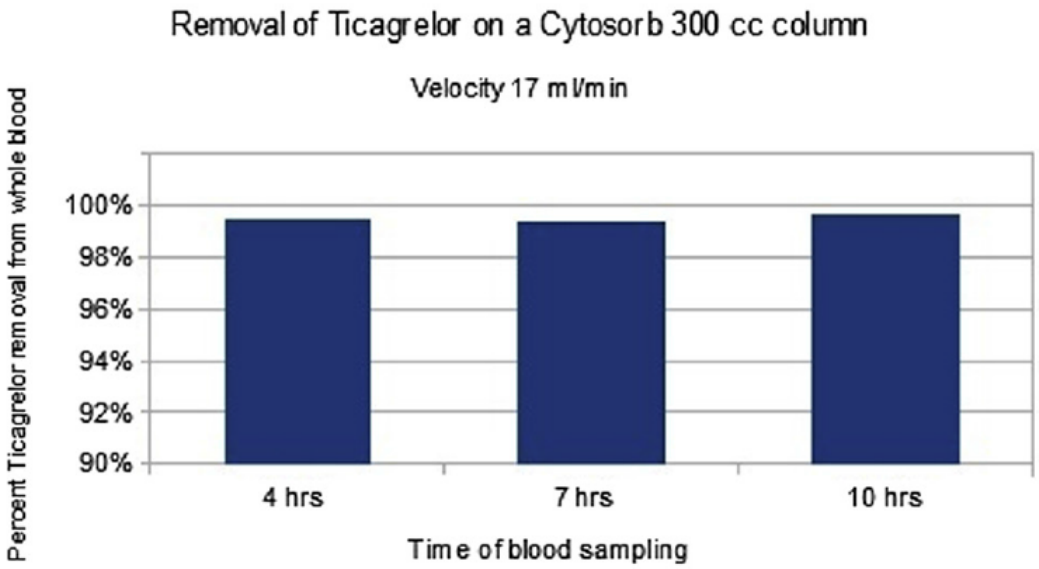
Thrombotic risk	Bleeding risk: High[a]	Bleeding risk: Low
High[b] ACS or recent stent PCI	Early Heart Team Consultation Ticagrelor/clopidogrel: stop 5 days before and bridge for 4 days. Prasugrel: stop 7 days and bridge for 5 days	Early Heart Team Consultation Ticagrelor/clopidogrel: stop 3 days before and bridge for 2 days. Prasugrel: stop 5 days before and bridge for 3 days
Low	Early Heart Team Consultation Clopidogrel/ticagrelor: stop 5 days before. Prasugrel: stop 7 days prior to CABG	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.

[a]Examples of high-bleeding risk: renal or hepatic insufficiency, advanced age, anaemia, small body surface area, cardiac failure, and redoes operation.
[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 atery 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]





Angheloiu GO et al. JACC Basic Trans Sci 2017

33rd EACTS Annual Meeting
Lisbon, Portugal, 3-5 October 2019

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. Javanbakht[1], K. Rahimi[2], F. Degener[3], D. Adam[3], F. Preissing[3], J. Scheier[4], SF. Cook[5],
E. Mortensen[6*]

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

Javanbakht M et al. Presented at EACTS 2019 meeting, Lisbon, Portugal, October 2019

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

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

Javanbakht M et al. Presented at EACTS 2019 meeting, Lisbon, Portugal, October 2019

Results: Urgent Cardiac Surgery (Cohort 2)

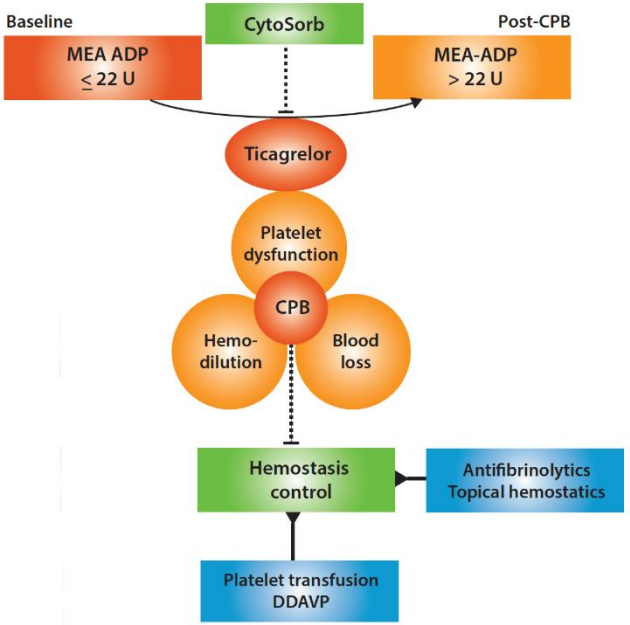
- In urgent CABG, CytoSorb was less costly (-£55) and more effective when compared to waiting for 5 days to allow for physiological washout of ticagrelor to reduce bleeding risk
- In all 3 comparators, waiting alone, waiting plus short acting antiplatelet agent, and waiting plus low molecular weight 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

Outcome per patient (Deterministic)	Without CytoSorb	With CytoSorb	Δ Incre-mental
Transfusions of red blood cells and platelets and (units) per patient	0.82	0.82	0
Hospital length of stay (days)	16	11	-5

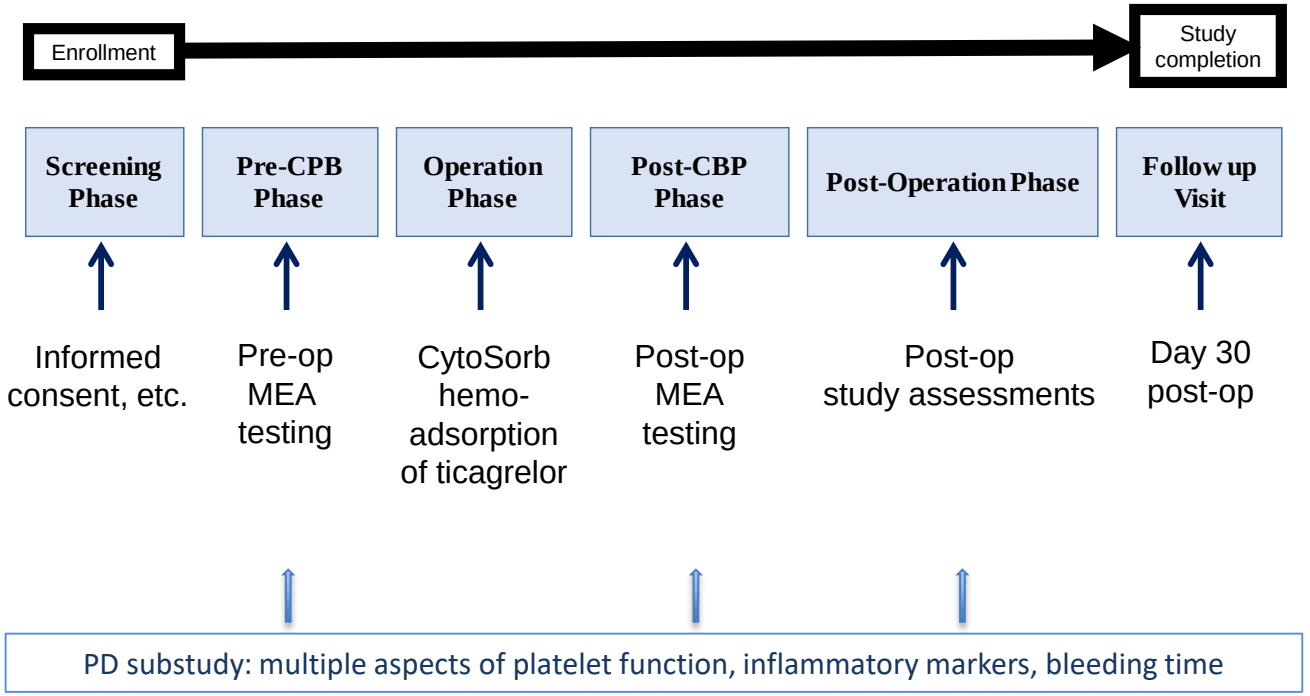
Javanbakht M et al. Presented at EACTS 2019 meeting, Lisbon, Portugal, October 2019

Ticagrelor CytoSorb Hemoadsorption (TISORB) study

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

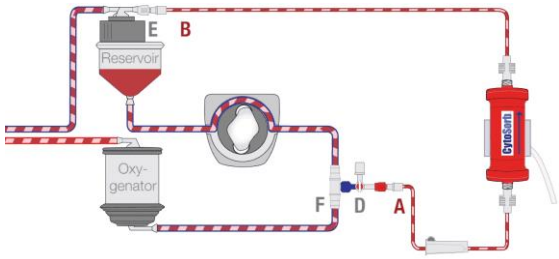


TISORB patient journey:
Surgery ≤ 48 hrs after last ticagrelor dose



TISORB primary effectiveness endpoint

intra-op ticagrelor removal from blood by CytoSorb



$[ticagrelor]_{Blood}$ pre-op

$[ticagrelor]_{Blood}$ post-op

Pharmacodynamic end point: ADP_{test} on MEA	compare	Pharmacodynamic end point: ADP_{test} on MEA

HYPOTHESIS:

< 22 U → > 22 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

SEMMELWEIS UNIVERSITÄT
MEDIZINISCHE FAKULTÄT
ASKLEPIOS CAMPUS HAMBURG

Intraoperative removal of Ticagrelor and Rivaroxaban during Emergency Cardiac Operations

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Head
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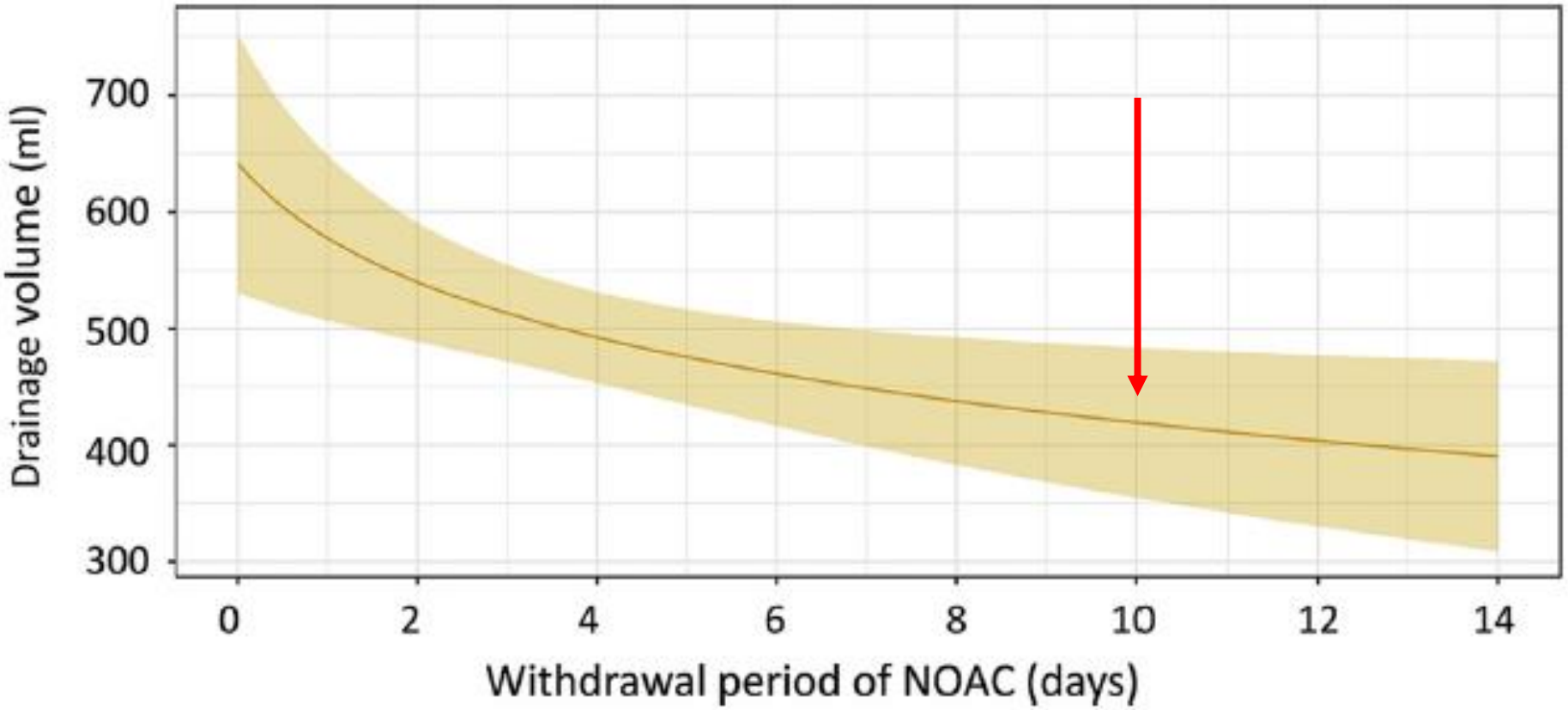
SEIT 1190

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%).

