

“The future in antiplatelet treatment”

Prof. Jean-Christophe Gris, M.D., Ph.D.,

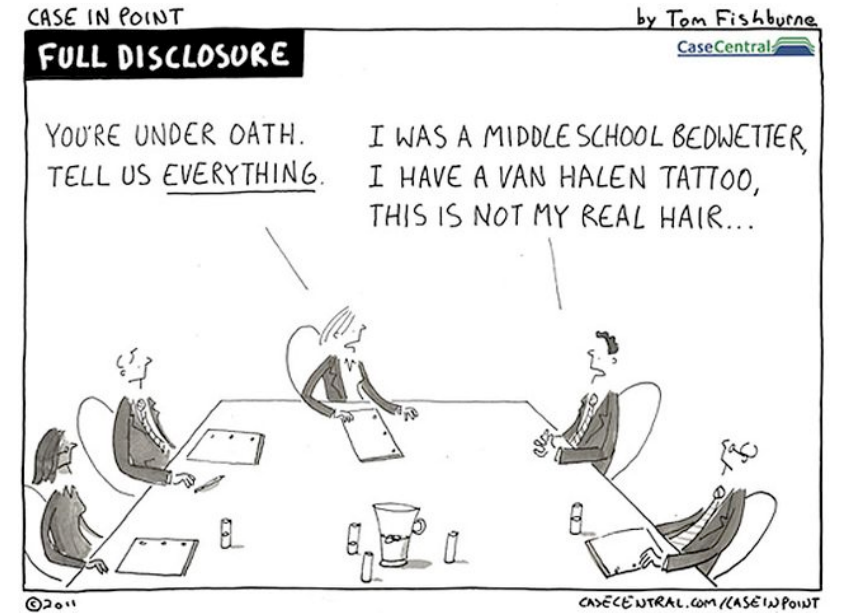
Department of Haematology, University Hospital, Nîmes and University of Montpellier, France;



Meet the Haemostasis Experts VII, Athens, September 2023

Disclosures

- Grants:
 - Bayer Healthcare SAS, Sanofi SA, Stago
- Scientific Advisory Boards:
 - Sanofi SA, LFB, Novo Nordisk, Coagulant Therapeutics
- Speaker / speaker bureau member, supports:
 - Alexion Pharma France, Amgen, Astra-Zeneca, Bayer, Bristol-Myers-Squibb, Boehringer-Ingelheim, Daichi-Sankyo, Fumouze diagnostics-Sofibel, Glaxo-Smith-Kline, Horiba ABX SAS, Laboratoire Français des Biotechnologies (LFB), Léo Pharma, Novo Nordisk, Oséus, Pfizer, Sanofi SA, Shire, Stago





Πυθία



Consultation of the Delphic oracle.
Red-figured ceramic kylix, circa 440-430 BC,
by the painter Kodros (Altes Museum Berlin, F2538, 141668).



John Collier, Priestess of Delphi, 1891,
National Museum of South Australia (Adelaide)

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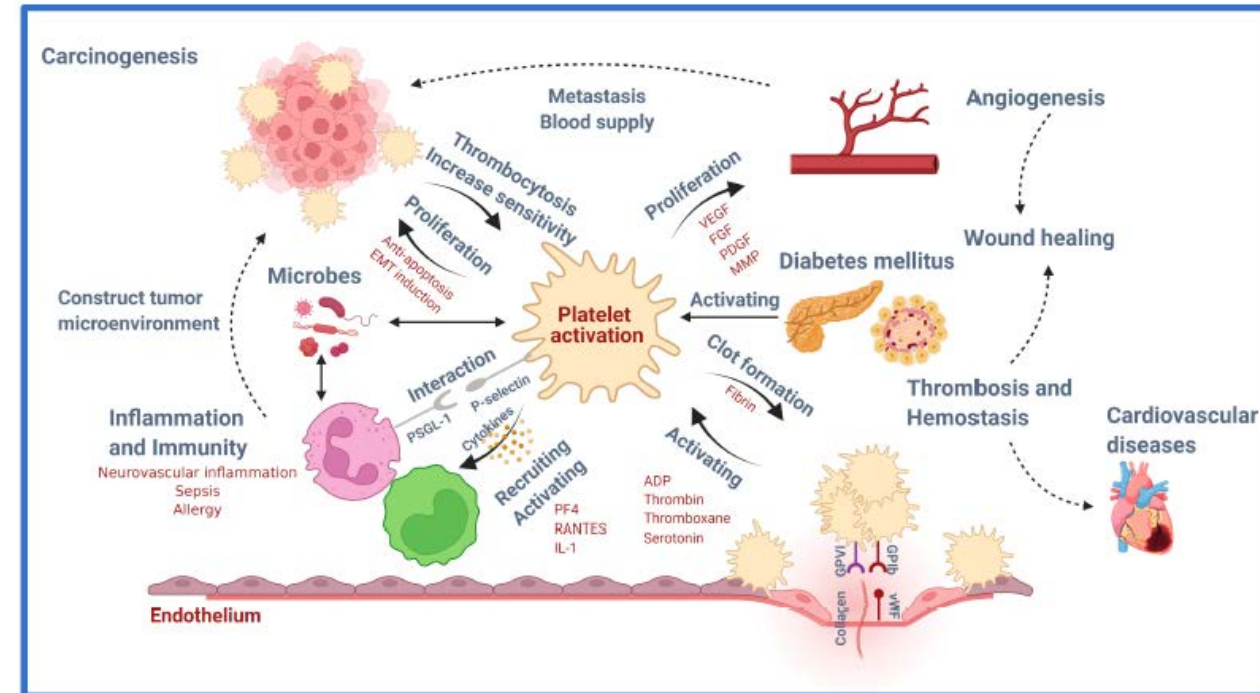
Antiplatelet treatments

- For non-thrombotic diseases?
- Thrombosis: for non-atherothrombotic diseases?
- Atherothrombotic diseases:
 - Bleeding risk; safer new drugs?
 - From population to patient-centered approaches?

Antiplatelet treatment outside thrombosis

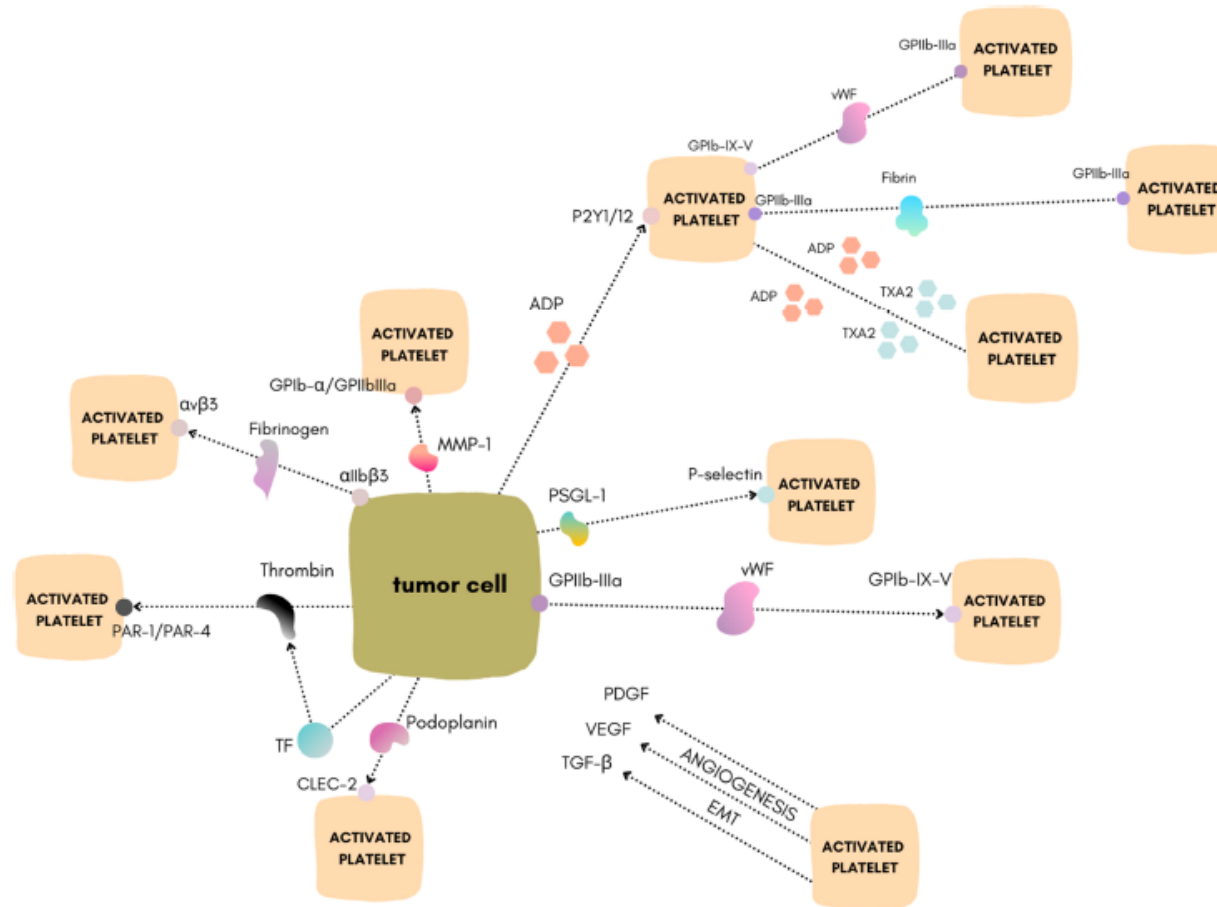
Platelets are versatile cells engaged in numerous pathophysiological processes

- Inflammation and infection
- Innate and acquired immunity
- Angiogenesis
- Regeneration
- Carcinogenesis
- Haemostasis, thrombosis



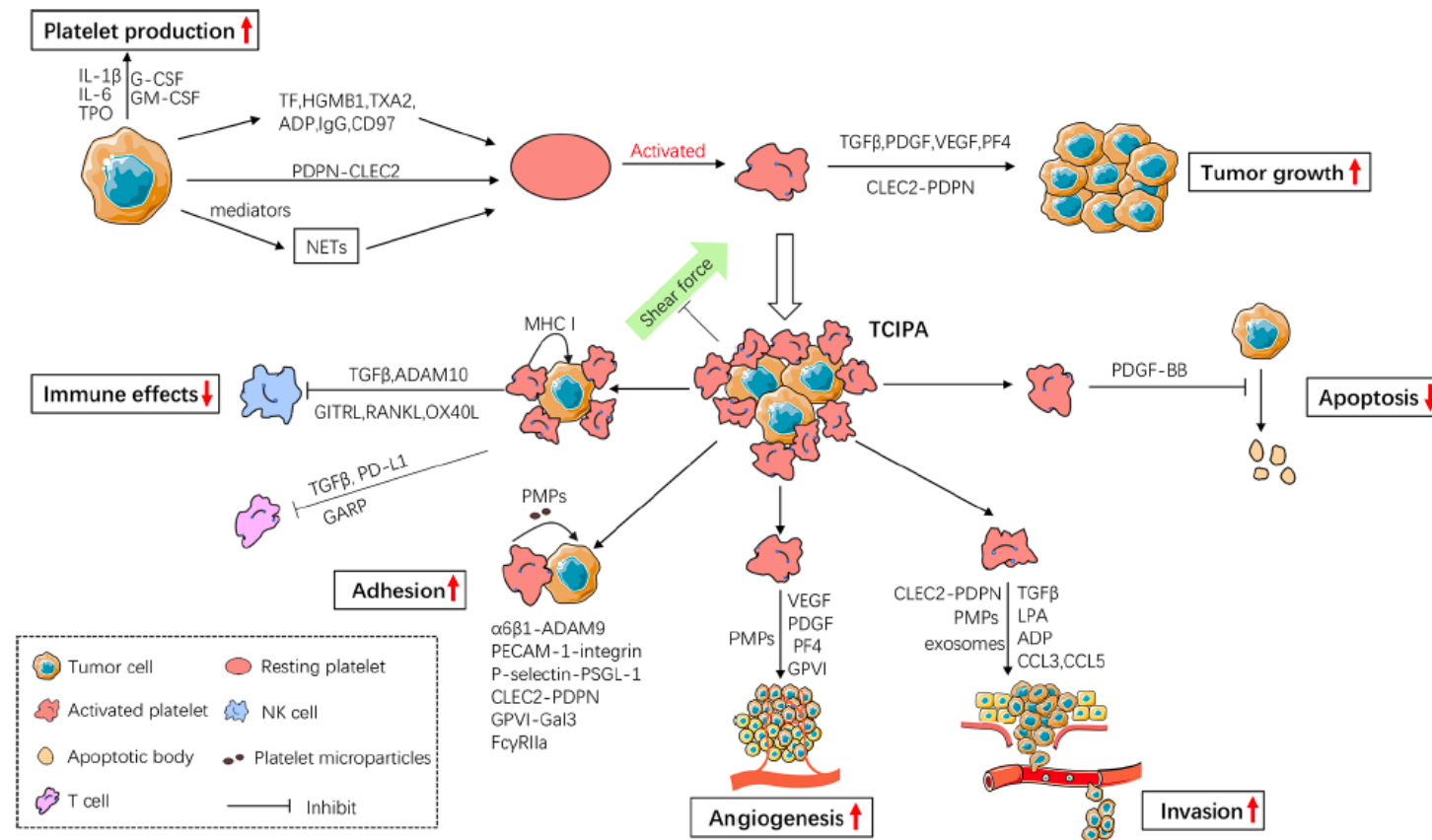
Cancer

Tumor-cell induced platelet aggregation: *an emerging therapeutic target for cancer therapy*



Cancer

Bidirectional interaction between cancer cells and platelets: *suggest potential strategies for cancer therapies.*



Cancer

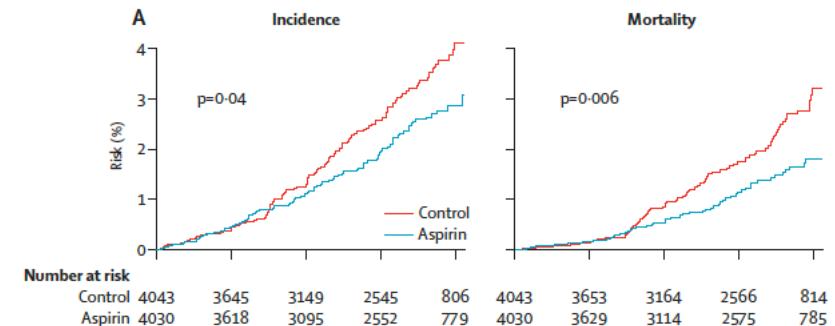
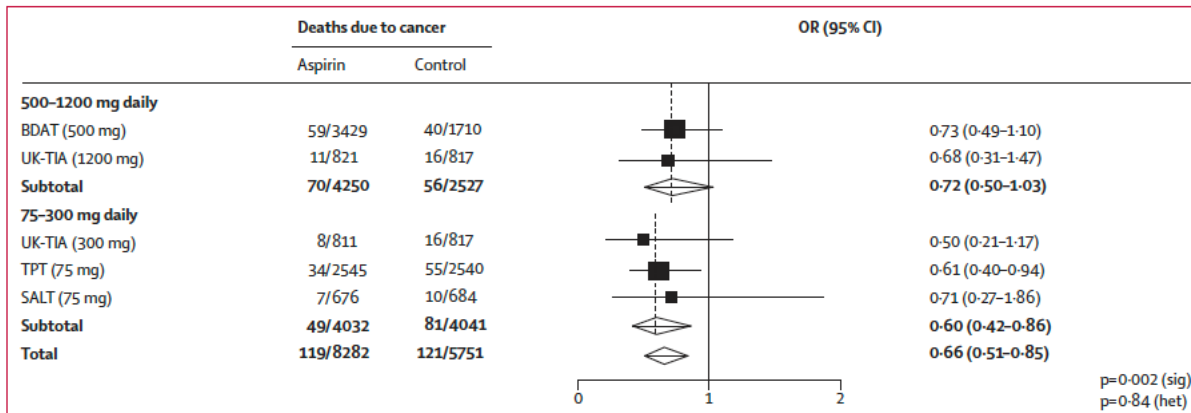
- Antiplatelet agents: **low-dose aspirin and colorectal cancer**
 - Taken daily (> 75mg) for years: brought down incidence and mortality
 - especially the *proximal colon cancer*, not prevented by screening with sigmoidoscopy or colonoscopy

Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials

Peter M Rothwell, Michelle Wilson, Carl-Eric Elwin, Bo Norrving, Ale Algra, Charles P Warlow, Tom W Meade

Lancet 2010; 376: 1741-50

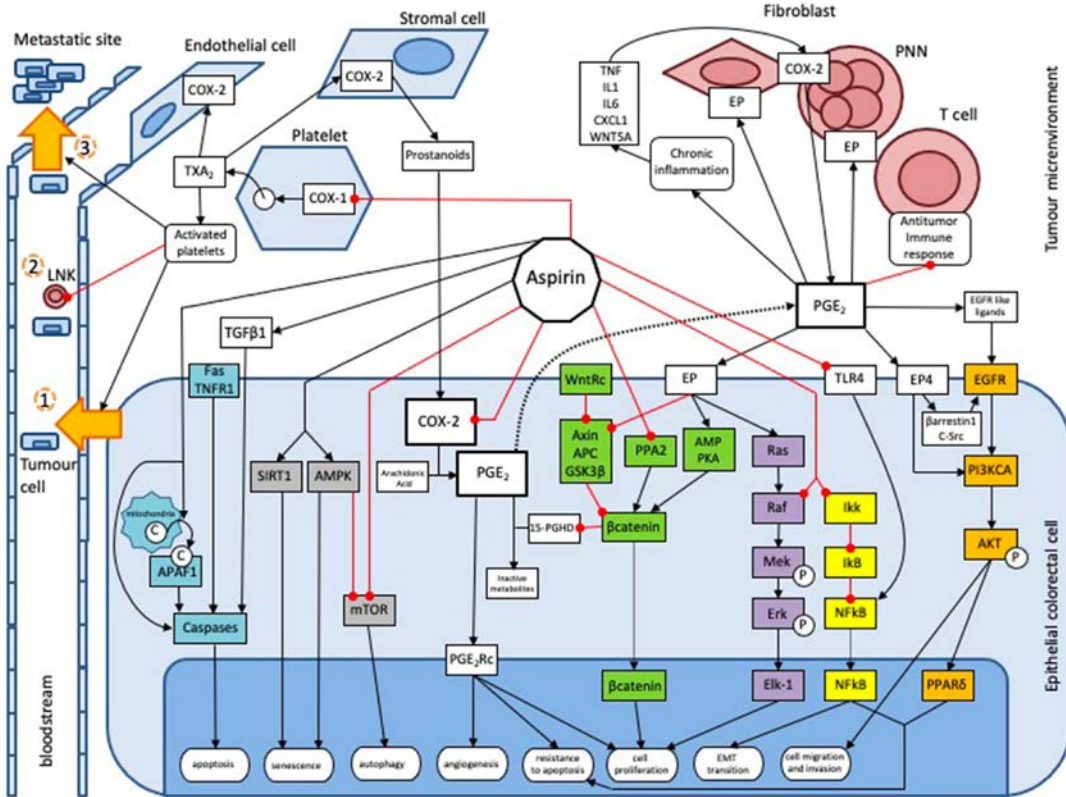
ClinicalTrials.gov database:
46 studies
currently recorded
on
colorectal cancer / aspirin



Pooled analysis of the effect of low-dose (75-300 mg) aspirin versus control

Cancer

- Antiplatelet agents: **low-dose aspirin and colorectal cancer**



Actions of aspirin on colorectal tumorigenesis

- Primary prevention of CRC in all patients aged 50 to 59 with a 10-y risk of cardiovascular events > 10% ? (USA)
- Benefit reduced in smokers and high-risk patients ?
- After cancer resection: especially in patients with *PIK3CA*-mutated tumors ?

- Antiplatelet agents: **low-dose aspirin and other cancers?**
 - Some positive results...
 - Decreases the risk of gastric cancer (Onco Target 2017; 8:4781-95), pancreatic cancer (Cancer Epidemiol Biomarkers Prev 2017;26:68.), cholangiocarcinoma (Hepatology 2016;64:785);
 - Increases the survival of advanced-stage prostate cancer (J Clin Oncol 2014;32:3716-22), breast cancer (Curr Oncol Rep 2017;19:48) and endometrial cancer (Obstet Gynecol 2016;128:127.)
 - But discrepancies: *no effect on*
 - cancer risk: prostate cancer; Eur J Cancer 2015; 51:725)
 - cancer-specific death: breast cancer; Breast Cancer Res 2014;16:R34;
endometrial cancer: Br J Cancer 2017;117:432
 - *More RCTs are needed to imagine what future will be.*

Cancer

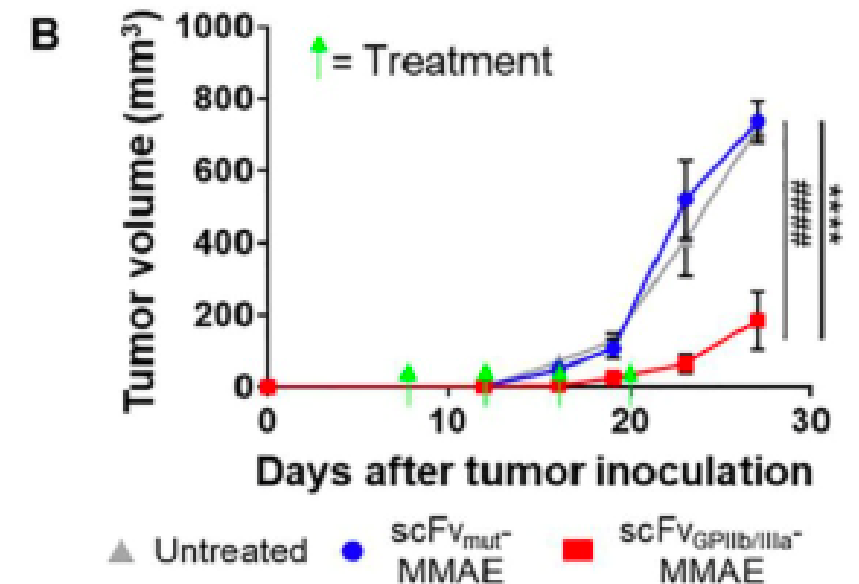
Activated platelets in the tumor microenvironment for targeting of antibody-drug conjugates to tumors and metastases

May Lin Yap^{1,2}, James D McFadyen^{1,3,4}, Xiaowei Wang^{1,3}, Melanie Ziegler¹, Yung-Chih Chen¹, Abbey Willcox^{1,3,4}, Cameron J Nowell⁵, Andrew M Scott^{6,7}, Erica K Sloan⁵, P Mark Hogarth^{2,8,9}, Geoffrey A Pietersz^{1,2,8,9,10*}, Karlheinz Peter^{1,3,9*}

Theranostics 2019; 9(4): 1154-1169.

Antibody-drug conjugate:

singe-chain antibody against the activated platelet integrin GpIIb/IIIa
linked to a chemotherapeutic microtubule inhibitor;
the linker is cleavable by cathepsin B: *drug activation/release mechanism*



Cancer

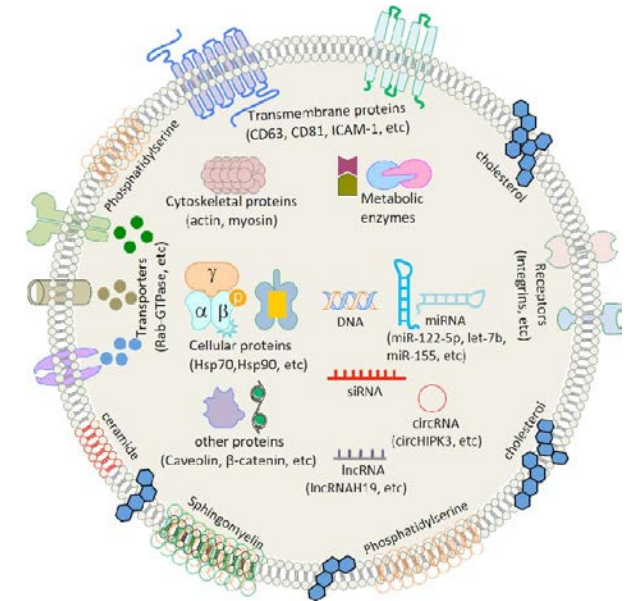
Platelet microparticles infiltrating solid tumors transfer miRNAs that suppress tumor growth

James V. Michael,^{1,2,*} Jeremy G. T. Wurtzel,^{1,2,*} Guang Fen Mao,² A. Koneti Rao,^{2,3} Mikhail A. Kolpakov,^{4,5} Abdelkarim Sabri,^{4,5} Nicholas E. Hoffman,^{6,7} Sudarsan Rajan,^{6,7} Dhanendra Tomar,^{6,7} Muniswamy Madesh,^{6,7} Marvin T. Nieman,⁸ Johnny Yu,^{9,10} Leonard C. Edelstein,^{9,10} Jesse W. Rowley,^{11,12} Andrew S. Weyrich,¹¹⁻¹³ and Lawrence E. Goldfinger^{1,2,14}

Blood 2017;130(5):567-580)

Key Points

- Platelet MPs infiltrate solid tumors and transfer platelet-derived miRNAs to tumor cells within solid tumors *in vivo*.
- Transfer of platelet miRNAs to tumor cells results in downregulation of tumor cell genes and inhibition of solid tumor growth.



**Autologous or *in vitro*-produced
platelet MPs
acting as cargo**

delivering chosen miRNAs prone to control tumor growth?

Thromboinflammation

The COVID-19 model:

No association of low-dose aspirin with severe COVID-19 in France: A cohort of 31.1 million people without cardiovascular disease

Jérémie Botton PhD, PharmD¹ | Laura Semenzato MSc¹ | Julie Dupouy PhD, MD² | Rosemary Dray-Spira PhD, MD¹ | Alain Weill MD¹ | Olivier Saint-Lary PhD, MD³ | Mahmoud Zureik PhD, MD^{1,3}

Res Pract Thromb Haemost 2022;6:e12743.

Effect of P2Y12 Inhibitors on Organ Support-Free Survival in Critically Ill Patients Hospitalized for COVID-19
A Randomized Clinical Trial

Jeffrey S. Berger, MD, MS; Matthew D. Neal, MD; Lucy Z. Kornblith, MD; Michelle N. Gong, MD; Harmony R. Reynolds, MD; Mary Cushman, MD, MSc; Andrew D. Althouse, PhD; Patrick R. Lawler, MD, MPH; Bryan J. McVerry, MD; Keri S. Kim, PharmD; Lisa Baumann Kreuziger, MD; Scott D. Solomon, MD; Mikhail N. Kosiborod, MD; Scott M. Berry, PhD; Grant V. Bochicchio, MD; Marco Contoli, MD, PhD; Michael E. Farkouh, MD; Joshua D. Froese, MS; Sheetal Gandotra, MD; Yonatan Greenstein, MD; Erin M. Hade, PhD; Nicholas Hanna, MD; Kristin Hudock, MD, MSTR; Robert C. Hyzy, MD; Fátima Ibáñez Estélez, MD; Nicole Iovine, MD, PhD; Ashish K. Khanna, MD; Pooja Khatri, MD; Bridget-Anne Kirwan, PhD; Matthew E. Kutcher, MD; Eric Leifer, PhD; George Lim, MD; Renato D. Lopes, MD, MHS, PhD; Jose L. Lopez-Sendon, MD, PhD; James F. Luther, MA; Lila Nigro Mala, MD; John G. Quigley, MD; Lana Wahid, MD; Jennifer G. Wilson, MD; Ryan Zarychanski, MD; Andrei Kindzelski, MD, PhD; Mark W. Geraci, MD; Judith S. Hochman, MD; for the ACTIV-4a Investigators

JAMA Network Open. 2023;6(5):e2314428.

No evidence for an effect of **low-dose aspirin** for primary cardiovascular prevention in reducing severe COVID-19;

fully adjusted models:
risk of hospitalisation: HR 1.03 (1.00-1.07)
risk of death/intubation: HR 1.04 (0.98-1.10)

RCT: Treatment with a **P2Y12 inhibitor** **did not improve** the number of days alive and free of cardiovascular and respiratory organ support

fully adjusted models:
survival: aOR 1.15 (0.84-1.55)
mortality rates at D90: 25.5% vs. 27.0%, aHR 0.96 (0.76-1.23)

Thromboinflammation

Article

<https://doi.org/10.1038/s41467-023-37990-z>

Cargo-free particles divert neutrophil-platelet aggregates to reduce thromboinflammation

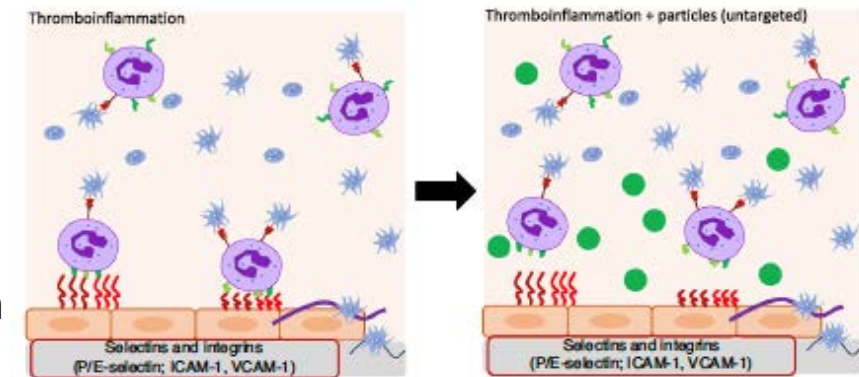
Nature Communications | (2023)14:2462

Alison L. Banka¹, M. Valentina Guevara¹, Emma R. Brannon¹,
Nhien Q. Nguyen², Shuang Song², Gillian Cady³, David J. Pinsky³,
Kathryn E. Uhrich², Reheman Adili⁴, Michael Holinstat^{3,4} &
Omolola Eniola-Adefeso^{1,5,6} ✉

Polymeric particles to divert platelets away from inflamed blood vessels

Micron-sized polymeric particles can reduce platelet adhesion to an inflamed endothelial monolayer *in vitro* in blood flow systems and *in vivo* in a LPS-induced systemic inflammation murine model.

Initial work in developing cargo-free, anti-platelet therapeutics specifically for conditions of thromboinflammation: **cargo-free MicroP can redirect platelets away from an area of inflammation via alteration in leukocyte adhesion**



Biodegradable, therapeutic polymer microparticles constructed from a salicylate-based poly(anhydride-ester) polymer.

**Thrombosis: antiplatelet treatment
in non-atherothrombotic diseases**

Low-Dose Aspirin for Preventing Recurrent Venous Thromboembolism

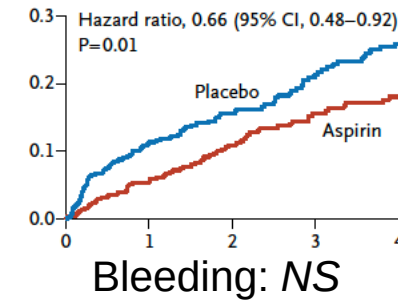
Timothy A. Brighton, M.B., B.S., John W. Eikelboom, M.B., B.S., Kristy Mann, M.Biostat., Rebecca Mister, M.Sc., Alexander Gallus, M.B., B.S., Paul Ockelford, M.B., Harry Gibbs, M.B., Wendy Hague, Ph.D., Denis Xavier, M.Sc., Rafael Diaz, M.D., Adrienne Kirby, M.Sc., and John Simes, M.D., for the ASPIRE Investigators*

N Engl J Med 2012;367:1979-87.

Patients, anticoagulation for a first episode of VTE;
then RCT:
LDA 100 mg daily vs. placebo, up to 4 years.

VTE recurrence: **NS**; HR 0.74 (0.52-1.05)

Rate of (VTE, MI, stroke, cardiovascular death): **p=0.01**



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N Engl J Med 2012;367:1979-87.

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

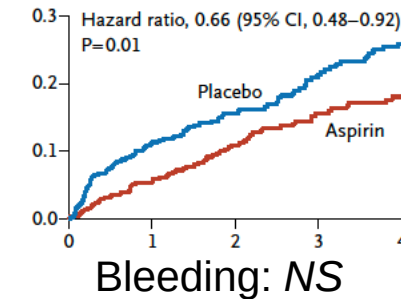
N Engl J Med 2017;376:1211-22.