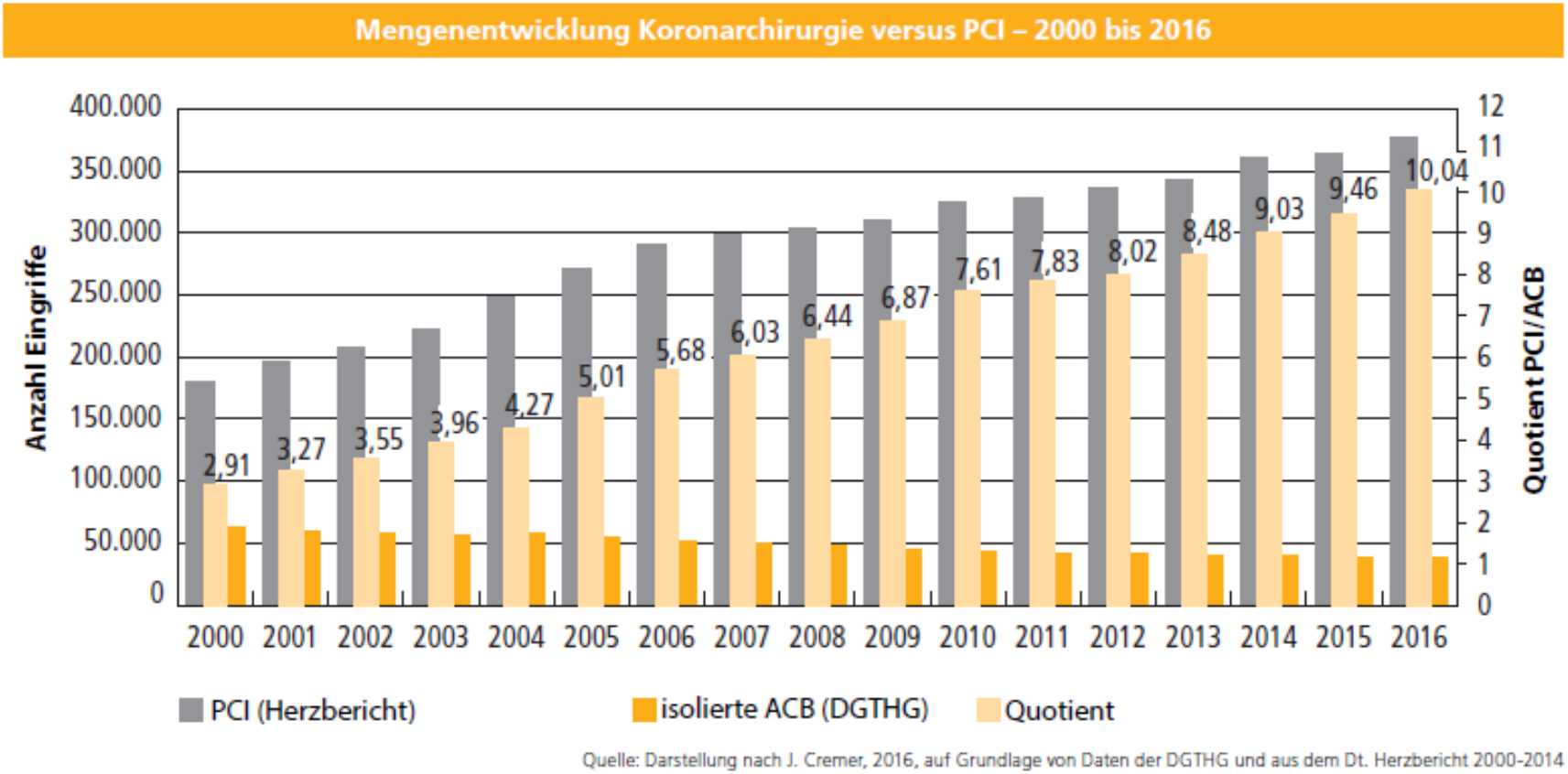
Results. Surgery was performed at a median 4 days (IQR: 3 to 6) after NOAC withdrawal. Reduced renal function was predictive for length of intensive care unit stay and administration of red blood cells ($p < 0.0001$ and $p = 0.0291$, respectively). The NOAC withdrawal interval significantly influenced postoperative drainage volume

0.0249). Intensive care unit stay was 2 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.

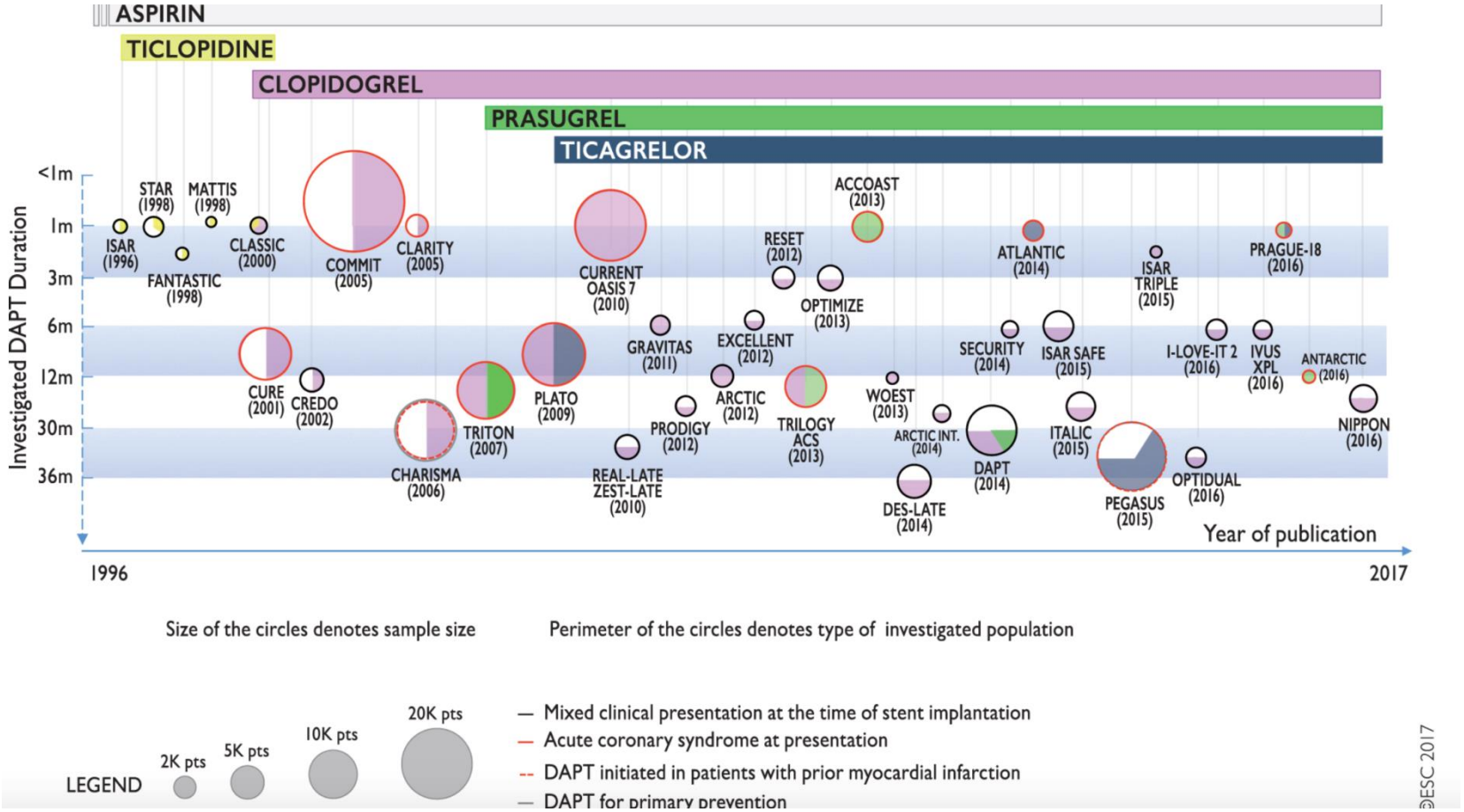
(Ann Thorac Surg 2018;105:702–8)

Evolution of PCI in Germany

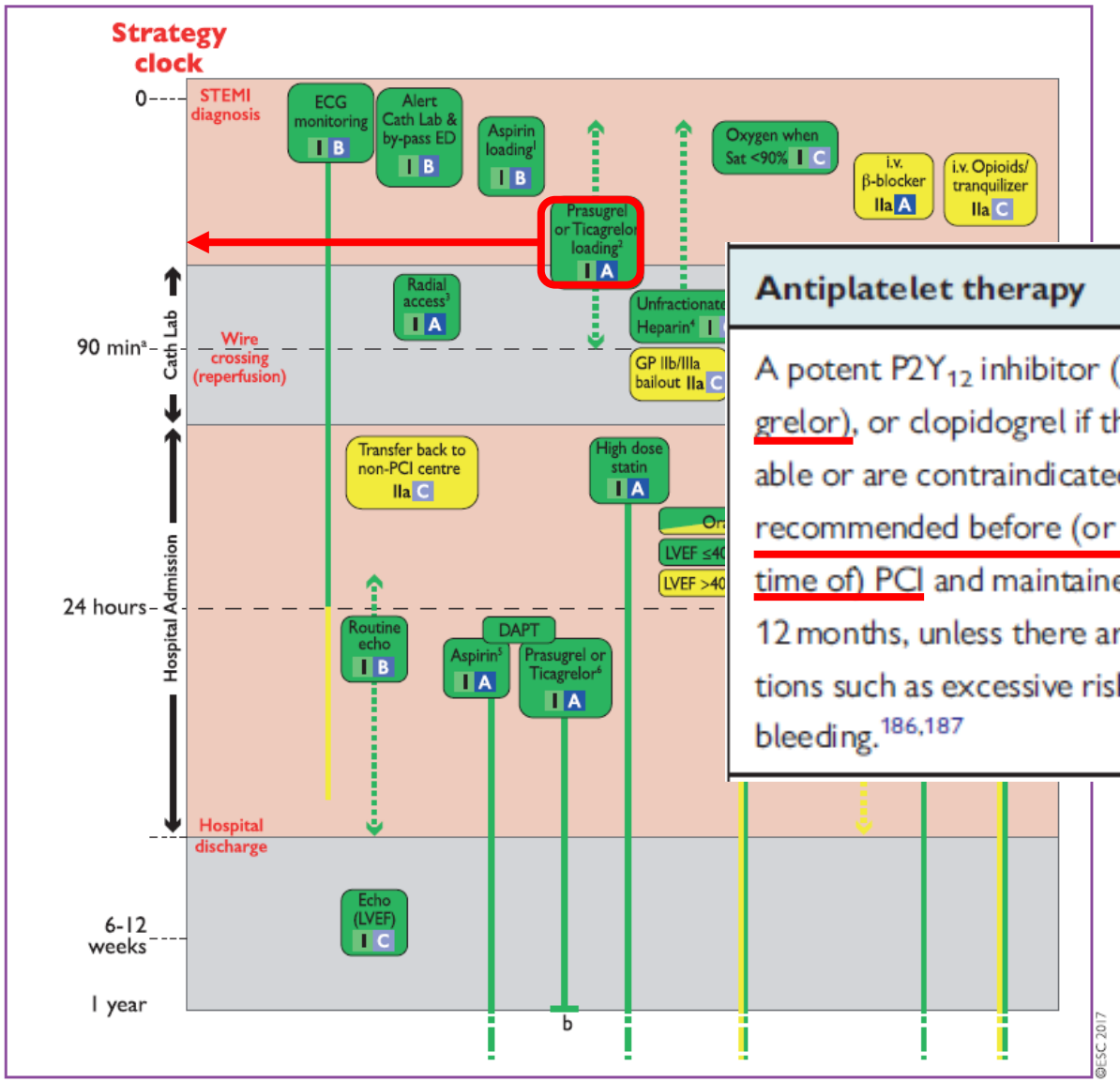


Quelle: Darstellung nach J. Cremer, 2016, auf Grundlage von Daten der DGTHG und aus dem Dt. Herzbericht 2000-2014

Evolution of antiplatelet therapy after PCI



2017 ESC Guidelines for STEMI patients



Antiplatelet therapy

A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.[186,187]

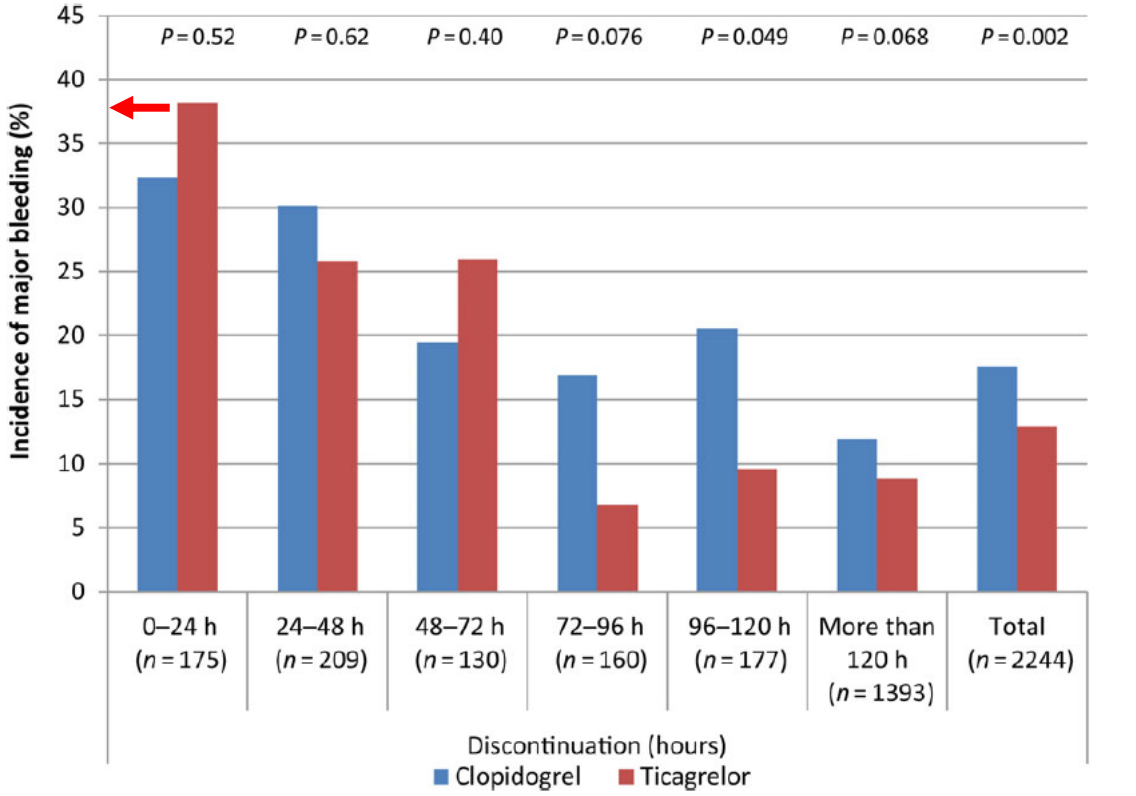
I	A

European Heart Journal (2016) **37**, 189–197
doi:10.1093/eurheartj/ehv381

Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study

Emma C. Hansson[1], Lena Jidéus[2], Bengt Åberg[3], Henrik Bjursten[4], Mats Dreifaldt[5], Anders Holmgren[6], Torbjörn Ivert[7], Shahab Nozohoor[4], Mikael Barbu[3], Rolf Svedjeholm[8], and Anders Jeppsson[1,9]*

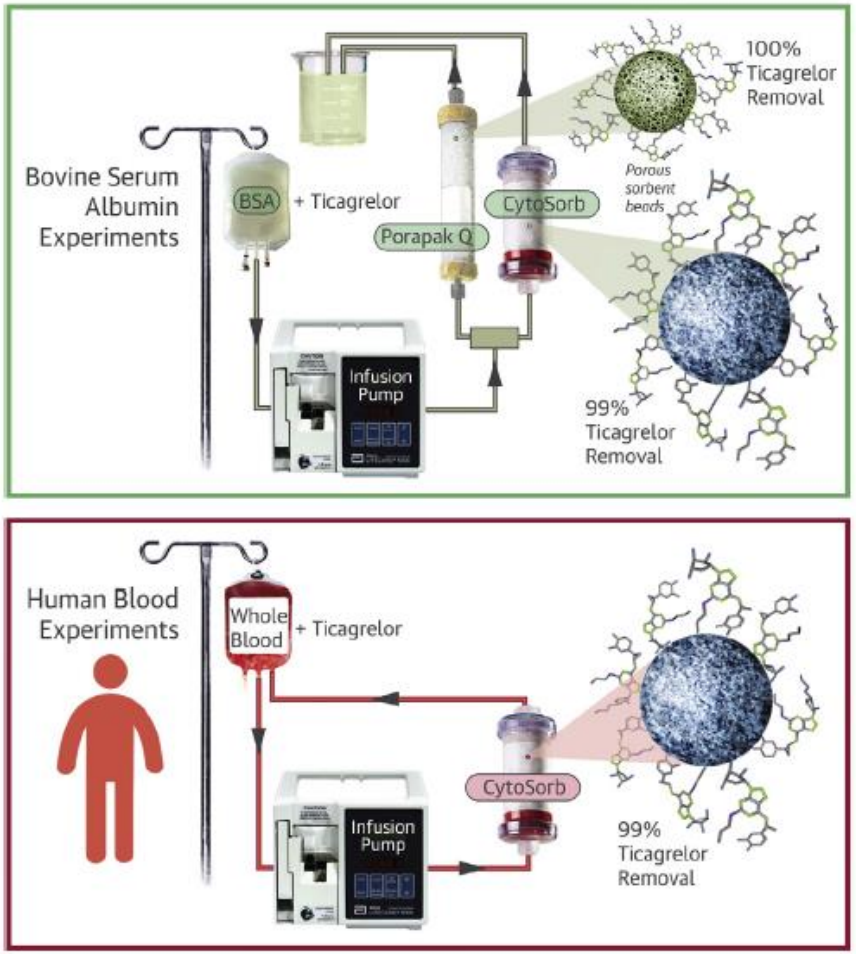
38% major bleeding !



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]

VISUAL ABSTRACT



Angheloiu, G.O. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(2):135-45.

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

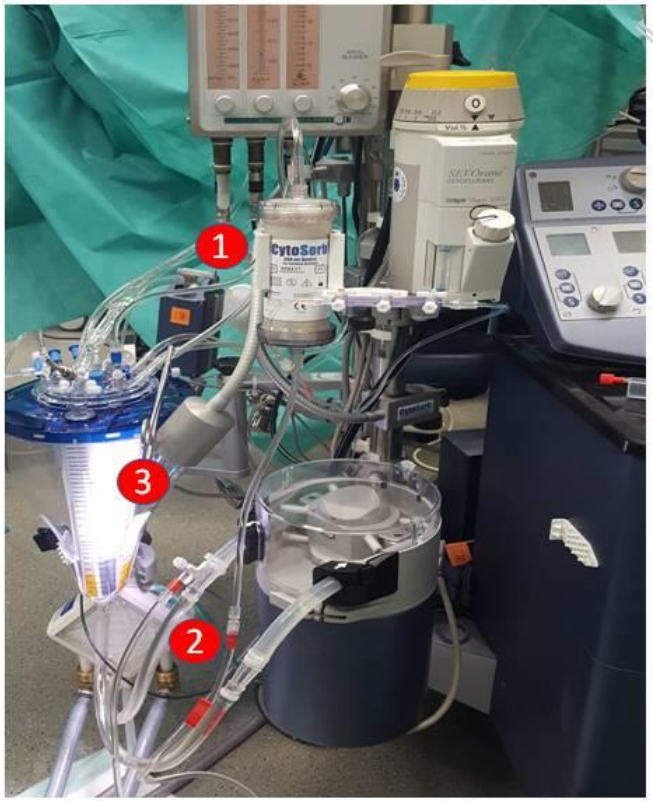
Hypothesis

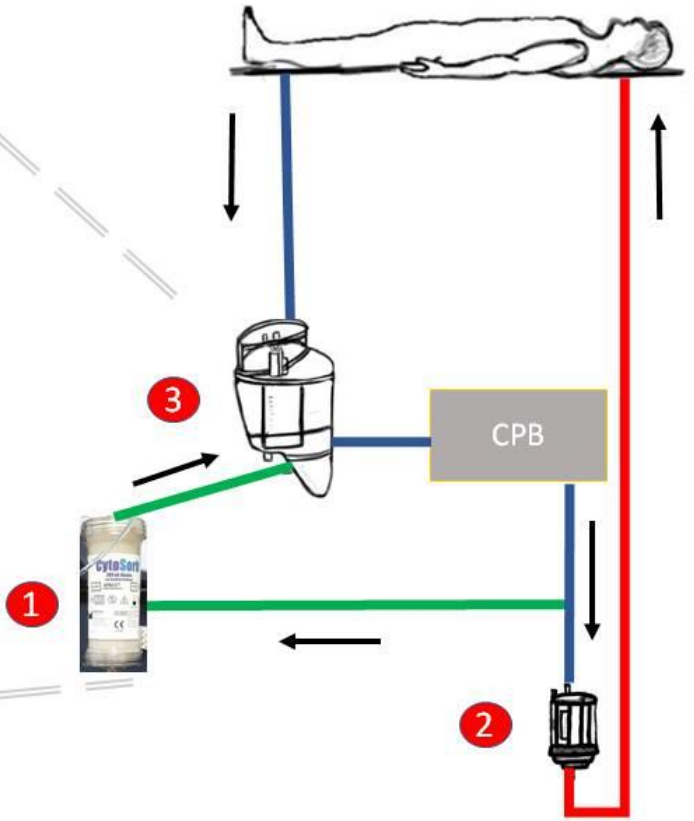
- **Platelet transfusion is not a definitive solution because of circulating Ticagrelor binding to transfused platelets.**
- **Using adsorber technology may reduce bleeding complications in patients treated with Ticagrelor.**
- **Similar effects may be expected in patients treated with NOACs**

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





Single center prospective cohort study

Emergency open-heart surgery
June 2016 – June 2018; n=217

n=55 (25.3%)

n=162 (74.7%)

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

Operations without previous Ticagrelor or Rivaroxaban therapy

since 04/2017

until 04/2017

Cytosorb adsorption of Ticagrelor (n=32)

Cytosorb adsorption of Rivaroxaban (n=7)

No Cytosorb adsorption of Ticagrelor (n=11)

No Cytosorb adsorption of Rivaroxaban (n=5)

Preoperative data I

Demography	Cytosorb Ticagrelor (n=32)	Cytosorb Rivaroxaban (n=7)	Control Ticagrelor (n=11)	Control Rivaroxaban (n=5)	p value
age (y)	66	77	69	72	.33
female (%)	19	57	18	20	.22
BMI (kg/m²)	27	26	27	27	.79
NYHA class (%)					
II	56	57	36	60	
III	38	43	64	40	
IV	6	0	0	0	
Comorbidities (%)					
hypertension	91	86	100	100	.99
periph. vasc. disease	28	29	18	40	.68
COLD	38	57	46	60	.92
Renal impairment					.95
normal	28	0	27	0	
moderate	41	71	55	80	
severe	31	29	18	20	

Preoperative data II

	Cytosorb Ticagrelor (n=32)	Cytosorb Rivaroxaban (n=7)	Control Ticagrelor (n=11)	Control Rivaroxaban (n=5)	p value
LVEF (%)					.73
good (>50%)	47	57	36	40	
moderate (31-50%)	47	14	64	40	
poor (<30%)	6	29	0	20	
Pathology (%)					
coronary artery dis.	100	100	100	100	
aortic valve disease	9	-	-	-	
mitral valve disease	3	-	9	-	
aortic dissection	3	-	-	-	
atrial fibrillation	13	100	18	100	
EuroSCORE II (%)	3.1	3.9	3.1	3.3	.56
Emergency (%)	100	100	100	100	