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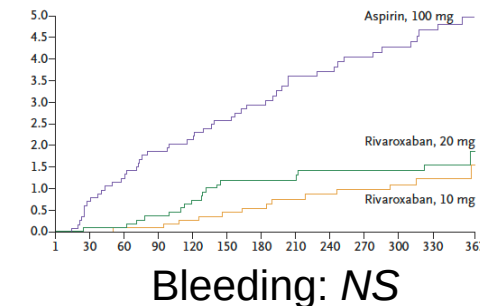


Patients, anticoagulation for a first episode of VTE;
then RCT:

LDA 100 mg daily vs. **Rivaroxaban (10-20 mg)**, up to 12 months.

VTE recurrence, 10 mg vs. LDA: HR 0.26 (0.14-0.47)

VTE recurrence, 20 mg vs. LDA: HR 0.34 (0.20-0.59)



Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

D.R. Anderson, M. Dunbar, J. Murnaghan, S.R. Kahn, P. Gross, M. Forsythe, S. Pelet, W. Fisher, E. Belzile, S. Dolan, M. Crowther, E. Bohm, S.J. MacDonald, W. Gofton, P. Kim, D. Zukor, S. Pleasance, P. Andreou, S. Doucette, C. Theriault, A. Abianui, M. Carrier, M.J. Kovacs, M.A. Rodger, D. Coyle, P.S. Wells, and P.-A. Vendittoli

N Engl J Med 2018;378:699-707.

RCT

Total hip or knee arthroplasty

Rivaroxaban 10 mg until postoperative day 5, then:

Low-dose aspirin (81 mg) vs. rivaroxaban 10 mg, 9 days for TKA, 30 days for THA

Following: 90 days

Outcome	Total Hip Arthroplasty			Total Knee Arthroplasty		
	Rivaroxaban (N=902)	Aspirin (N=902)	P Value	Rivaroxaban (N=815)	Aspirin (N=805)	P Value
	no. (%)	no. (%)		no. (%)	no. (%)	
Venous thromboembolism	5 (0.55)	4 (0.44)	1.00*	7 (0.86)	7 (0.87)	1.00†
Pulmonary embolism	2 (0.22)	2 (0.22)		4 (0.49)	3 (0.37)	
Proximal deep-vein thrombosis	1 (0.11)	1 (0.11)		3 (0.37)	3 (0.37)	
Pulmonary embolism and proximal deep-vein thrombosis	2 (0.22)	1 (0.11)		0	1 (0.12)	
Major bleeding	3 (0.33)	3 (0.33)	1.00	2 (0.25)	5 (0.62)	0.29
All bleeding‡	7 (0.78)	11 (1.22)	0.48	10 (1.23)	11 (1.37)	0.83

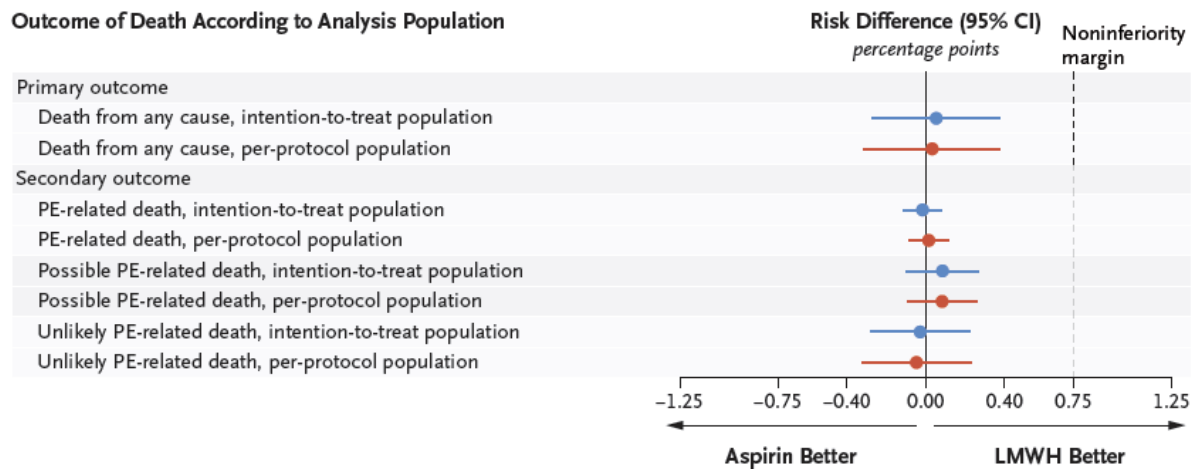
Aspirin or Low-Molecular-Weight Heparin for Thromboprophylaxis after a Fracture

Major Extremity Trauma Research Consortium (METRC)*

N Engl J Med 2023;388:203-13.

Aspirin noninferior to LMWH in preventing death

Outcome of Death According to Analysis Population



Noninferiority, RCT

Fracture of an extremity:

hip to midfoot, or shoulder to wrist: treated operatively;
any pelvic or acetabular fracture.

Enoxaparin 30 mg bid vs. LDA 81 mg bid
while in the hospital.

Primary outcome: death from any cause at D90.

Secondary outcomes: non-fatal PE; DVT; bleeding.

Median age: 45 years

Lower extremity injury: 88%

Low incidence of DVT: 2.5% vs. 1.7%, NS
PE: 1.5% in each group.

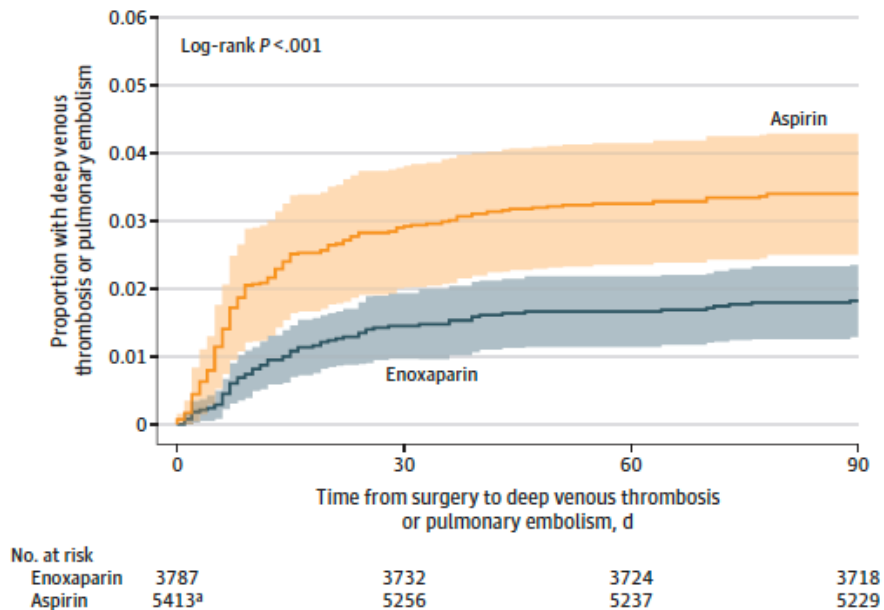
Incidence of bleeding complications: similar.

Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty The CRISTAL Randomized Trial

CRISTAL Study Group

JAMA. 2022;328(8):719-727.

3.45% vs. 1.82%, p=0.007



Hospital(cluster)-randomised,
crossover, registry-nested trial
31 hospitals in Australia
(16: crossover after target met)
Hip or knee arthroplasty (THA, TKA)
LDA (100 mg/d) vs. Enoxaparin (40 mg/d)
THA: 35 days; TKA: 14 days.

Primary outcome: symptomatic VTE within 90 days
Noninferiority margin: 1%

Median age: 70 years

Significant higher rate of symptomatic VTE
within 90 days,
defined as below- or above-knee DVT or PE
in patients taking LDA

Dual-pathway inhibition to reduce VTE?

i.e.
an antiplatelet agent (low-dose aspirin LDA) plus a DOAC to prevent VTE in high-risk patients?

Currently: no available specific trial

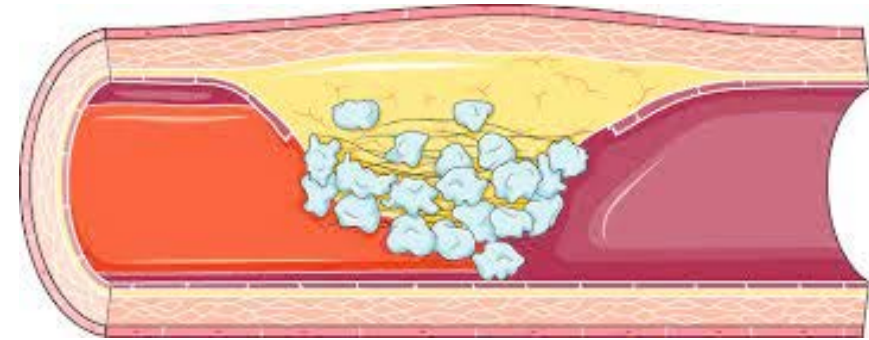
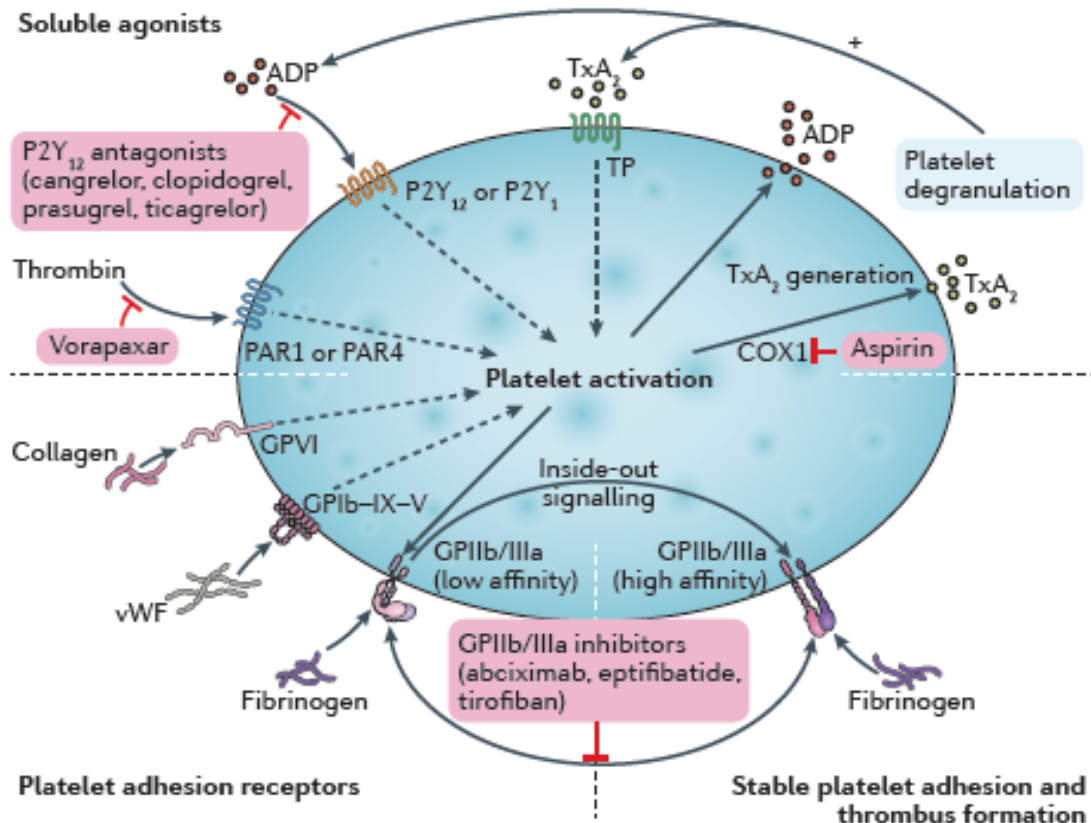
The APEX trial (N Engl J Med 2016; 375:534-44) and the MARINER trial (N Engl J Med 2018; 379: 1118-27) successfully tested a DOAC (betrixaban, rivaroxaban) in acutely ill medical patients;
around 50% of the included population reported baseline LDA use ;
apparently no significant increase in major bleeding in those receiving dual-pathway inhibition.

Medically ill patients: a prospective RCT comparing no treatment or extended thromboprophylaxis with a low-dose DOAC with or without an antiplatelet arm (ASA) has to be conducted

The advent of **FXI inhibitors**, with little or no disruption of haemostasis:
safer anticoagulant platform for dual-pathway inhibition?

Antiplatelet treatment in atherothrombotic diseases

Antiplatelet agents:



Central to the armamentarium
used to prevent and treat
arterial thrombosis

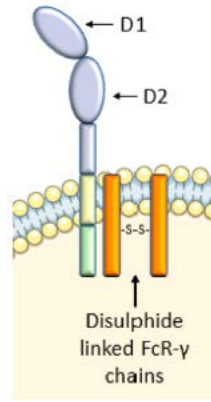
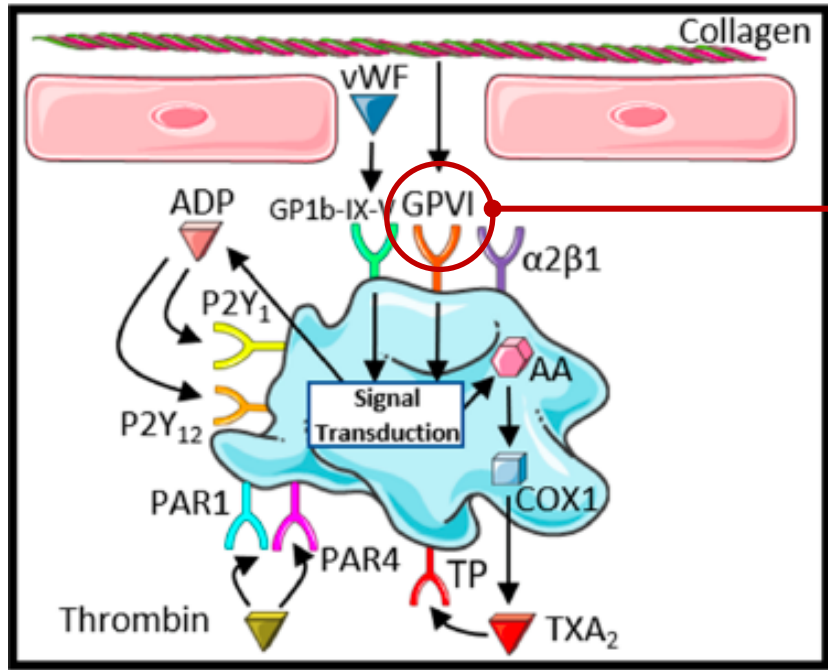
Major limitation of their use:
bleeding

Prescription: population-based (RCTs),
not patient-based.

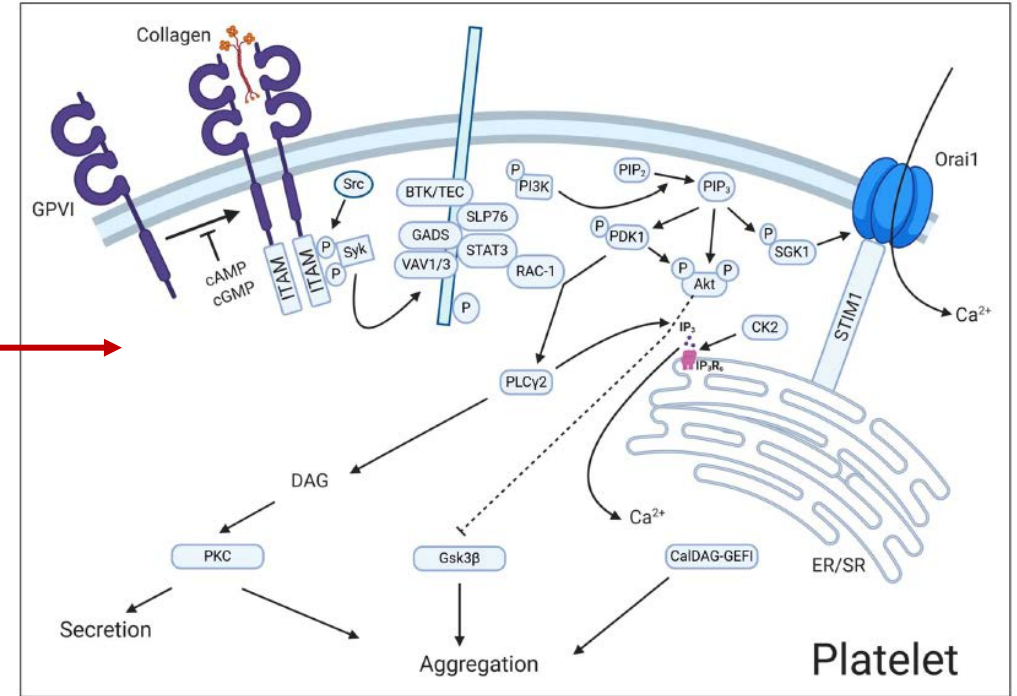
Safer New Antiplatelet Agents?