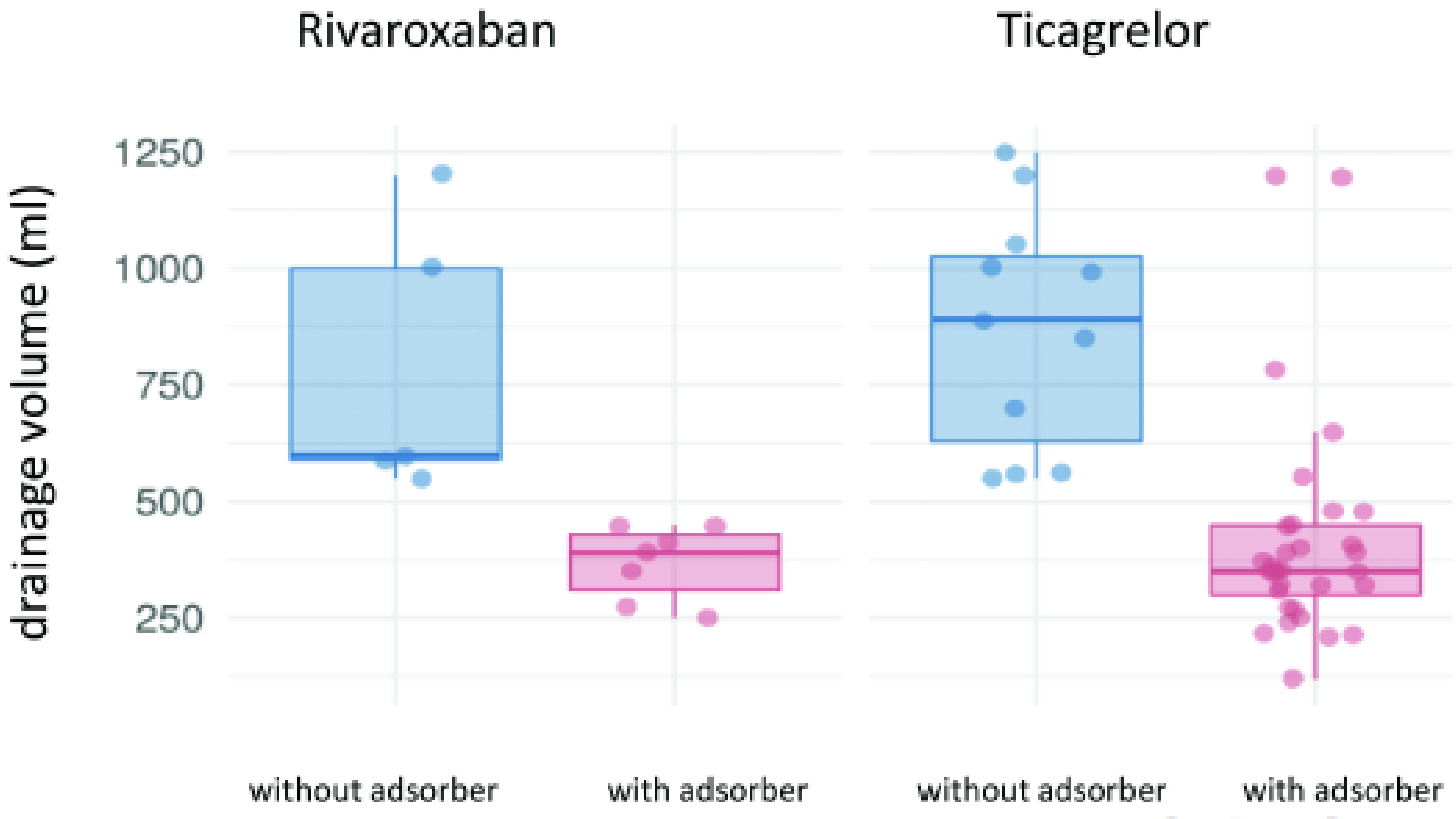
Results

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

Bleeding / Length of stay

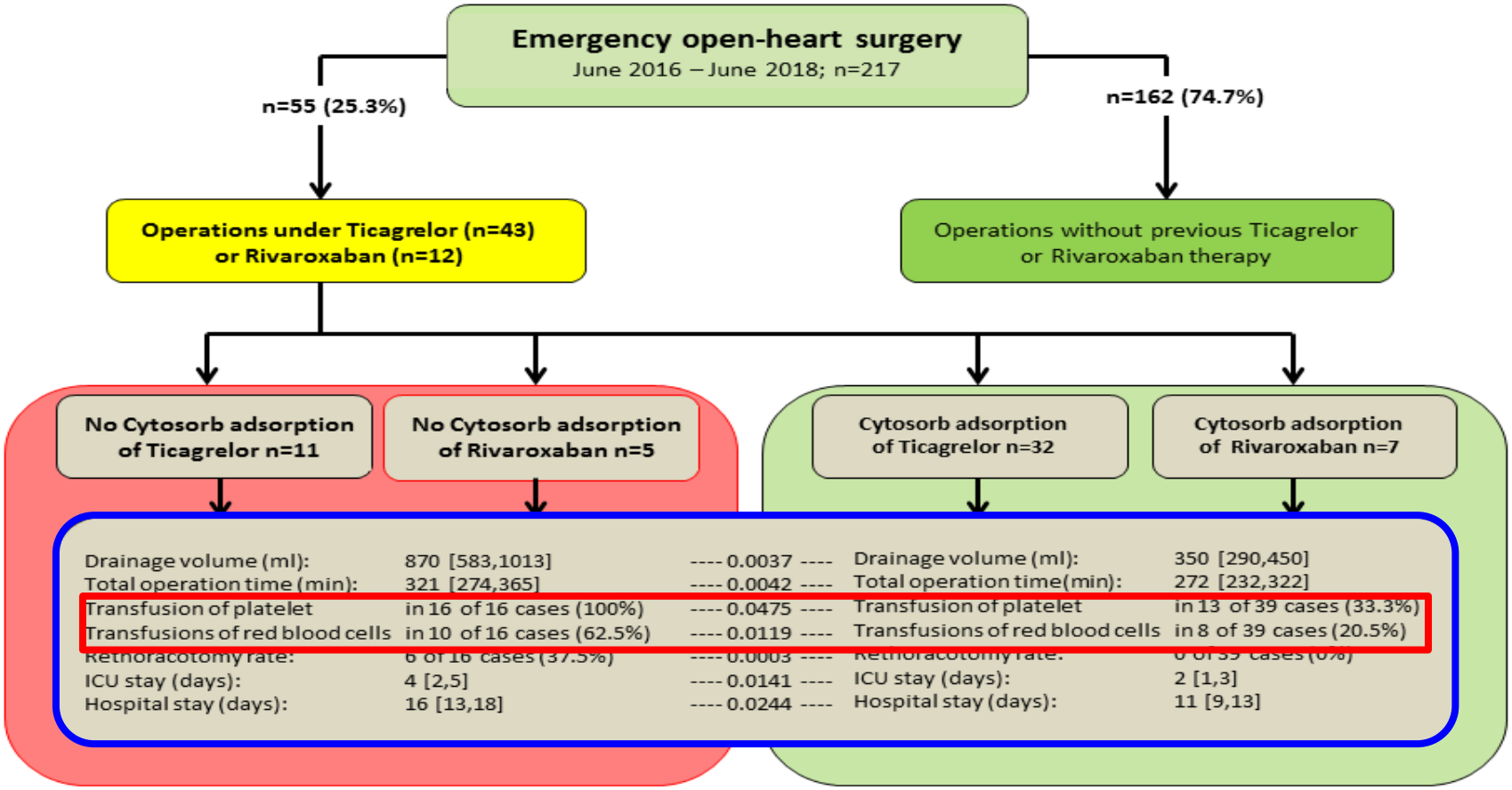
	Cytosorb Ticagrelor (n=32)	Cytosorb Rivaroxaban (n=7)	Control Ticagrelor (n=11)	Control Rivaroxaban (n=5)	p value
Rethoracotomy	0	0	36	40	.0003
Drainage volume (24hrs)	350	390	890	600	.004
Days in ICU	2	2	3	6	.01
Total length of stay (days)	11	11	14	18	.02

Postoperative drainage volume



p = 0.004

Summary



Conclusions: Cytosorb adsorbtion 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…

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

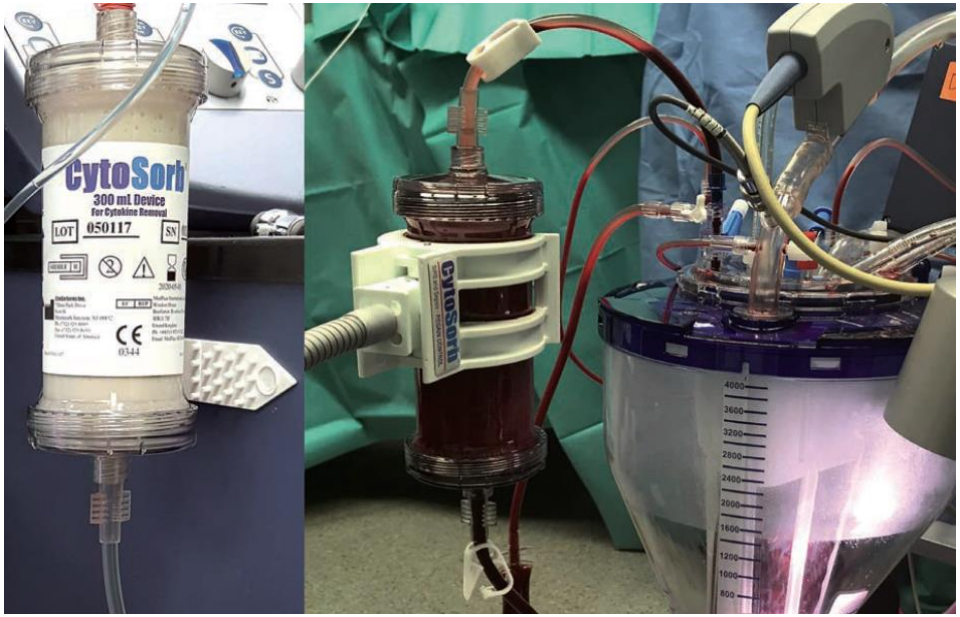
From 01/2020-05/2020 cytosorb adsorption in 18% of all pats.

Alternatives: Ticagrelor / NOAC antidots

PB2452 **(PhaseBio Pharma. Inc.)**	**for Ticagrelor** **monoclonal ab, phase I (2019)**
Idarucizumab (Praxbind)	**for Dabigatran**
5g (100ml)	**US$ 8,385.20**
Andexanet alfa (Ondexxya)	**for Apixaban, Rivaroxaban**
US$ 2,873.38/ 100 mg vial	**low dose: 400 mg bolus + 480 mg iv** **total US$ 25,850.90**
US$ 5,744.38/ 200 mg vial	**high dose: 800 mg bolus + 960 mg iv** **total US$ 48,828.42**

Clinical perspective

Standard procedure:



Cytosorb adsorption in all ticagrelor and/or

NOAC-loaded patients during emergency cardiac surgery

Thank you for your attention !

m.schmoeckel@asklepios.com

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

Baim Institute

Harvard Medical School

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.**

Disclosures

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SCAD Alliance
Baim Institute

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Equity: nference, Inc.

Consultant
Amarin
Angel Medical Corporation
AstraZeneca
Bayer
Boston Clinical Research Institute
Caladrius Biosciences
Cardiovascular Research Foundation
CeleCor Therapeutics
Eli Lilly
Eidos Therapeutics
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Pfizer
Somahlution
Thrombolytic Science
Verseon Corporation
WedMD

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

Spouse: Employee of Boston Clinical Research Institute in which she has equity position

Amarin
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Syneos Health
Thrombolytic Science
Verseon Corporation

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.

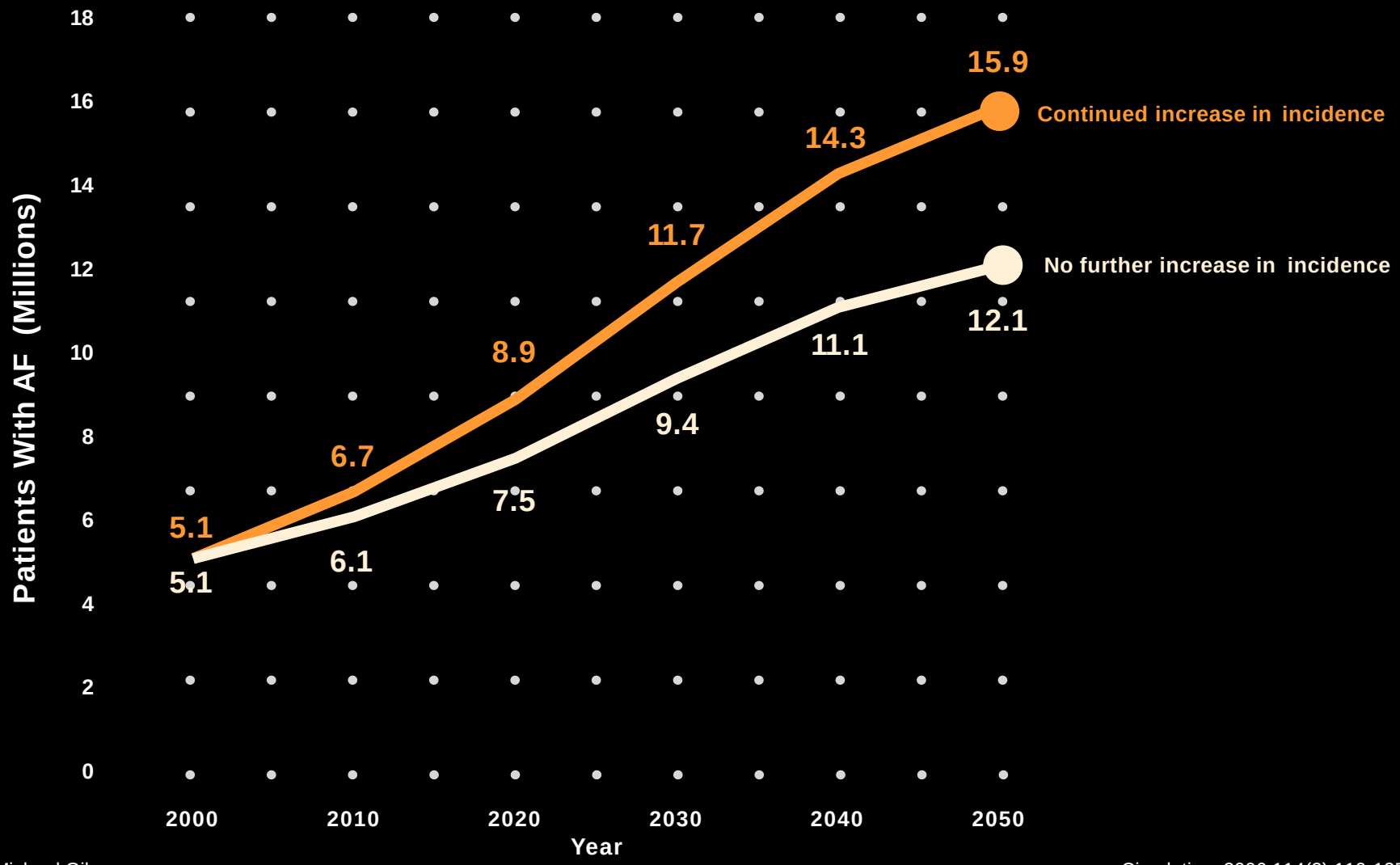
Slide by C. Michael Gibson, M.S., M.D.

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.**

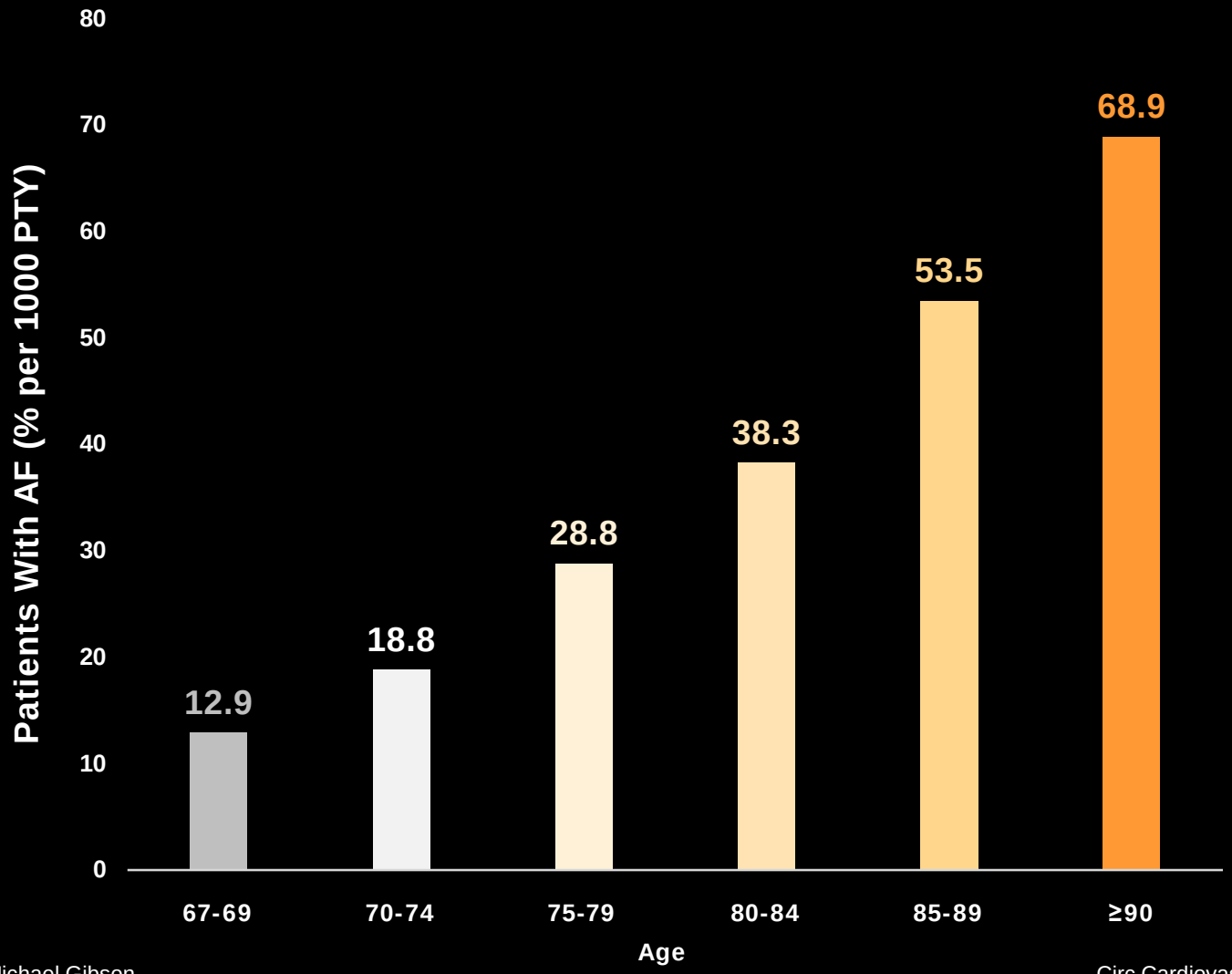


Slides by C. Michael Gibson

Circulation. 2006;114(2):119-125

Atrial Fibrillation Prevalence Increases with Age

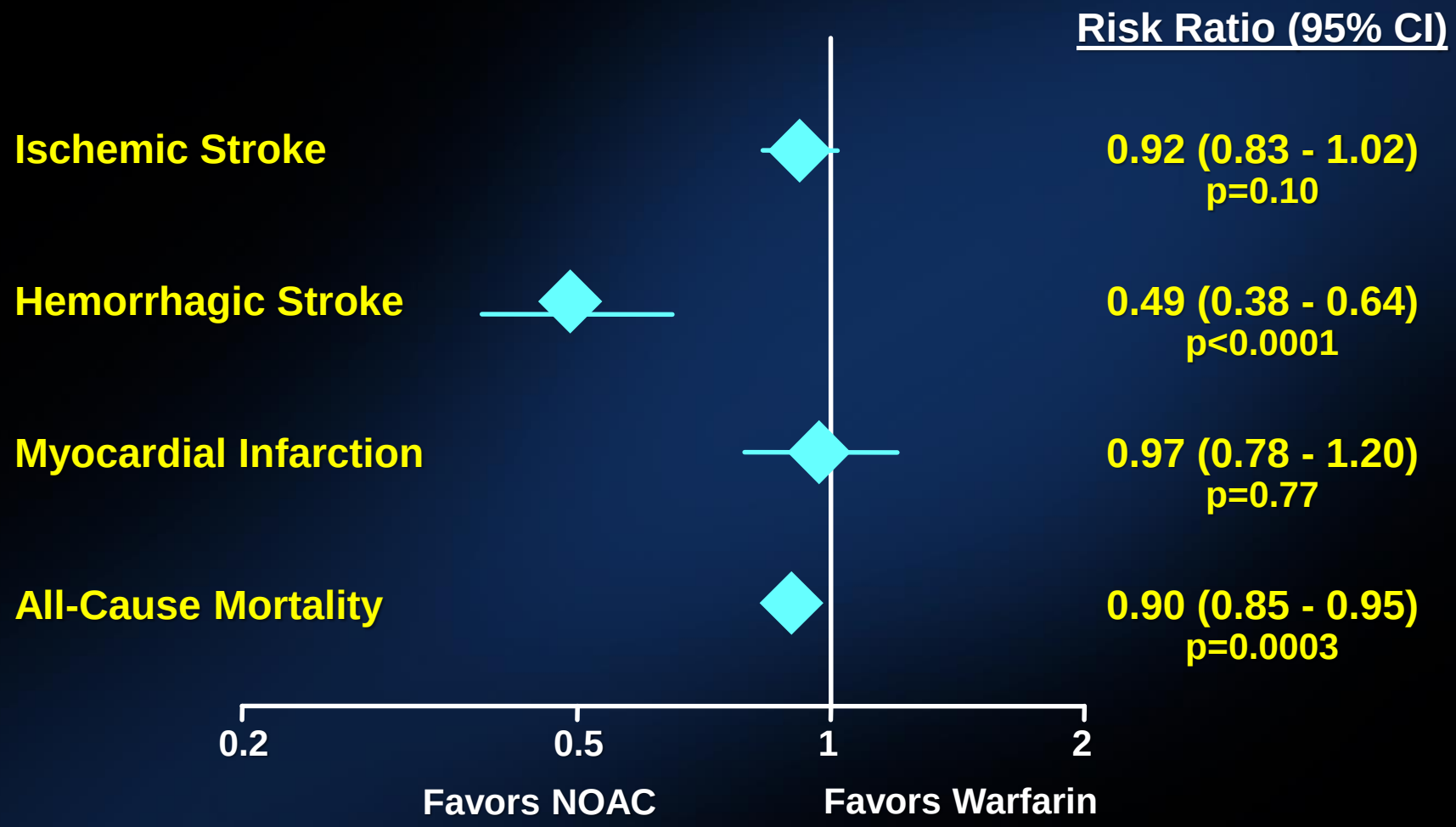
- **Atrial fibrillation prevalence increases with age.**