Targeting platelet glycoprotein VI (GpVI)?

crucial role in collagen-induced activation and aggregation of platelets



Dimeric GpVI:
higher affinity for collagen



Constitutive or acquired human GpVI deficiencies: **mild bleeding phenotype**

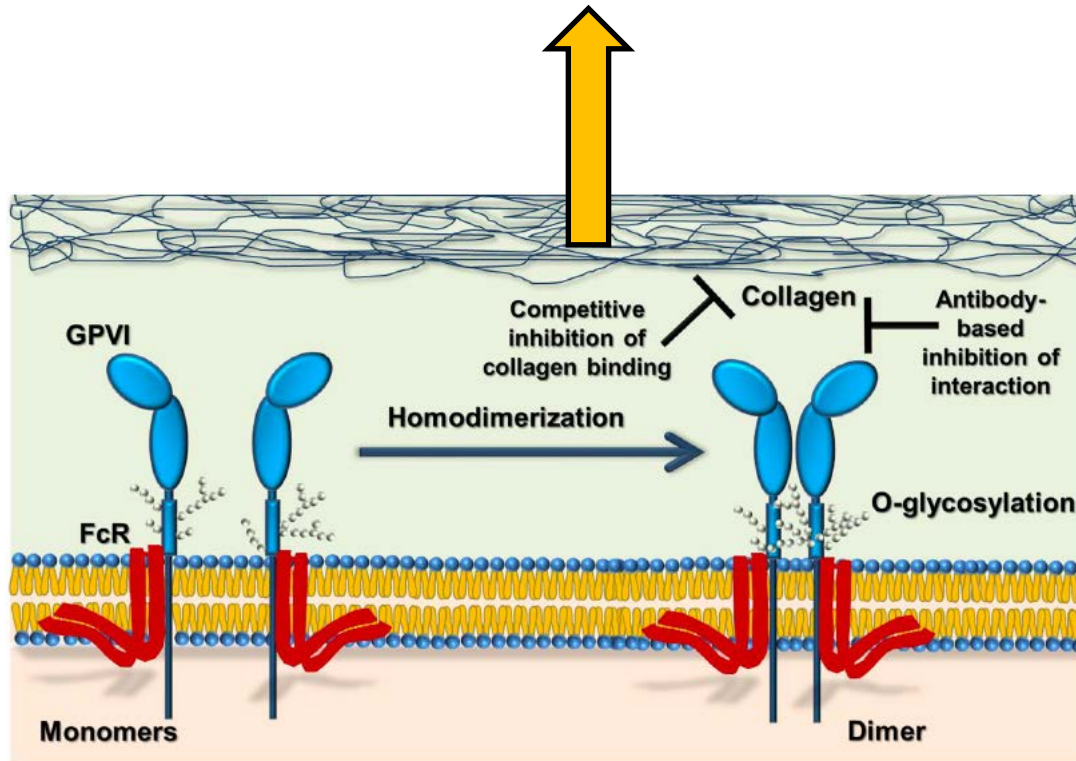
epistaxis, petechiae, occasional postsurgery bleeding

Platelet-specific, strongly involved in the pathogenesis of arterial thrombosis

without great impact on normal haemostasis

Recombinant soluble dimeric form
of the GpVI ectodomain fused to IgG₁-Fc:

Revacept®
(vascular coating)



Strategies targeting platelet GpVI

Revacept, an Inhibitor of Platelet Adhesion in Symptomatic Carotid Stenosis: A Multicenter Randomized Phase II Trial

Timo Uphaus¹, MD; Toby Richards², MD; Christian Weimar, MD; Hermann Neugebauer, MD; Sven Poli³, MD; Karin Weissenborn⁴, MD; Christopher Imray⁵, MD; Dominik Michalski⁶, MD; Hisham Rashid, MD; Ian Loftus, MD; Christian Rummey⁷, PhD; Martin Ritter⁸, MD; Till-Karsten Hauser⁹, MD; Götz Münch¹⁰, MD; Klaus Gröschel¹¹, MD*; Holger Poppert¹², MD*

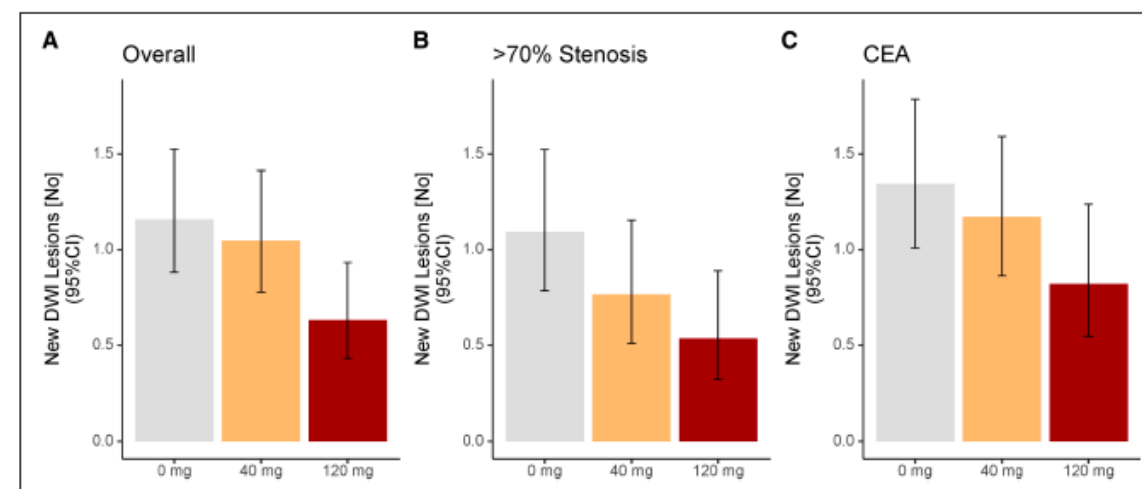
Stroke 2022; 53:2718-29.

Symptomatic carotid artery stenosis
International, multi-center,
3 arms, randomised (1:1), placebo-controlled

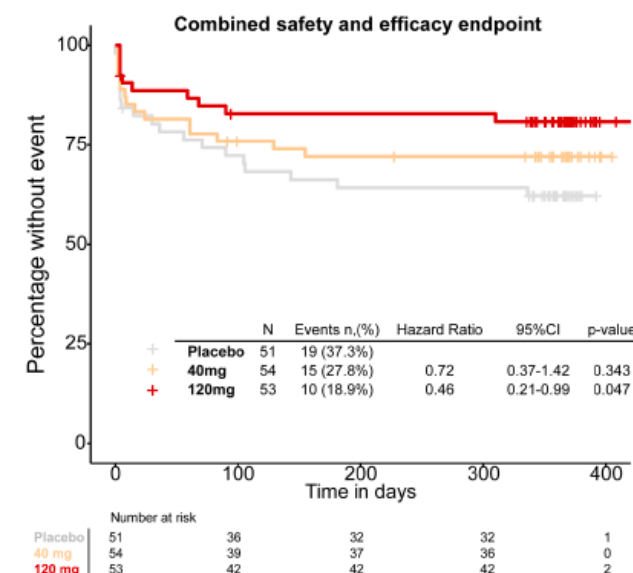
In addition to guideline-conform antiplatelet therapy:
single infusion over 20 minutes;
Placebo vs. Revacept® 40 mg vs. Revacept® 120 mg

Revacept® 120 mg
reduced the combined safety and efficacy end point
in patients with symptomatic internal carotid artery stenosis

160 patients

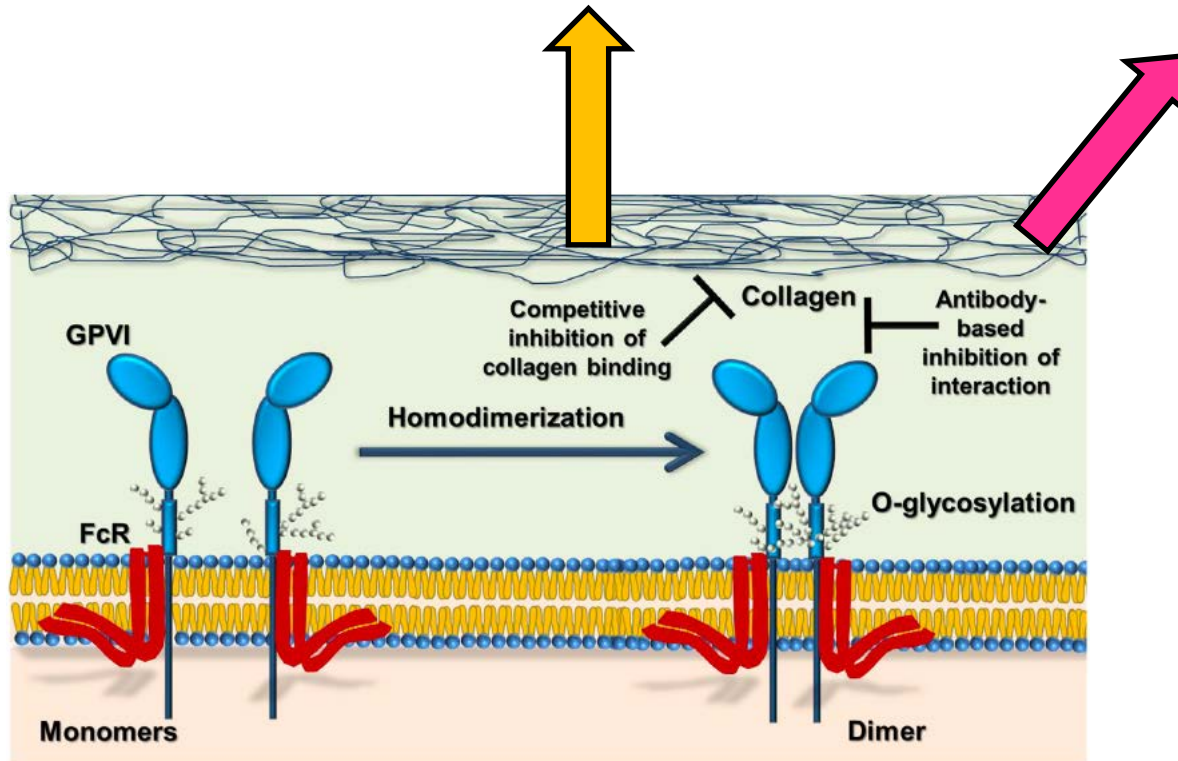


Efficacy end point of new diffusion-weighted MRI lesions



Recombinant soluble dimeric form
of the GpVI ectodomain fused to IgG₁-Fc:

Revacept®
(vascular coating)

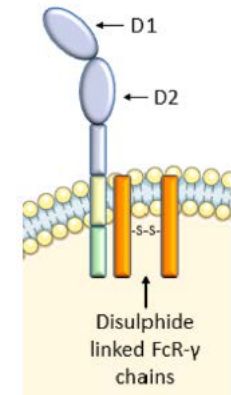


Humanized Fab fragment
derived from mouse mAbs against GpVI.

Glenzocimab (ACT017) :
nanomolar affinity for GpVI
and inhibits GpVI interactions with collagen

Key Points

- Crystallization studies map the binding of glenzocimab to the site of dimerization in the D2 domain of GPVI.



Strategies targeting platelet GpVI

Blood Adv 2023; 7:1258-68

**GLENZOCIMAB, A NOVEL
ANTITHROMBOTIC, IS ASSOCIATED WITH
REDUCED INTRACRANIAL HEMORRHAGE
AND MORTALITY RATES WHEN COMBINED
WITH STANDARD-OF-CARE REPERFUSION
THERAPIES: THE ACTIMIS STUDY**

M. Mazighi¹, S. Richard², C. Molina³, D. Toni⁴, P. Lyrrer⁵, R. Lemmens⁶, A. Comenducci⁷, J.-M. Grouin⁸, Y. Plétan⁷, A. Sari⁷, A. Meilhoc⁷, M. Jandrot-Perrus⁹, S. Binay⁷, G. Avenard⁷, M. Köhrmann¹⁰, J.C. Grotta¹¹, on behalf of ACTIMIS Study Group [Serena J., Peeters A., Obadia M., Sibon I. et al.]

Eur Stroke J 2022; 7(Suppl1):574 (1758)

acute ischaemic stroke, thrombolysis or thrombectomy

double-blind, placebo-controlled, 1:1 parallel group design
glenzocimab 1000 mg vs. placebo
(Phase 2a)

166 patients, median age 75 years

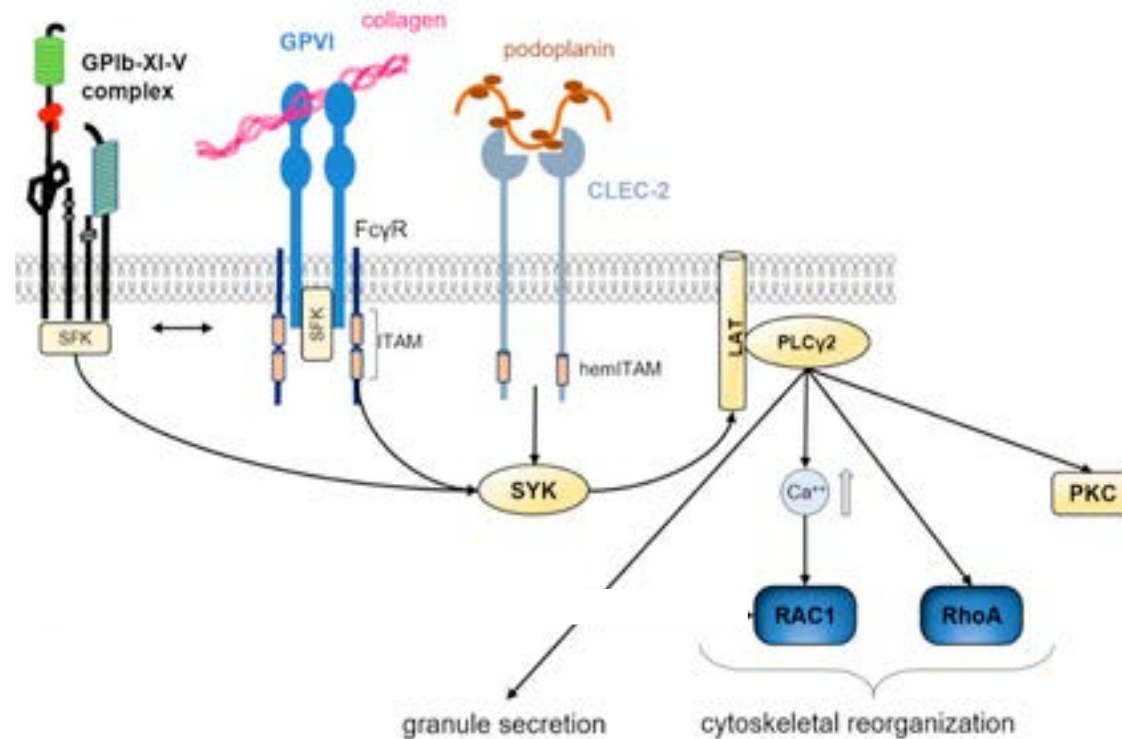
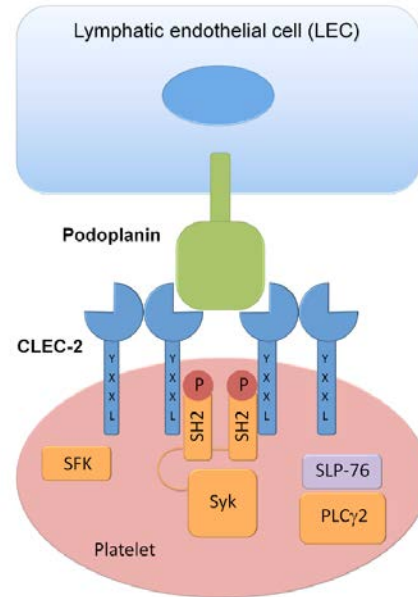
Symptomatic intracranial haemorrhage ICH:
Glenzocimab: 1% vs. P: 8%

Non-symptomatic ICH:
Glenzocimab: 29% vs. P: 47%

Death:
Glenzocimab: 8% vs. P: 19%

Glenzocimab: reduced ICH and mortality.