Slides by C. Michael Gibson

Circ Cardiovasc Qual Outcomes. 2012;5(1):85-93

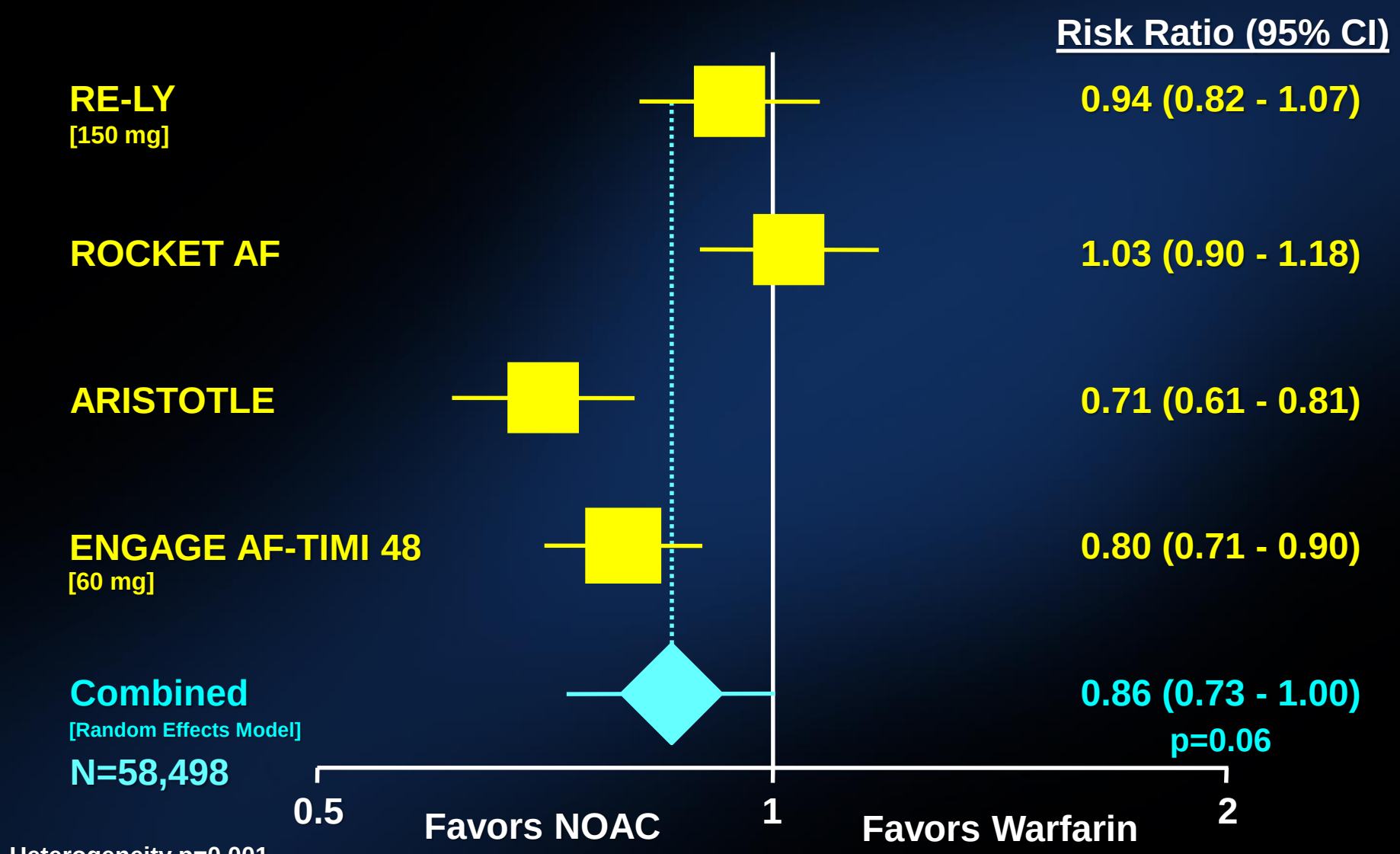
NOAC in Atrial Fibrillation



Heterogeneity p=NS for all outcomes

Ruff CT, et al. Lancet 2014;383:955-962

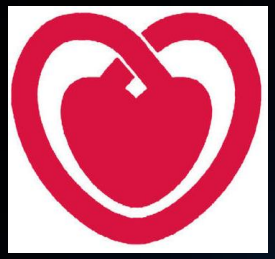
NOAC in Atrial Fibrillation
Major Bleeding

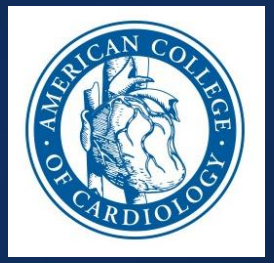


Heterogeneity p=0.001

Ruff CT, et al. Lancet 2014;383:955-962

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



1. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016 Feb;149(2):315-52.
2. Ansell J. Universal, class-specific and drug-specific reversal agents for the new oral anticoagulants. *J Thromb Thrombolysis*. 2016 Feb;41(2):248-52.

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

NEWS PROVIDED BY
Transparency Market Research →
May 03, 2019, 06:00 ET

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.

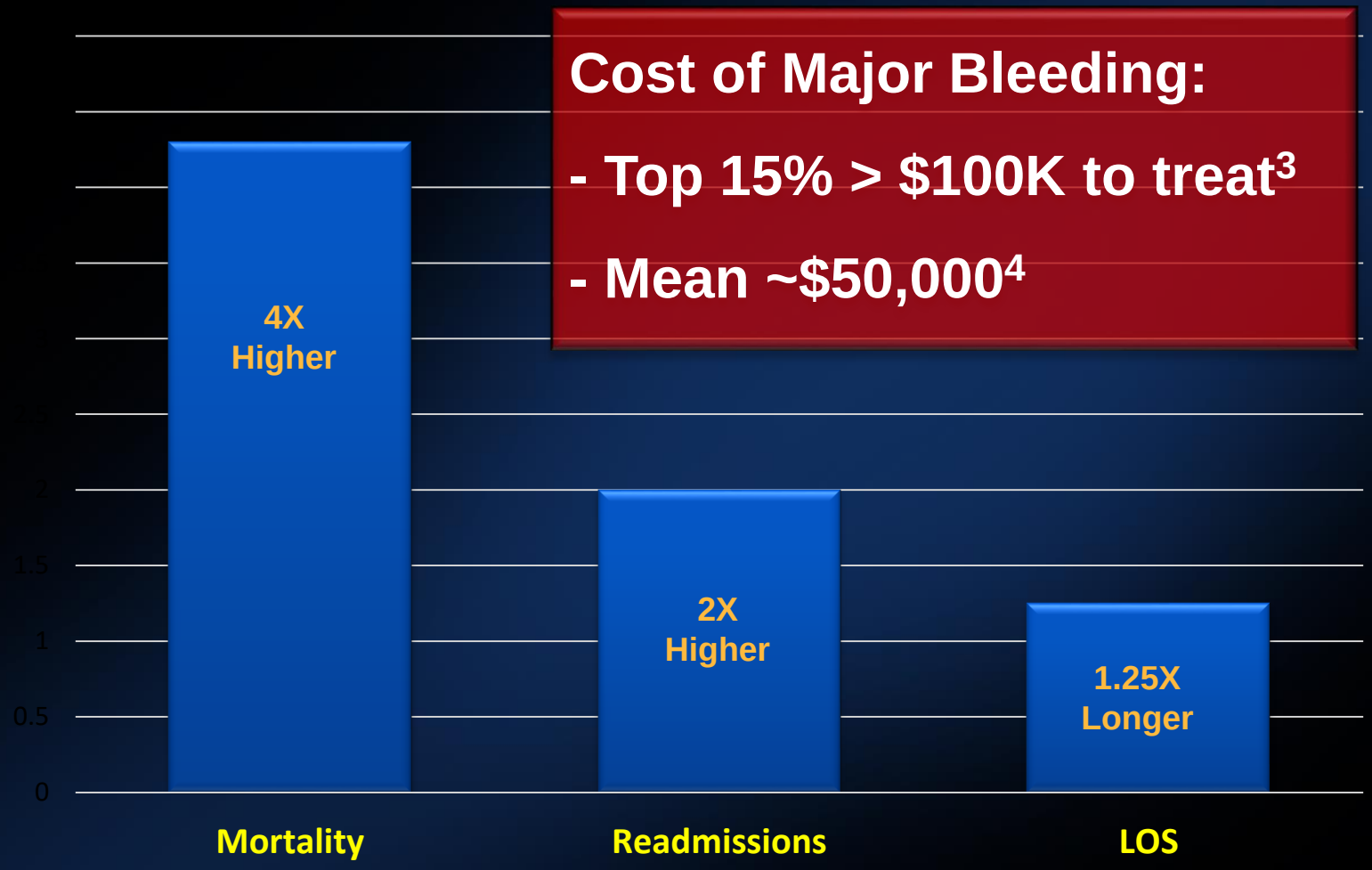
ED Visits for ADEs By Drug Class (2005-2014)

Drug Class	ED Visits National Estimate, % (95% CI)				
	2005-2006	2007-2008	2009-2010	2011-2012	2013-2014
Antibiotics	19.2 (17.7-20.7)	18.6 (16.8-20.4)	18.6 (16.7-20.6)	17.9 (16.6-19.3)	16.1 (14.4-17.8)
Anticoagulants	**7.3 (4.6-9.9)**	**9.9 (7.6-12.2)**	**11.2 (8.2-14.1)**	**13.3 (11.1-15.4)**	**17.6 (14.2-21.0)**
Antineoplastic agents	1.8 (0.8-2.8)	1.6 (0.8-2.4)	2.5 (1.2-3.9)	2.4 (1.3-3.4)	3.0 (1.6-4.3)
Antiplatelets	3.7 (2.1-5.2)	4.6 (2.7-6.5)	4.6 (2.9-6.2)	4.8 (3.2-6.4)	6.6 (4.7-8.5)
Antipsychotics	2.8 (2.2-3.4)	3.0 (2.5-3.5)	3.0 (2.6-3.4)	3.1 (2.5-3.7)	2.7 (2.1-3.2)
Diabetes agents	10.9 (7.3-14.5)	12.8 (9.1-16.6)	12.0 (9.1-14.9)	12.0 (9.1-14.8)	13.3 (10.8-15.8)
NSAIDs	4.1 (3.4-4.8)	3.5 (3.0-3.9)	3.2 (2.8-3.6)	3.2 (2.7-3.7)	2.8 (2.4-3.2)
Opioid analgesics	7.7 (6.9-8.6)	7.9 (7.1-8.8)	7.2 (6.6-7.8)	7.9 (7.2-8.5)	6.8 (6.3-7.4)
RAS inhibitors	2.4 (1.9-2.9)	2.5 (1.9-3.0)	2.9 (2.2-3.7)	3.2 (2.4-4.0)	3.5 (2.6-4.4)
Sedative/hypnotic agents	3.2 (2.7-3.7)	3.2 (2.8-3.6)	3.6 (3.1-4.2)	3.4 (2.8-3.9)	3.0 (2.4-3.5)

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

JAMA 316.20 (2016): 2115-2125

Increased Morbidity and Mortality in Patients Admitted on a NOAC As Compared to Non-Anticoagulated Patients



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%.
4. Amin et al. *J Manag Care Spec Pharm*. 2015;21(10):965-72

Management for Patients on NOAC Today

NOAC	Treatment for Life-Threatening Bleeding
Pradaxa® (dabigatran)	**Praxbind** (idarucizumab)
Xarelto® (rivaroxaban)	**Andexxa (andexanet alfa)**
Eliquis® (apixaban)	
Savaysa® (edoxaban)	

1. Praxbind® prescribing information. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. 2015.
2. Mo Y, Yam FK. Recent advances in the development of specific antidotes for target-specific oral anticoagulants. *Pharmacotherapy*. 2015;35:198-207.
3. Cytosorb. Instructions for use.
5. AndexXa™ prescribing information. South San Francisco, CA. Portola Pharmaceuticals, 2016.