Targeting the C-type Lectin-like Receptor (CLEC-2) ?



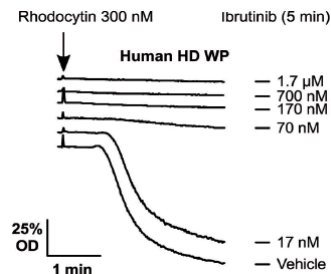
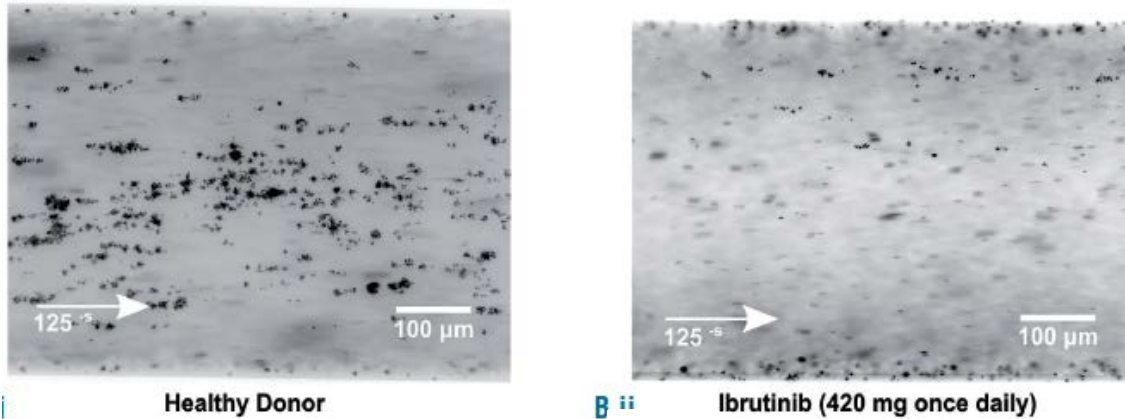
Dimer on platelets (low levels: myeloid and dendritic cells)

Natural ligand (podoplanin): absent from the circulating blood; inflammation: upregulation in the vessel wall
Role in arterial thrombosis as an adhesion receptor; trigger venous thrombosis at sites of inflammation in animals
No known consitutive or acquired deficiency in humans

Low-dose Btk inhibitors selectively block platelet activation by CLEC-2

Phillip L.R. Nicolson,^{1,2} Sophie H. Nock,³ Joshua Hinds,¹ Lourdes Garcia-Quintanilla,¹ Christopher W. Smith,¹ Joana Campos,¹ Alexander Brill,^{1,4} Jeremy A. Pike,^{1,5} Abdullah O. Khan,¹ Natalie S. Poulter,^{1,5} Deidre M. Kavanagh,^{1,5} Stephanie Watson,¹ Callum N. Watson,¹ Hayley Clifford,⁶ Aarnoud P. Huissoon,⁶ Alice Y. Pollitt,³ Johannes A. Eble,⁷ Guy Pratt,² Steve P. Watson^{1,5} and Craig E. Hughes³

Haematologica 2021
Volume 106(1):208-219



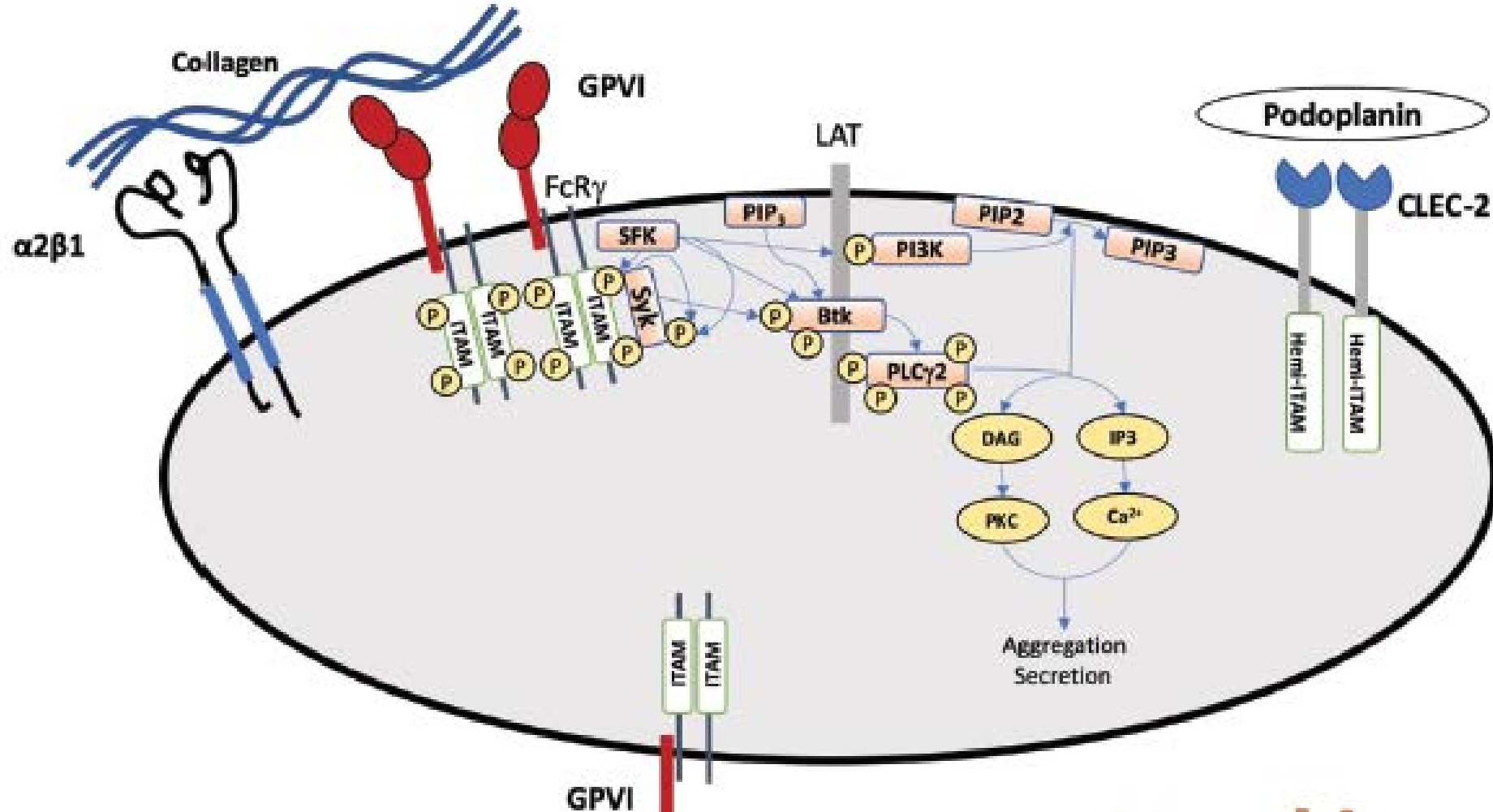
Bruton tyrosine kinase
lies downstream of Syk
in human platelets.

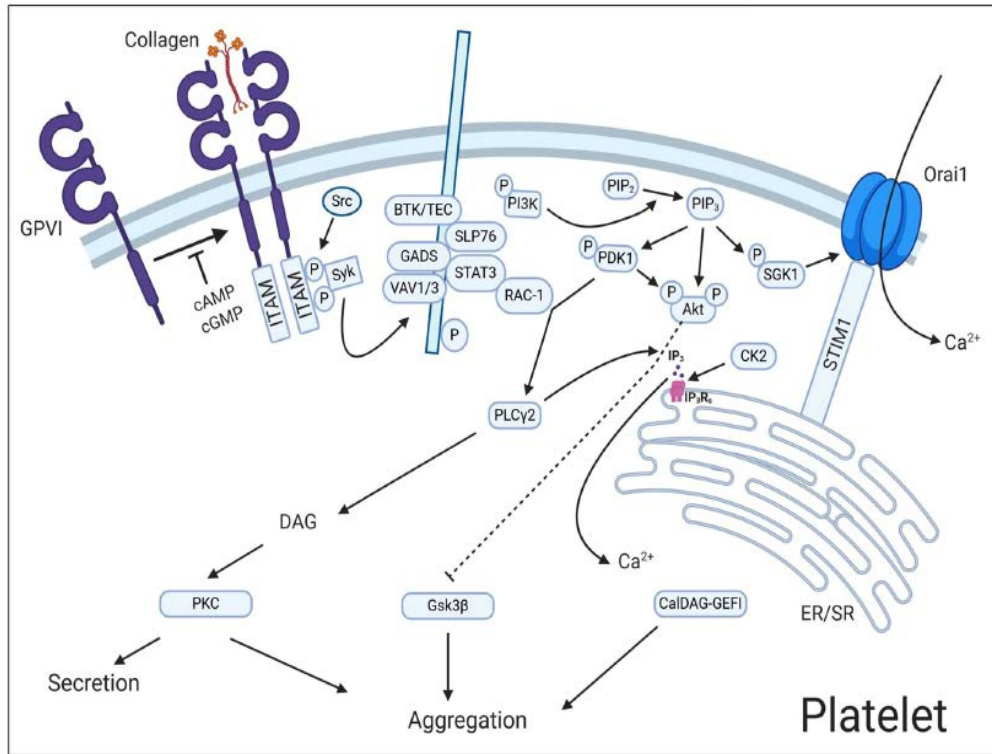
Btk inhibitors block human CLEC-2-mediated platelet functions at concentrations 20-fold lower than those that block GpVI signaling.

*Suggests that Btk inhibitors
can be used at low doses in patients
to target CLEC-2 in thromboinflammatory diseases*

Targeting Tyrosine Kinases that are downstream of the GpVI and CLEC-2 signaling cascades?

Src, Syk and Tec family kinases





Src family kinases:

likely to have the greatest number of off-target actions
widespread distribution and **lack of selectivity**.
Forget it.

Syc and Tec kinases:

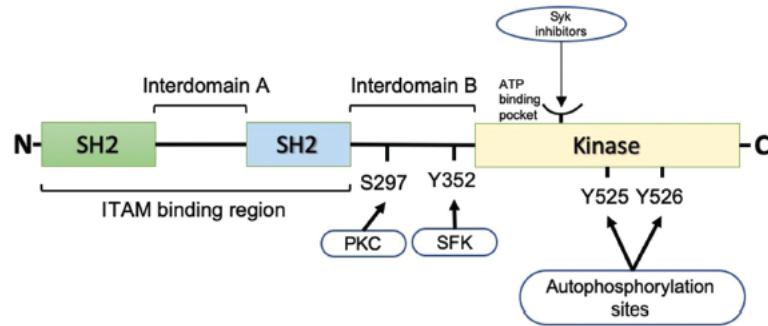
restricted to haematopoietic cells;
2 predominant family members in platelets,
Spleen tyrosine kinase **Syc** and Bruton tyrosine kinase **Btk**,
only expressed in a subset of these.

Syc:

downstream of GpVI, CLEC-2, GpIb and GpIIb/IIIa
limited role in the signaling of G protein-coupled receptors
such as *PARs*, *P2Y₁₂* and *TXA₂* receptors

**Might be an effective strategy against thrombosis
while preserving haemostasis**

Syk

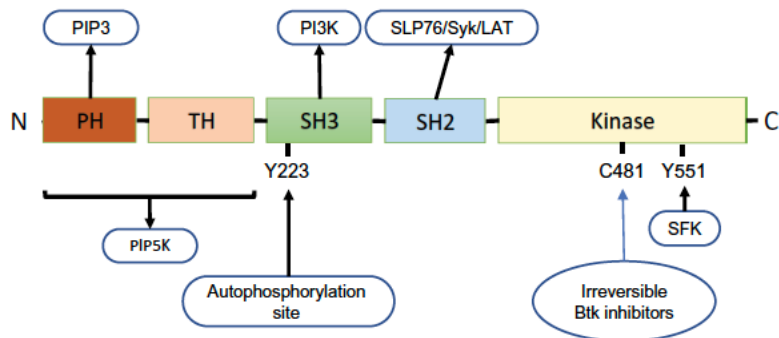


Cevidoplenib, Entospletinib, Fostamatinib, Lanraplenib,

...

Do not appear to cause bleeding in patients in published trials

Btk



Acalabrutinib, Ibrutinib, Evobrutinib, Remibrutinib, Rilzabrutinib, Tirabrutinib, Zanubrutinib,...

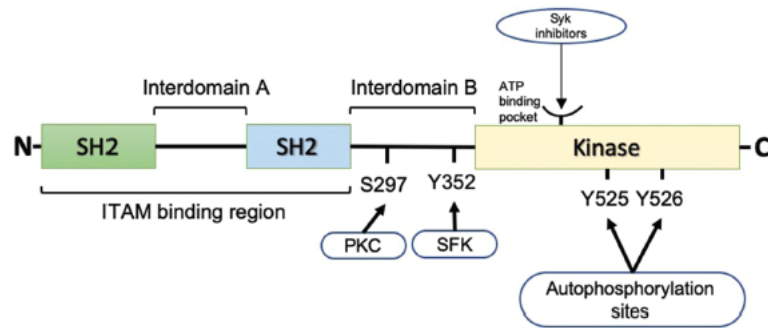
Ibrutinib, early clinical trials: low grade bleeding tendency in 50% of the patients (bruising, petechiae).

3 years follow-up study: 7.6% rate of major bleeding.

Explained by co-inhibition of Tec and Src.

More specific, 3rd generation Remibrutinib and Rilzabrutinib: no apparent excess bleeding in phase II clinical trials.

Syk

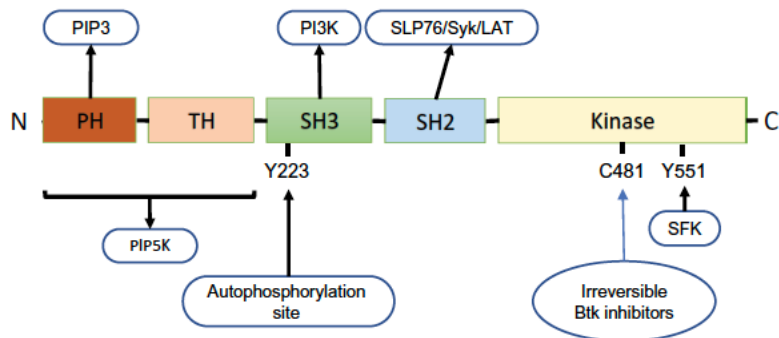


Cevidoplenib, Entospletinib, Fostamatinib, Lanraplenib,

...

Preclinical mouse models:
protect against arterial thrombosis
and cerebral infarct progression

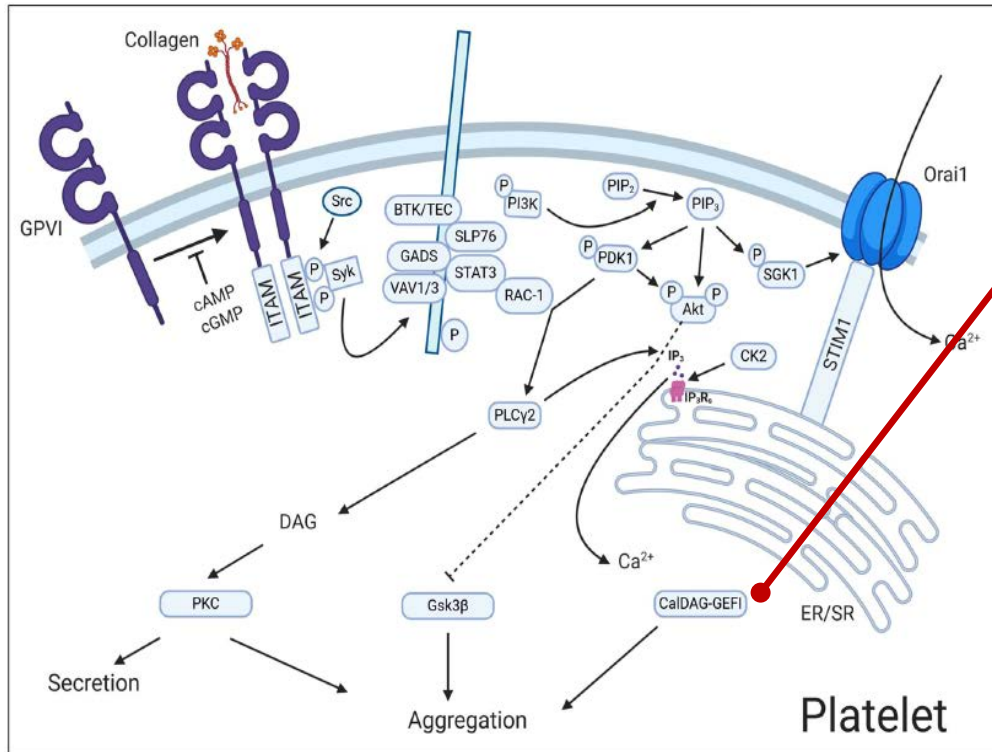
Btk



Acalabrutinib, Ibrutinib, Evobrutinib, Remibrutinib,
Rilzabrutinib, Tirabrutinib, Zanubrutinib,...

Selectively inhibit thrombus formation
induced by atherosclerotic plaque in humans
without affecting platelet adhesion to collagen
mediated by $\alpha 2\beta 1$.
(Blood 2018; 131:2605-16)

Low-dose may selectively inhibit the role of CLEC-2
in thromboinflammation



CalDAG-GEFI

Human CalDAG-GEFI gene (*RASGRP2*) mutation affects platelet function and causes severe bleeding

Matthias Canault,^{1,2,3} Dorsaf Ghalloussi,^{1,2,3} Charlotte Grosdidier,^{1,2,3} Marie Guinier,⁴ Claire Perret,^{5,6,7} Nadjim Chelghoum,⁴ Marine Germain,^{5,6,7} Hana Raslova,⁸ Franck Peiretti,^{1,2,3} Pierre E. Morange,^{1,2,3} Noemie Saut,^{1,2,3} Xavier Pillois,^{9,10} Alan T. Nurden,¹⁰ François Cambien,^{5,6,7} Anne Pierres,^{3,11,12} Timo K. van den Berg,¹³ Taco W. Kuijpers,¹³ Marie-Christine Alessi,^{1,2,3} and David-Alexandre Tregouet^{5,6,7}

J. Exp. Med. 2014 Vol. 211 No. 7 1349-1362

Group of diseases:

mutations in genes for signaling proteins that are critical to the inside-out activation of $\alpha\text{IIb}\beta 3$ (reduced ability to activate Rap1).

A very large deficient Gypsy inbred family diagnosed and followed by our team

Heterozygous members: no bleeding,

but their platelets fail to undergo normal adhesion under flow and spreading.

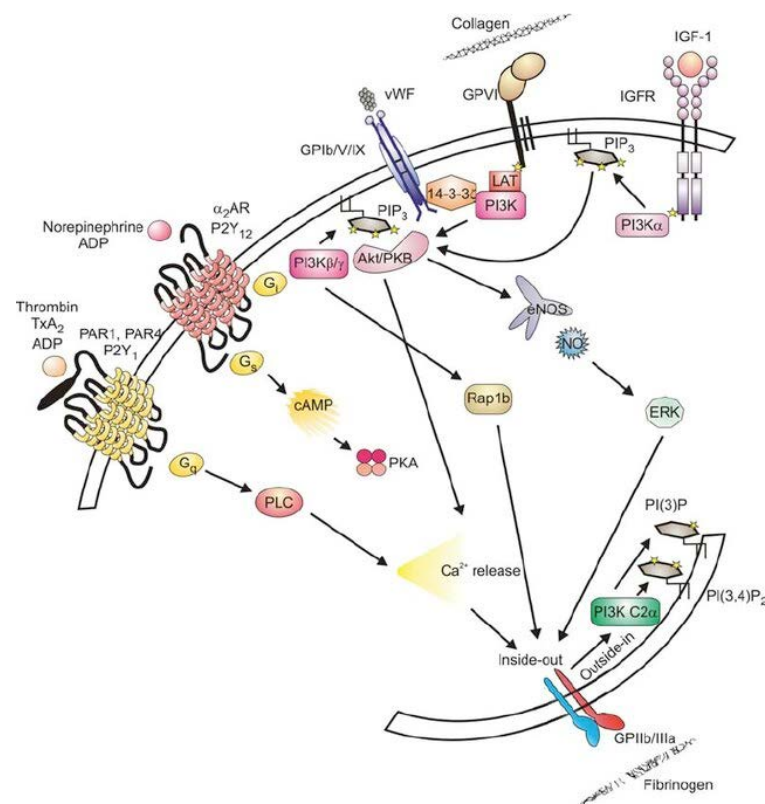
Makes CalDAG-GEFI a potentially safe therapeutic target to prevent thrombosis

Targeting Phosphoinositide 3-kinase β (PL3K β)

Activates and modulates several effector proteins

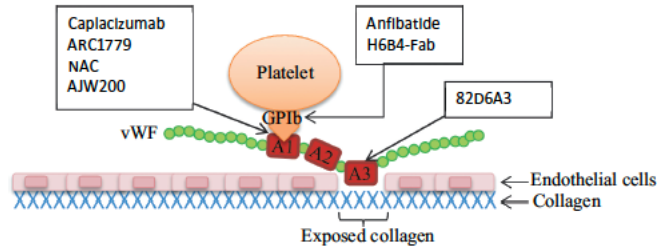
Regulates: integrin GpIIbIIIa-dependent adhesion,
 Akt activation mediated by GpVI and ADP,
 ERK activation (including subsequent TXA₂ synthesis)

Depletion in animals prevents occlusive thrombosis whilst preserving primary haemostasis



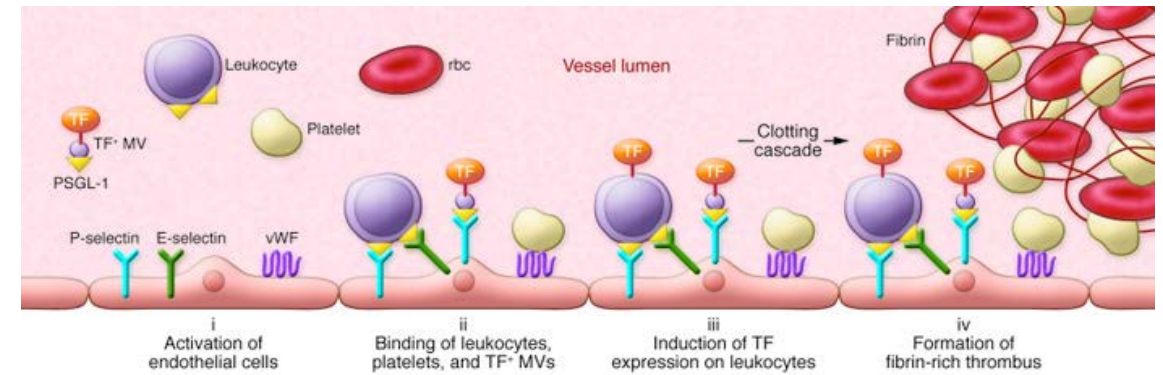
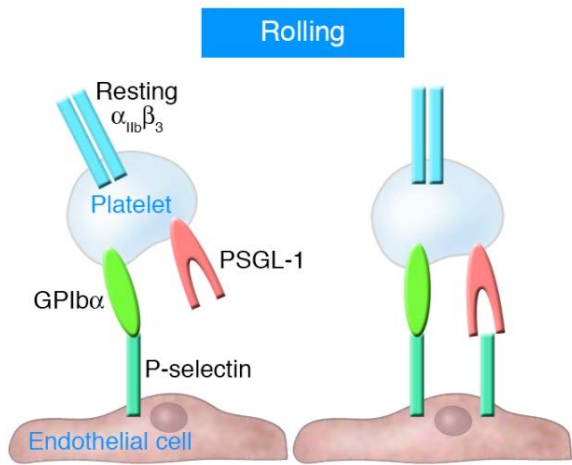
Platelet targets & their inhibitors	Class of inhibitor	Mode of action	Antiplatelet properties	Risk of Bleeding	Route	The current level of development
PI3K β AZD6482	Small molecule	Binds to ATP binding site of PI3K β	Blocked platelet aggregation-stimulated by low concentrations of multiple agonists and inhibited platelet aggregation and adhesion When combined aspirin, it provided more significant inhibition of platelet activation than that observed with aspirin and clopidogrel	Safe, it did not increase bleeding time in healthy volunteers during phase I Less impact on bleeding when combined with aspirin than aspirin plus clopidogrel	IV	Clinical trials: Phase I completed

Targeting the GpIb-IX-V-VWF axis



Platelet targets & their inhibitors	Class of inhibitor	Mode of action	Antiplatelet properties	Risk of Bleeding	Route	The current level of development
GPIb-IX-V- VWF						
ARC1779	1 st generation aptamer	Neutralizes the VWF A1 domain	Inhibited <i>ex vivo</i> VWF-dependant platelet adhesion and aggregation in healthy volunteers during phase I study Reduced thromboembolism in stroke patients	Safe with no bleeding events reported in healthy volunteers during phase I However, increased bleeding when combined aspirin in stroke patients undergoing CEA during phase II	IV	Clinical trials: Phase I completed Phase II ceased
ARC15105	2 nd generation aptamer	Neutralizes the VWF A1 domain	Inhibited VWF activity in samples from ACS patients	Has not been tested in humans yet Did not cause bleeding in monkeys	IV	Pre-clinical
Anfibatide	Toxin-derived C-type lectin-like protein	Binds to GPIb α	Inhibited platelet aggregation mediated by VWF and ristocetin Prevented human platelet adhesion and thrombus formation on collagen under shear rate <i>ex vivo</i>	Did not increase tail bleeding time, or cause bleeding diathesis in mice No effect on coagulation or bleeding time reported in phase I	IV	Clinical trials: Phase I completed Phase II completed

**Bleeding risk?
(acquired VWD)**



Platelet targets & their inhibitors	Class of inhibitor	Mode of action	Antiplatelet properties	Risk of Bleeding	Route	The current level of development
<i>P</i> -selectin Inclacumab	Monoclonal antibody	Binds to <i>P</i> -selectin	Reduced soluble <i>P</i> -selectin levels and total <i>P</i> -selectin activity and reduced platelet-leukocyte aggregate formation	Safe, it did affect bleeding time or coagulation in healthy subjects during phase I trial No bleeding events reported in CABG patients following inclacumab infusion	IV	Clinical trials: Phase I completed Phase II completed
Crizanlizumab	Monoclonal antibody	Binds to <i>P</i> -selectin	Blocked <i>P</i> -selectin function	Safe, no severe bleeding reported in phase I and II trials	IV	Clinical trials: Phase I completed Phase II completed Phase III in process
PSI-697	Small molecule	Binds to <i>P</i> -selectin	Blocked <i>P</i> -selectin activity <i>in vitro</i> , and reduced inflammation and thrombosis in animal models No effect was seen on platelet-monocyte aggregation in healthy smokers during phase I trial	Safe, no bleeding events reported in healthy smokers during phase I	Oral	Clinical trials: Phase I completed

Targeting P-selectin (CD62P)

Targeting Protein Disulfide isomerase DPI

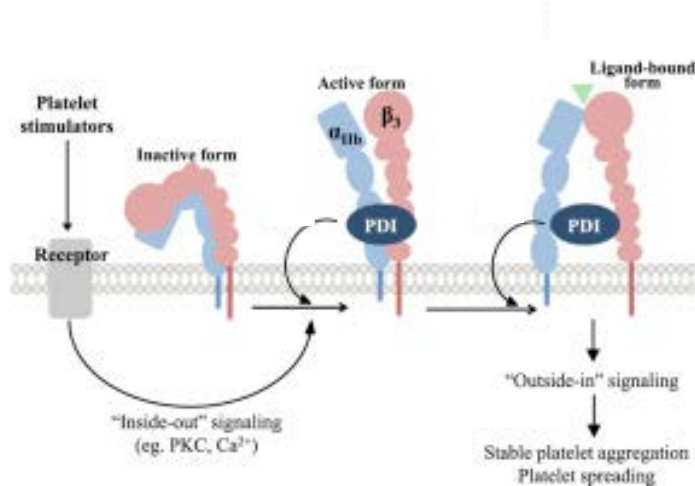
Secreted by activated platelets from the dense tubular system

Support platelet aggregation and secretion

Stimulates GPIIb/IIIa activation, enhances GPIIb/IIIa-dependent platelet-neutrophil interactions (thrombo-inflammation)

Support thrombosis formation

Deficiency in animals: does not affect haemostasis



Platelet targets & their inhibitors	Class of inhibitor	Mode of action	Antiplatelet properties	Risk of Bleeding	Route	The current level of development
PDI						
Quercetin-3-rutinoside	Small molecule	Binds to the substrate-binding b'x domain of PDI	Inhibited human and mouse platelet aggregation Inhibited thrombus formation in an animal model	Safe, it is a dietary flavonoid	Oral	Pre-clinical
Isoquercetin	Small molecule	Binds to the substrate-binding b'x domain of PDI	Decreased infarct size in the rat model of ischemic stroke Reduced thrombin generation, D-dimer formation, and soluble P-selectin level in healthy volunteers and patients.	Safe, no bleeding events reported in cancer patients during phase II trial	Oral	Clinical trials: Phase I completed Phase II completed Pre-clinical
ML359	Small molecule	Binds to the substrate-binding b'x domain of PDI	Inhibited platelet -thrombus formation in a murine model of arterial thrombosis	Unknown; has not been assessed yet	Given intravenously to mice during the pre-clinical study	
HPW-RX40	Small molecule	Binds to catalytic a' domain of PDI	Inhibited platelet aggregation, GPIIb/IIIa stimulation, diminished thrombus formation in human blood under flow conditions and protected mice from arterial occlusion	Unknown; has not been assessed yet	Given via intraperitoneal injection to mice during the pre-clinical study	Pre-clinical

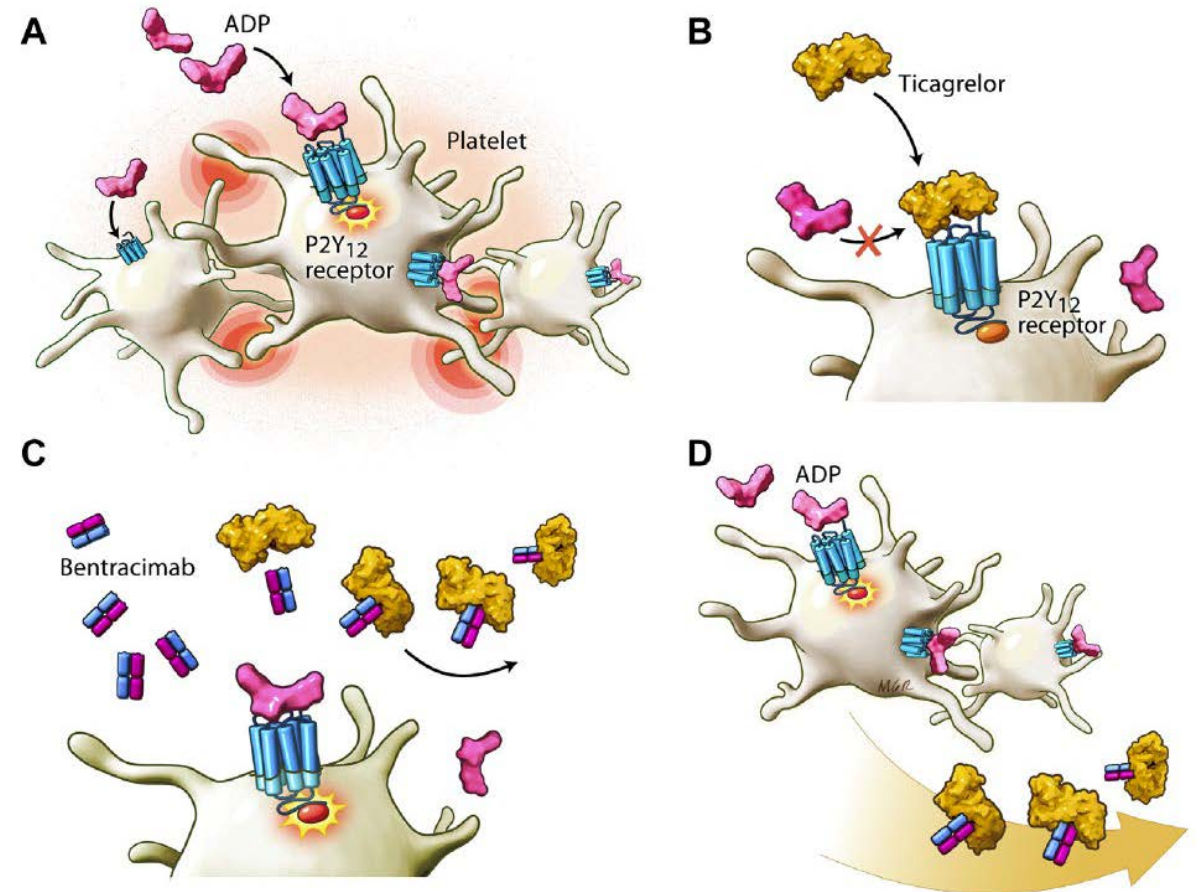
**Reversal agents
for Safer Antiplatelet Treatments?**