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

NOAC	Prevention of Bleeding	Treatment for Life-Threatening Bleeding
Pradaxa® (dabigatran)	**CytoSorb®**	**Praxbind** (idarucizumab)
Xarelto® (rivaroxaban)		**Andexxa (andexanet alfa)**
Eliquis® (apixaban)		
Savaysa® (edoxaban)		

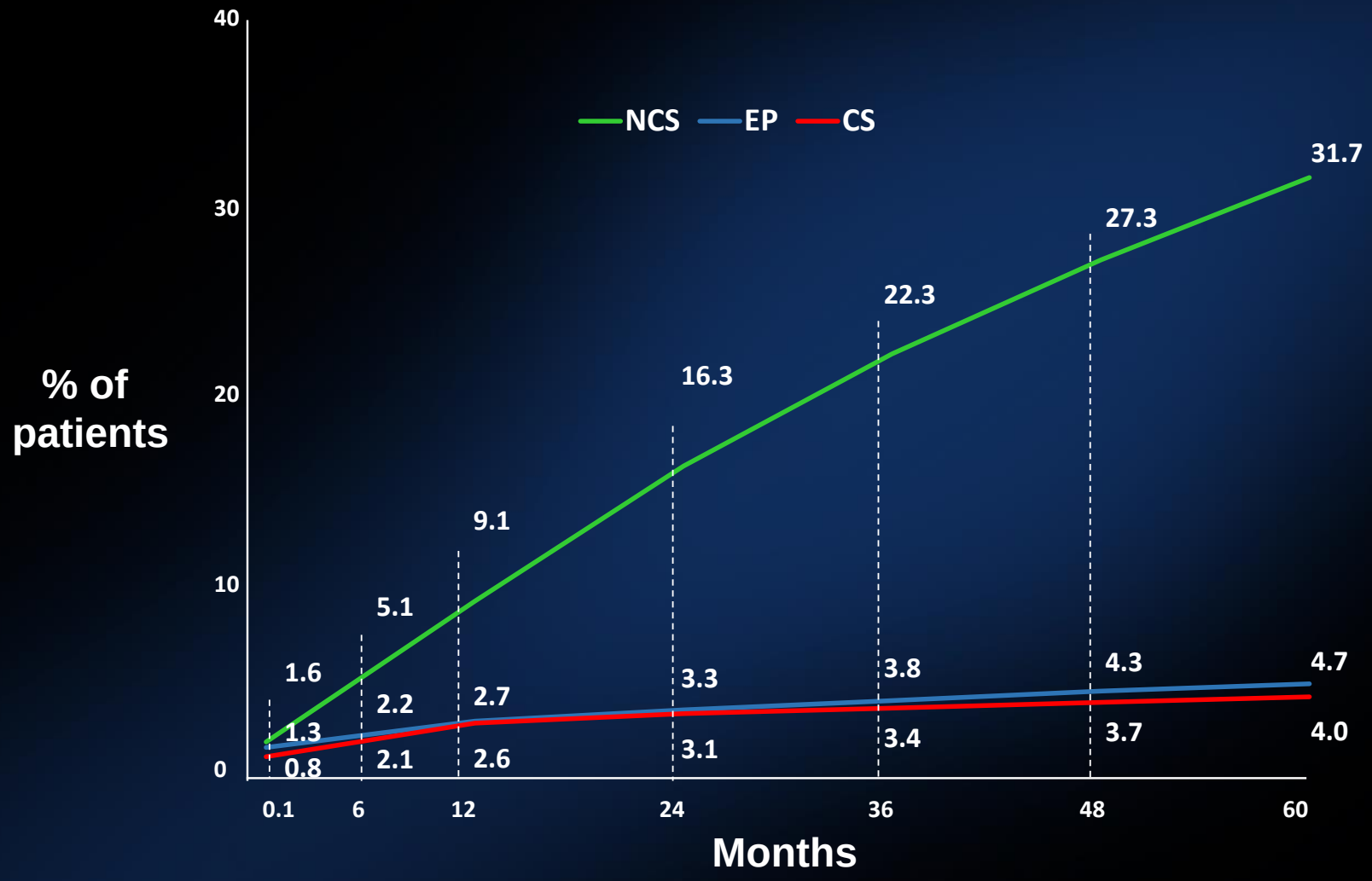
Preventing Bleeding in Cardiac Surgery

55 patients

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

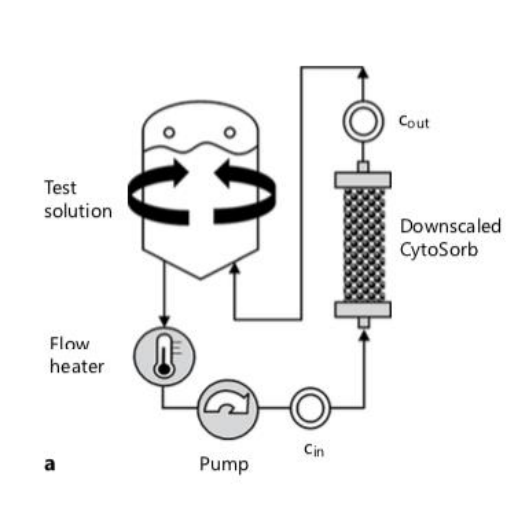
Hassan K et al. Ann Thorac Surg 2019;108:45-51

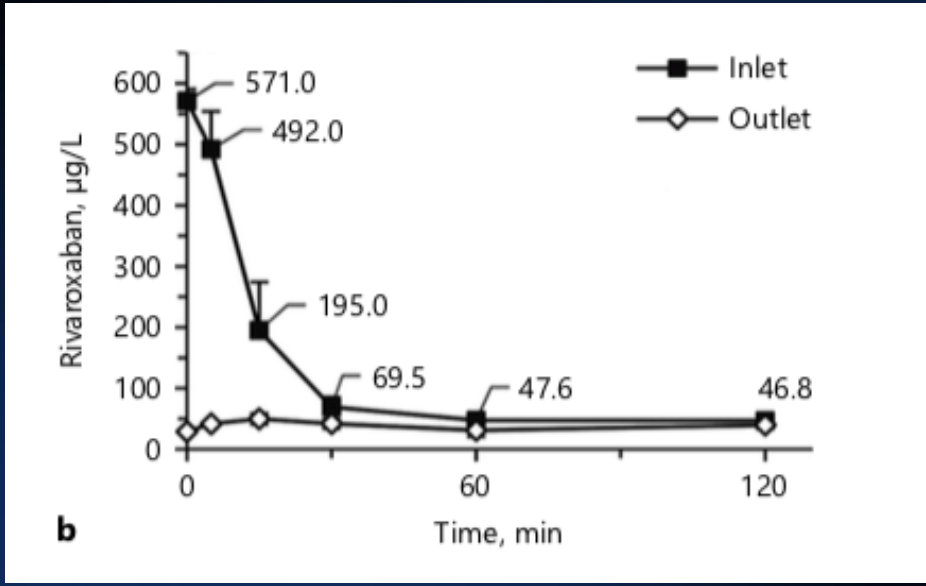
Cardiac Surgery vs. Non-Cardiac Surgery

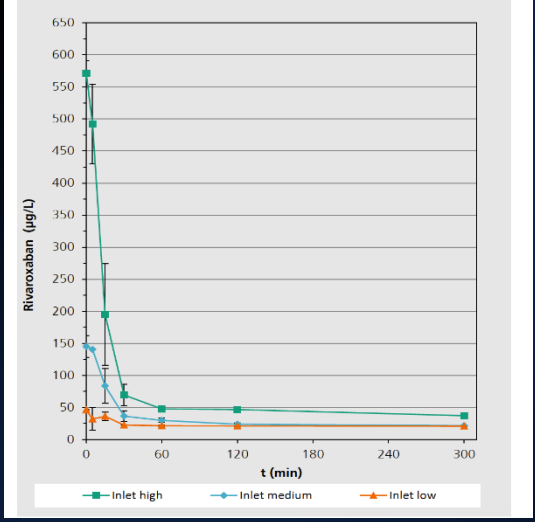


Saia F., et al. Surgery after Stent. Circulation CV Qual Outcomes 2016.

In-vitro Removal of Rivaroxaban by CytoSorb







"Within 1 hour 91.6% of circulating rivaroxaban was removed."

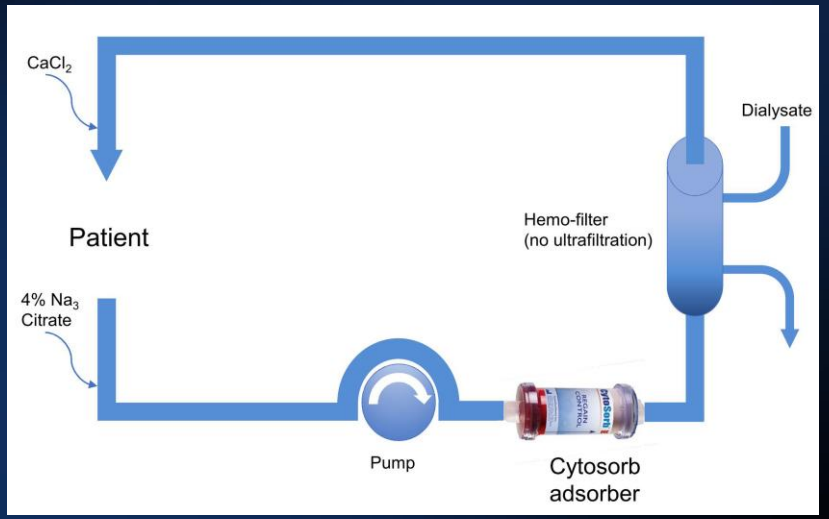
"For normal therapeutic concentrations below 300 µg/L, we expect plasma concentration to be reduced below the critical threshold in 30 to 60 minutes."

Koertge A et al. Extracorporeal Hemoperfusion as a Potential Therapeutic Option for Critical Accumulation of Rivaroxaban. Blood Purification 2017. Epub DOI: 10.1159/000484923

Ticagrelor + Rivaroxaban Removal off-pump

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



Dual antithrombotic removal (TIC + RIV) without CPB

Mair H et al. Ann Thor Surg 2020 doi.org/10.1016/j.athoracsur.2020.03.108

In-vitro Removal of Dabigatran by CytoSorb

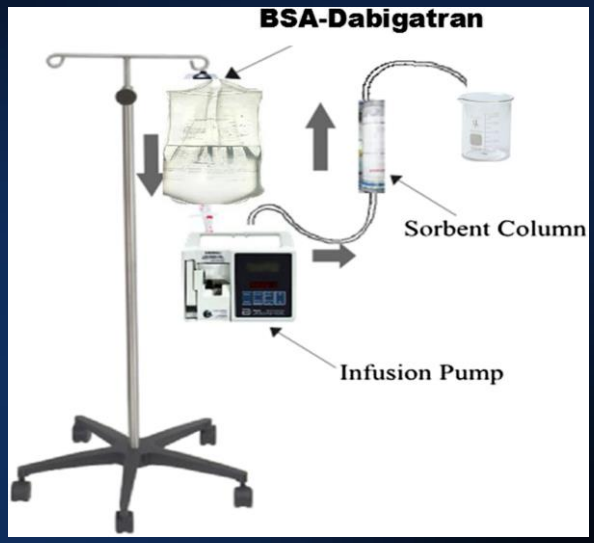
Contents lists available at ScienceDirect

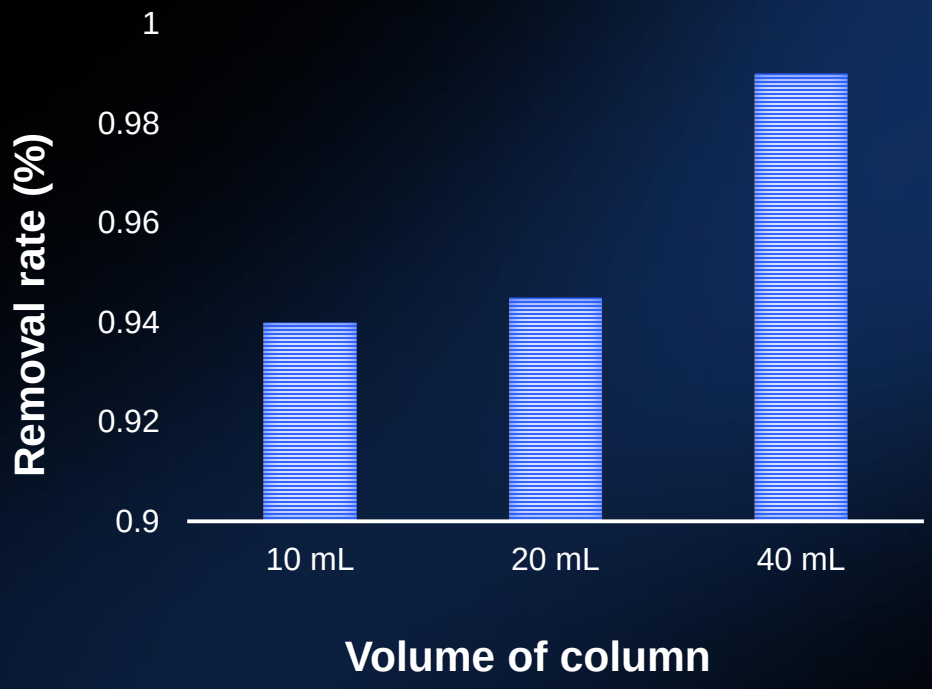
International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Removal of dabigatran using sorbent hemadsorption☆

Alexandra A. Angheloiu [a], George O. Angheloiu [b,c,*]





"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."