Population pharmacokinetic–pharmacodynamic modeling of PB2452, a monoclonal antibody fragment being developed as a ticagrelor reversal agent, in healthy volunteers

Steven J. Kathman¹ | Jeffery J. Wheeler¹ | Deepak L. Bhatt² | Susan E. Arnold³ | John S. Lee³

Bentracimab

Neutralizing monoclonal antibody fragment that binds free plasma ticagrelor and its major active metabolite,

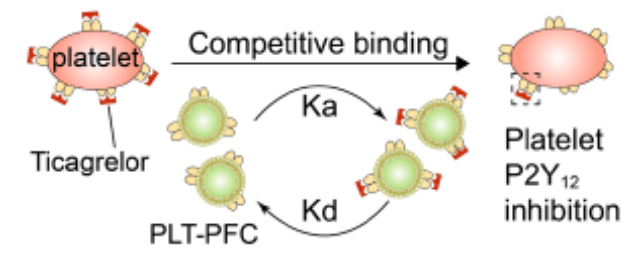
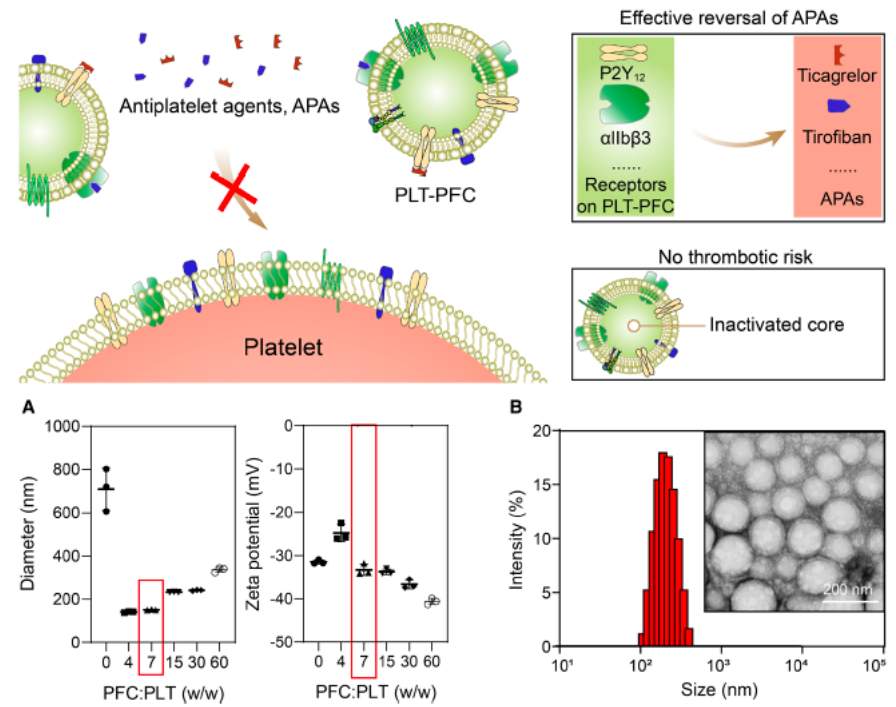
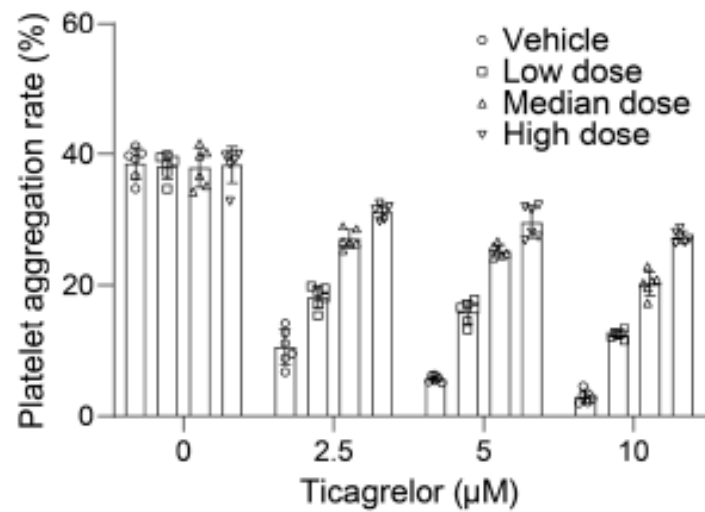
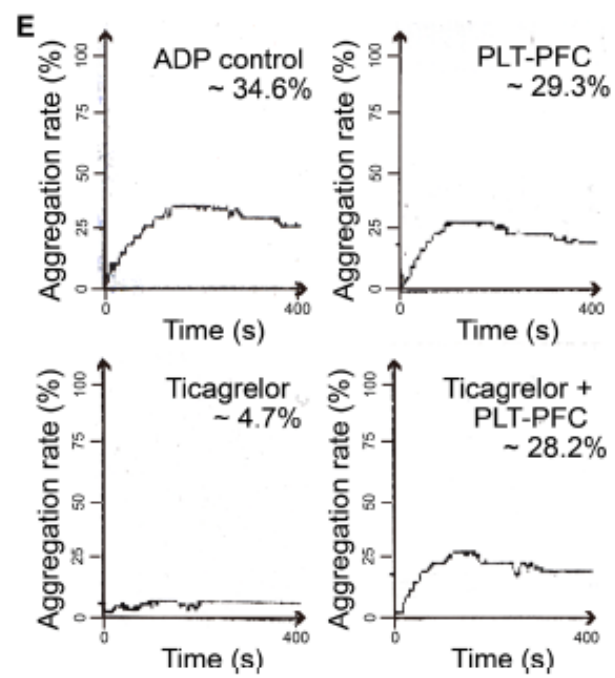


Platelet-Mimicking Nanosponges for Functional Reversal of Antiplatelet Agents

Junchao Xu*, Na Yan*, Chunling Wang, Chao Gao, Xuexiang Han, Chengzhi Yang, Jiaqi Xu, Kun Wang, Michael J. Mitchell, Yinlong Zhang, Guangjun Nie

Circ Res 2023; 132:339-54

Platelet-mimicking perfluorocarbon-based nanosponges coated with platelet membranes

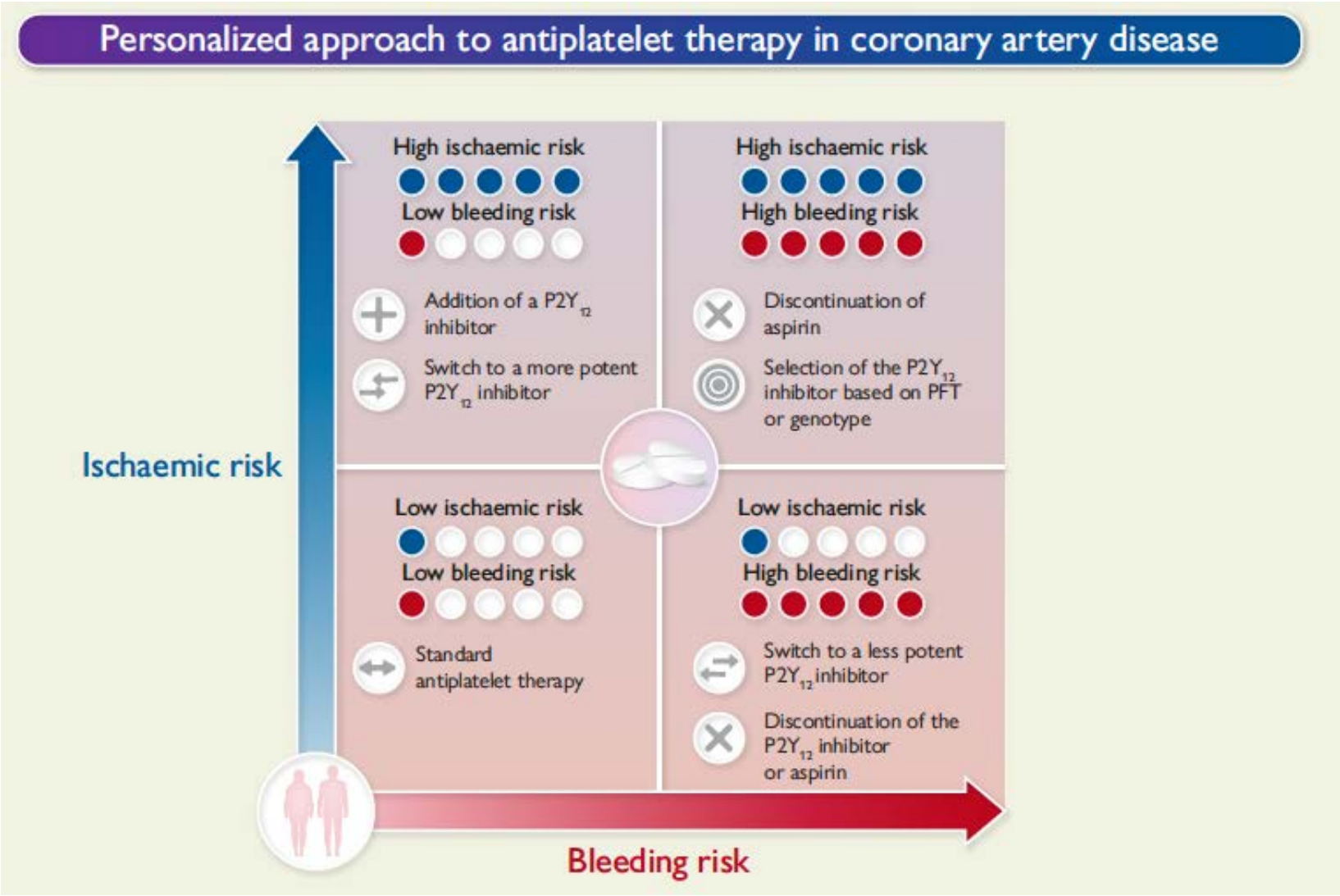


**From population to patient-centered
approaches?**

- **Studies: substantial interpatient variability in the responsiveness to antiplatelet therapy:**
 - Clinical outcomes
 - Laboratory methods
- True pharmacological resistance is *extremely rare*
- High residual on-Treatment Platelet Hyperreactivity HTPR on ASA or dual antiplatelet therapy DAPT:
 - increases the risk of future CV events
 - *Once drug interactions and non-compliance have been ruled out...*
- Low on-Treatment Platelet Reactivity LTPR
 - increases the risk of bleeding



Proposed strategies for tailoring antithrombotic therapy according to individual ischaemic and bleeding risks



Scores predicting individual ischemic and bleeding risk ?

- Many scores and risk stratifying models are available:
 - *but increased body of evidences for a fluctuation in time,
for dependency on patient characteristics including ethnicity,...*
 - Asian patients: lower rate of ischemic events after PCI compared to Caucasian, while bleeding risk is higher...

Recent standardised definition of high bleeding risk, validated in ACS and CAD in patients undergoing PCI

Validation of high bleeding risk criteria and definition as proposed by the academic research consortium for high bleeding risk

Noé Corpataux¹, Alessandro Spirito¹, Felice Gragnano¹, Lukas Vaisnora¹, Roberto Galea¹, Stefano Svab¹, Giuseppe Gargiulo², Thomas Zanchin¹, Christian Zanchin¹, George C.M. Siontis¹, Fabien Praz¹, Jonas Lanz¹, Lukas Hunziker¹, Stefan Stortecy¹, Thomas Pilgrim¹, Lorenz Räber¹, Davide Capodanno^{3,4}, Philip Urban⁵, Stuart Pocock⁶, Dik Heg⁷, Stephan Windecker¹, and Marco Valgimigli^{1,8*}

Eur Heart J 2020; 41:3743-9.

Isolated risk factor present	Nr of patients	BARC 3 or 5 (%)	Cumulative incidence	p-value	p-value
	N=16580	events	[95% CI]	vs score 0	vs 4%
			1 2 4 8 16 32		
No criteria [score 0]	n=7464	134	1.90 [1.61 - 2.25]	[Ref.]	<0.001
Age ≥75 years [minor]	n=1804	75	4.53 [3.62 - 5.67]	<0.001	0.301
Oral anticoagulation [major]	n=452	11	2.52 [1.40 - 4.50]	0.344	0.048
Chronic kidney disease [minor]	n=522	14	3.10 [1.85 - 5.19]	0.081	0.272
Chronic kidney disease [major]	n=40	4	10.97 [4.25 - 26.74]	<0.001	0.180
Hemoglobin [minor]	n=708	23	3.53 [2.36 - 5.27]	0.006	0.517
Hemoglobin [major]	n=125	10	8.89 [4.88 - 15.92]	<0.001	0.069
Prior Bleeding [minor]	n=4	0			
Prior Bleeding [major]	n=26	1	3.85 [0.55 - 24.31]	0.468	0.967
Thrombocytopenia [major]	n=45	7	16.27 [8.09 - 31.19]	0.000	0.030
Chronic Bleeding Diathesis [major]	n=2	1	50.00 [8.96 - 99.40]	0.000	0.193
Liver Cirrhosis with portal hypertension [major]	n=5	1	20.00 [3.08 - 79.62]	0.018	0.371
Long-term use NSAIDs or Steroids [minor]	n=196	9	4.77 [2.51 - 8.97]	0.006	0.619
Active malignancy [major]	n=78	8	10.83 [5.57 - 20.50]	<0.001	0.059
Prior Stroke [minor]	n=130	2	1.65 [0.42 - 6.45]	0.832	0.043
Prior Stroke [major]	n=99	2	2.19 [0.55 - 8.46]	0.865	0.235
Surgery or Trauma within 30 days [major]	n=47	5	11.06 [4.75 - 24.61]	0.000	0.131

Minor (0.5 point) and major (1 point) criteria

Academic Research Consortium
for the identification of high bleeding risk patients