Angeloiu A. et. Int J Cardiol. 2019 Oct 15;293:73-75

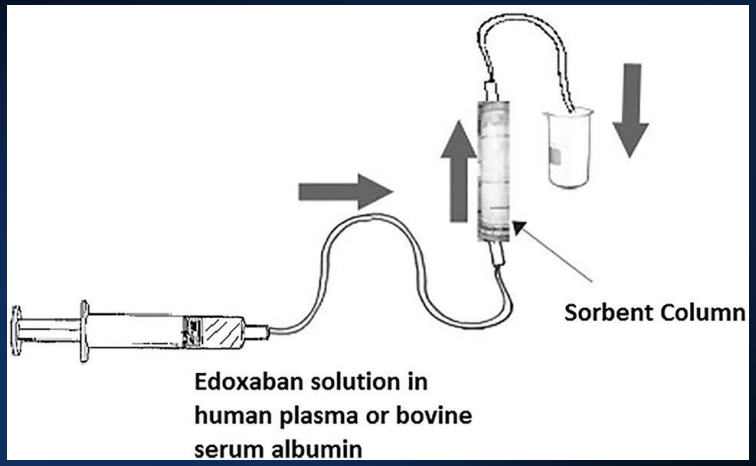
In-vitro Removal of Edoxaban by CytoSorb

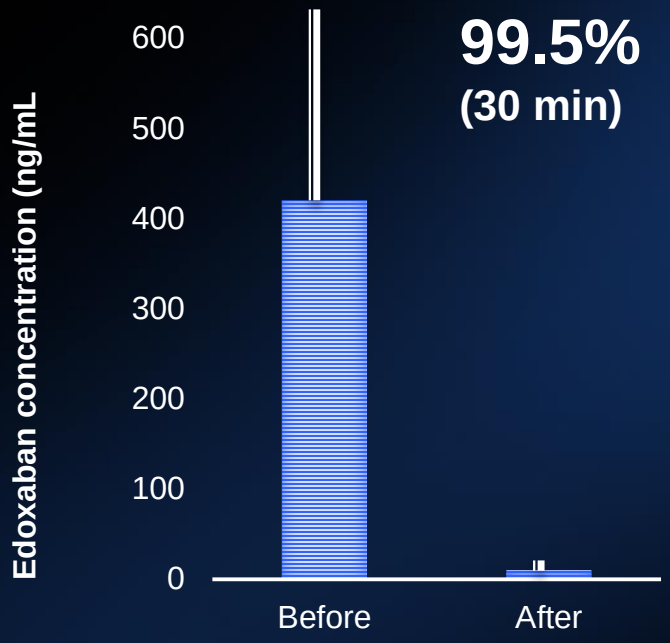
Drugs in R&D
https://doi.org/10.1007/s40268-020-00308-1

ORIGINAL RESEARCH ARTICLE

In-Vitro Sorbent-Mediated Removal of Edoxaban from Human Plasma and Albumin Solution

Alexandra A. Angheloiu[1] · Yanglan Tan[2,3] · Cristian Ruse[4] · Scott A. Shaffer[2,3] · George O. Angheloiu[5]





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

Angheloiu AA et al. Drugs in R&D 2020 May 15. doi: 10.1007/s40268-020-00308-1

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

Efthymios N. Deliargyris, MD, FACC, FESC, FSCAI
Chief Medical Officer
CytoSorbents Corporation

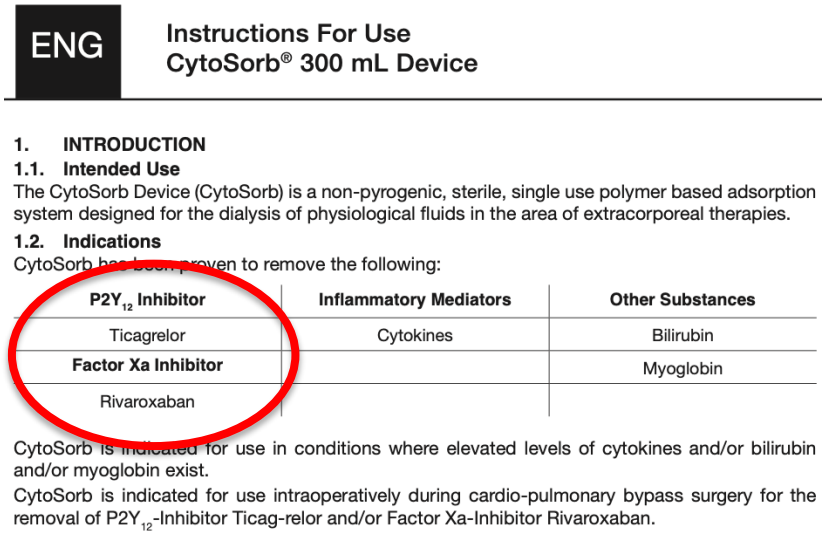
Regulatory Status & Clinical Activities

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



ENG

Instructions For Use
CytoSorb® 300 mL Device

1. INTRODUCTION

1.1. Intended Use

The CytoSorb Device (CytoSorb) is a non-pyrogenic, sterile, single use polymer based adsorption system designed for the dialysis of physiological fluids in the area of extracorporeal therapies.

1.2. Indications

CytoSorb has been proven to remove the following:

$P2Y_{12}$ Inhibitor	Inflammatory Mediators	Other Substances
Ticagrelor	Cytokines	Bilirubin
Factor Xa Inhibitor		Myoglobin
Rivaroxaban		

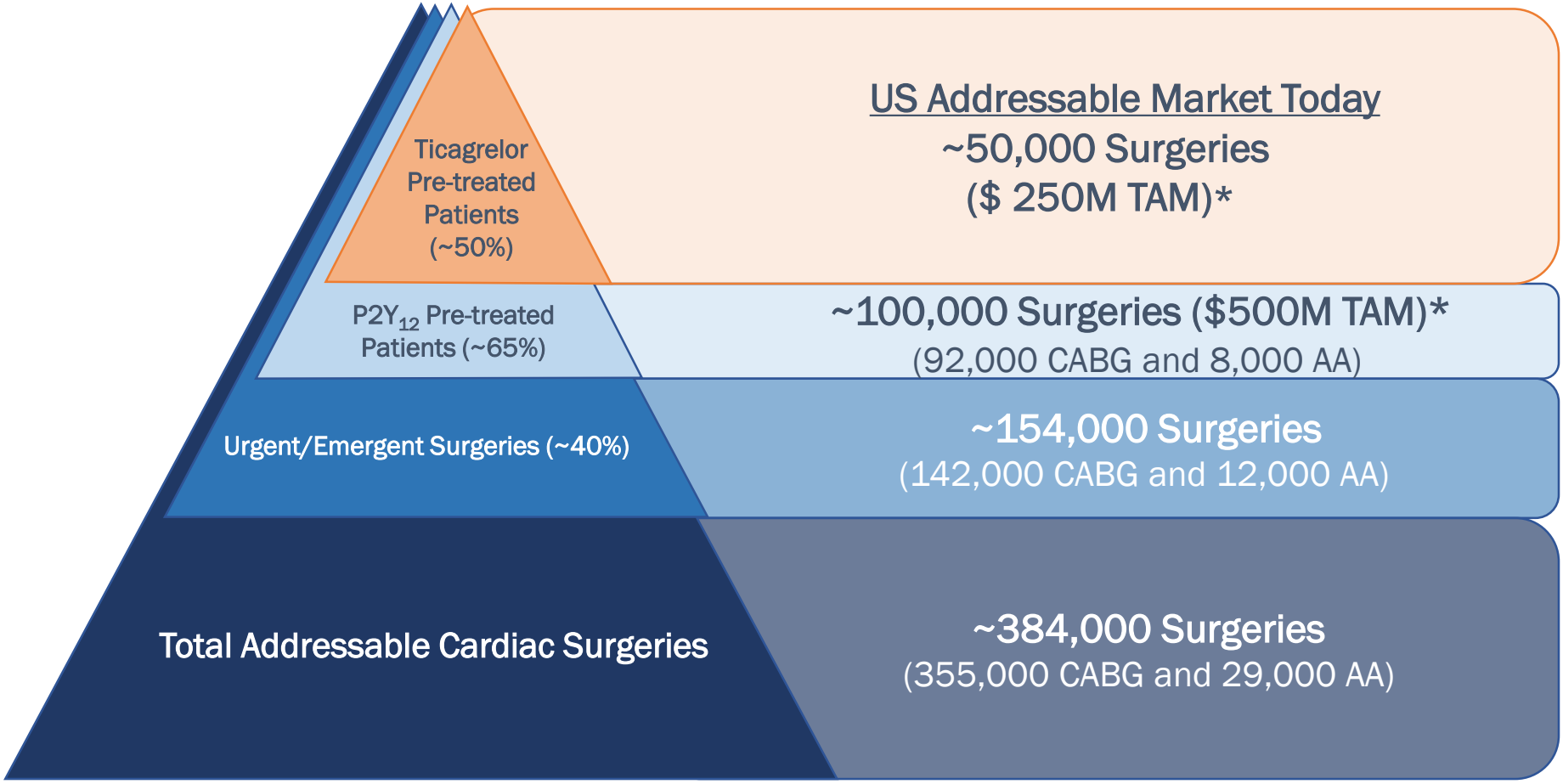
CytoSorb is indicated for use in conditions where elevated levels of cytokines and/or bilirubin and/or myoglobin exist.

CytoSorb is indicated for use intraoperatively during cardio-pulmonary bypass surgery for the removal of $P2Y_{12}$-Inhibitor Ticag-relor and/or Factor Xa-Inhibitor Rivaroxaban.

Study	Design	Region	Start
TISORB Ticagrelor CytoSORB Hemoadsorption	Prospective, open label trial	United Kingdom	Q3 '20 Continued
CYTATION The CYtoSorb® Ticagrelor HemoAdsorpTION 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

Total Addressable Market For Ticagrelor Removal

United States

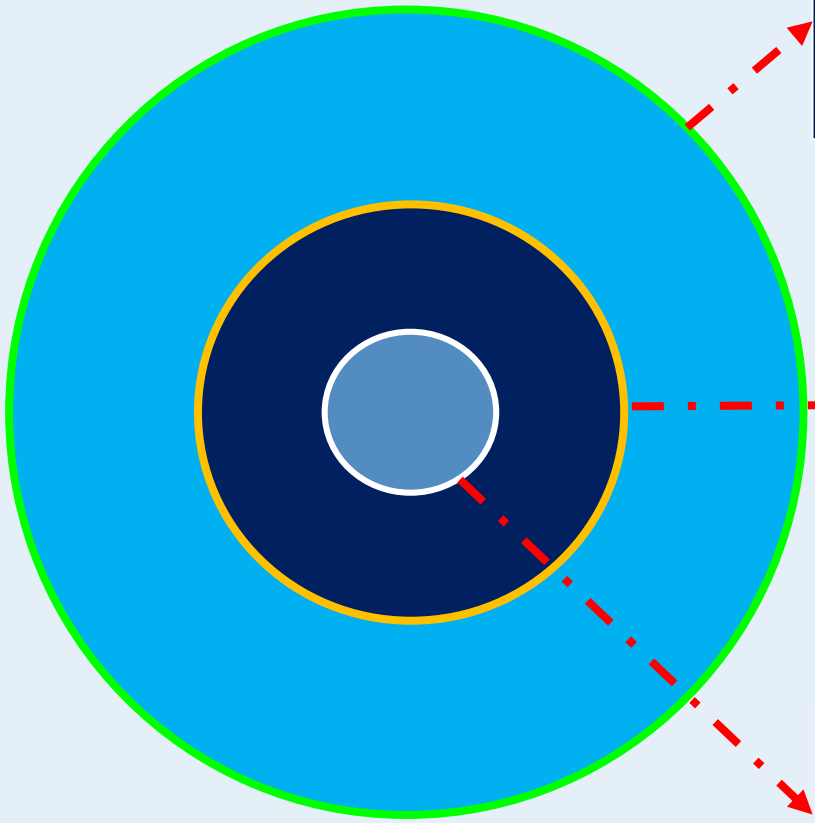


- **CABG:** Coronary Artery Bypass Graft surgery
- **AA:** Aortic Aneurysm Repair

* CytoSorb price = $5,000

CytoSorbents™

US Market – Sequential Growth



TICAGRELOR + NOAC
All surgery
$1.5B

TICAGRELOR + NOAC
Cardiac surgery
$500M

TICAGRELOR
Cardiac surgery
(Today)
$250M

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

CytoSorbents™