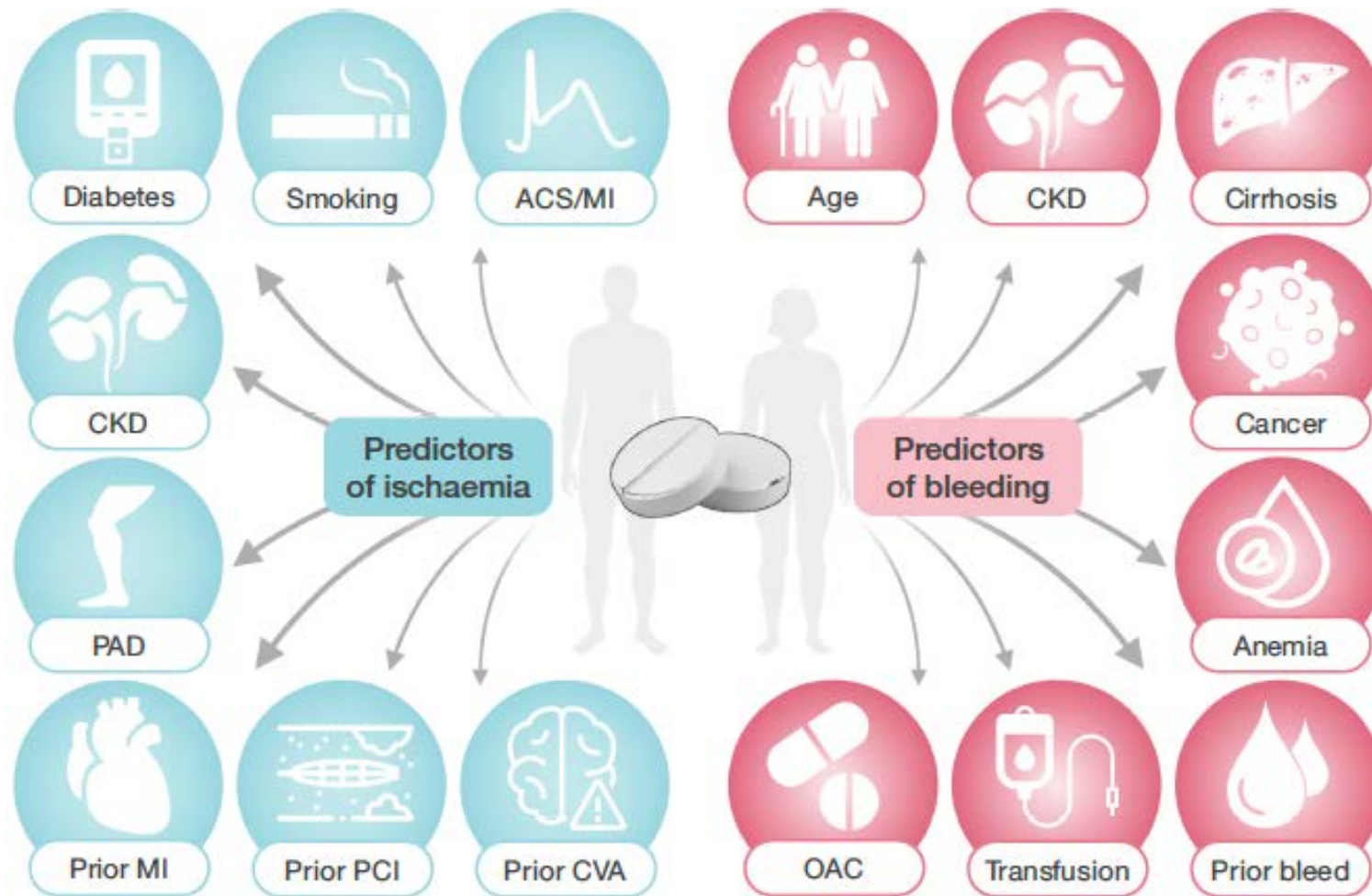
	Nr of patients	BARC 3 or 5	Cumulative incidence *		p-value	p-value
	N=16580	events	[95% CI]		vs score 0	vs 4%
				1 2 4 8 16 32		
				BARC 3 or 5 (95% CI)		
Score 0	n=7464	134	1.90 [1.61 - 2.25]		[Ref.]	<0.001
score 0.5	n=3364	123	4.01 [3.36 - 4.77]		<0.001	0.988
score 1	n=2342	128	5.98 [5.05 - 7.08]		<0.001	<0.001
score 1.5	n=1479	98	7.42 [6.13 - 8.98]		<0.001	<0.001
score 2	n=996	74	8.60 [6.90 - 10.69]		<0.001	<0.001
score 2.5	n=506	54	12.21 [9.47 - 15.66]		<0.001	<0.001
score 3	n=260	28	12.29 [8.62 - 17.36]		<0.001	<0.001
score >3	n=169	24	17.64 [12.11 - 25.30]		<0.001	<0.001

* At one year

Advanced age, anemia, thrombocytopenia, liver cirrhosis, use of oral anticoagulants, steroids or NSAID drugs, chronic kidney disease, history of spontaneous bleeding, stroke, active malignancy, chronic bleeding diathesis, planned surgery, trauma or surgery within 30 days before PCI

A number of available risk-assessment models (RAMs) stratifying ischaemic and bleeding risks

- DAPT
- PARIS
- CALIBER
- CREDO Kyoto
- Also:
 - TRA2P-TIMI 50
 - ADAPT-DES
 - HORIZON AMI
 - TRILOGY ACS
 - CRUSADE
- **Patients with acute activation of the atherothrombotic process**
 - ACS, ischaemic stroke or TIA, acute limb ischaemia
- **Extended diffuse atherosclerotic disease**
 - PAD, diffuse coronary atherosclerosis, aortic and carotid plaques
- **High burden of risk factors...**
 - Smoking, diabetes, arterial hypertension
- **... and/or comorbidities**
 - low ejection fraction < 30%, heart congestive disease, previous MI and previous PCI

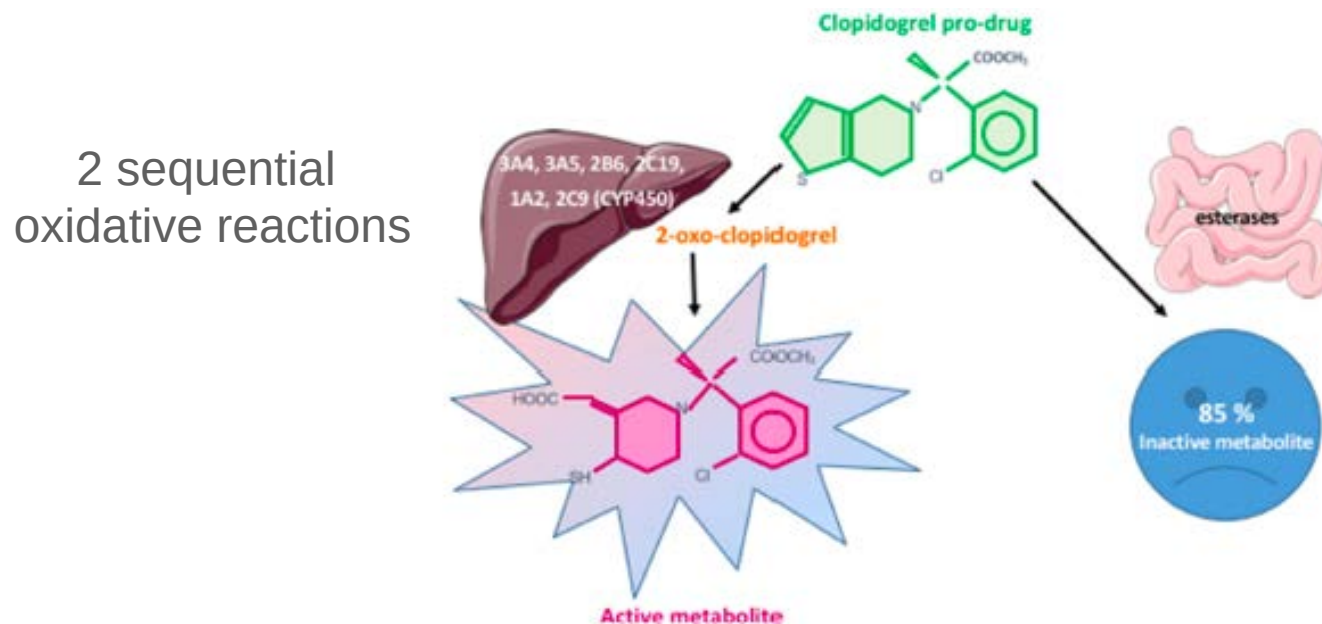


Problem: scores and RAMs which still need to be tested in prospective RCTs to verify their real predictive value in guiding antiplatelet therapy

especially that their discrimination ability in retrospective validation studies is at best... moderate-to-good, not excellent (c-index: 0.65-0.75)

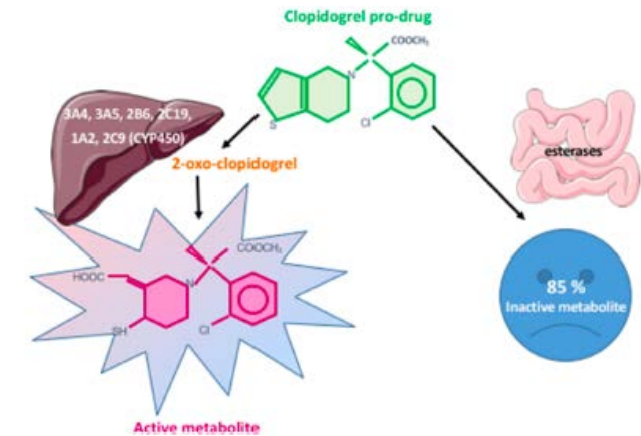
Pharmacogenomics of antiplatelet therapy ?

- ASA and clopidogrel the most studied
 - Associated with HTPR, *high residual on-treatment platelet hyperreactivity*
 - ASA: some associations, but not clinically-elavant to date
 - Clopidogrel: strongest association with CYP2C19 (***bioactivation***)



Pharmacogenomics of antiplatelet therapy ?

- Clopidogrel: CYP2C19 (bioactivation)
 - Enzyme highly variable in the population

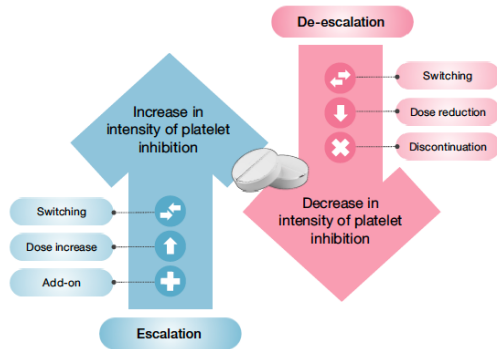


- **At least 8 alleles of various levels of activity**, classified in 4 categories
 - Ultra-rapid metabolisers having at least one increased-activity allele (*17) 20% Europe
 - **Extensive metabolisers, wild-type fully functional alleles (1*) 69.5% Europe**
 - Intermediate : one loss-of-function allele plus one functional or increased-activity allele
 - Poor metabolisers : 2 loss-of-function alleles (*2-*9): 12% Europe
- Poor active metabolite production: HTPR;
 - can be overcome by increasing the dose if loss-of-function allele only in heterozygous, but not if homozygous.

Phenotype (genotype)	Implications for clopidogrel	Therapeutic recommendations
Ultrarapid metabolisers (*1/*17, *17/*17) and Extensive metabolisers ((*1/*1)	Normal (Extensive) or increased (Ultrarapid) platelet inhibition; normal (Extensive) or decreased (Ultrarapid) residual platelet aggregation	Clopidogrel label-recommended dosage and administration
Intermediate metabolisers (*1/*2)	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Plasugrel or ticagrelor (if no contraindication)
Poor metabolisers (*2/*2)	Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	Plasugrel or ticagrelor (if no contraindication)

Clopidogrel therapy based on CYP2C19 phenotype for ACS/PCI patients initiating antiplatelet therapy

Strategy trials of modulation of antiplatelet therapy guided by genetic testing in patients undergoing PCI (treatment effect: investigational strategy vs. standard dual antiplatelet therapy)



Trial	Intervention	n	Population	Follow-up	Primary endpoint	Findings
Trials of genetic guidance						
PHARMCLO ⁷⁸	Genotype-guided de-escalation by switch	888	ACS	12 months	NACE	HR, 0.58; 95% CI, 0.43–0.78; $P < 0.001$
POPULAR GENETICS ⁷⁹	Genotype-guided de-escalation by switch	2488	ACS	12 months	NACE	ARD, -0.7%; upper limit of the 95% CI, 0.7%; $P < 0.001$ for noninferiority
ADAPT-PCI ⁸⁰	Genotype-guided escalation by switch	509	CCS or ACS	~16 months	Use of prasugrel or ticagrelor	OR, 1.60; 95% CI, 1.07–2.42; $P = 0.03$
TAILOR-PCI ⁸¹	Genotype-guided escalation by switch	1849	CCS or ACS	12 months	MACE	HR, 0.66; 95% CI, 0.43–1.02; $P = 0.06$
Al-Rubaish et al. ⁸²	Genotype-guided escalation by switch	755	ACS	12 months	NACE	OR, 0.34; 95% CI, 0.20–0.59; $P = NA$

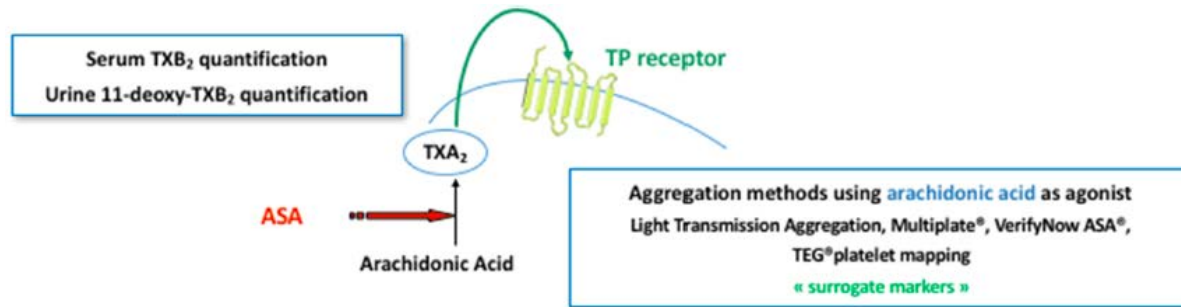
ACS: acute coronary syndrome; ARD: absolute risk difference; HPR: high platelet reactivity; LOF: loss of function; MACE: major adverse cardiac events; NACE: net adverse cardiac events; PCI: percutaneous coronary intervention; PFT: platelet function testing.

Global validation of genotype-guided antiplatelet treatment modulation in that setting?

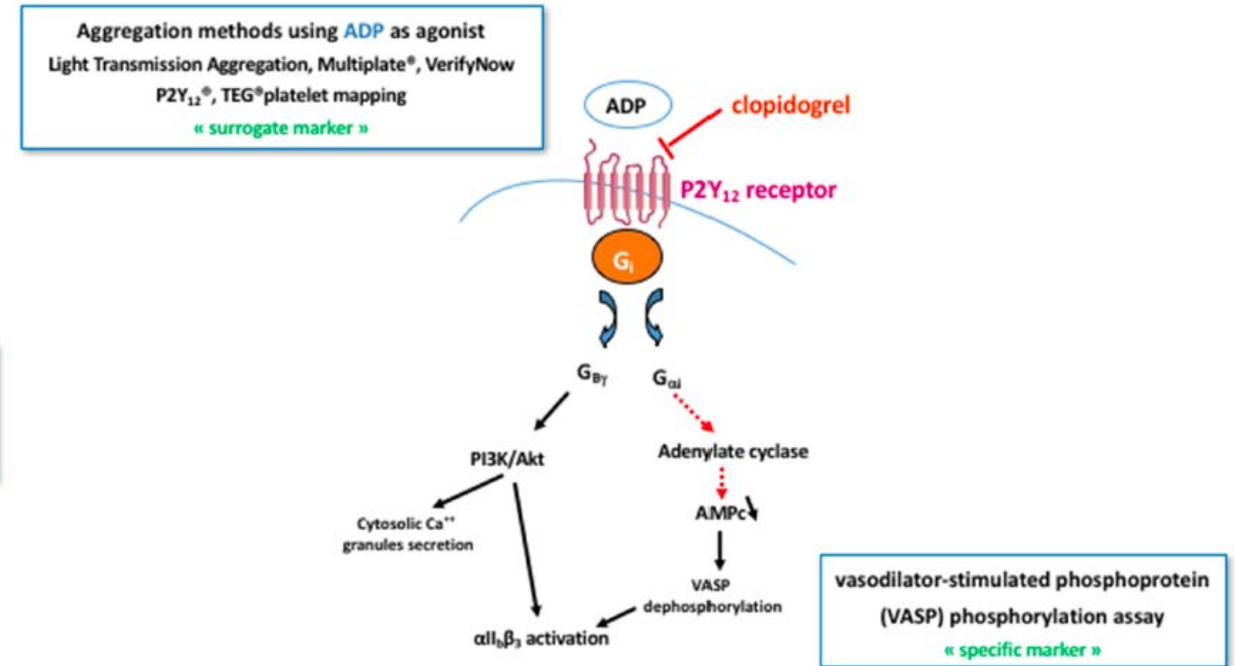
Acute ischemic stroke, TIA and cerebrovascular intervention: all has still to be done...

Platelet function tests for modulation ?

- Which test should be used?



ASA



Clopidogrel

Platelet function tests for modulation ?

Prevalence of poor biological response to clopidogrel

A systematic review

Nora Mallouk¹; Carine Labruyère^{2,3}; Jean-Luc Reny^{4,5}; Céline Chapelle²; Michèle Piot¹; Pierre Fontana⁶; Jean-Christophe Gris⁵;
Xavier Delavenne¹; Patrick Mismetti^{1,2}; Silvy Laporte^{1,2,3}

Thromb Haemost 2012; 107: 494–506

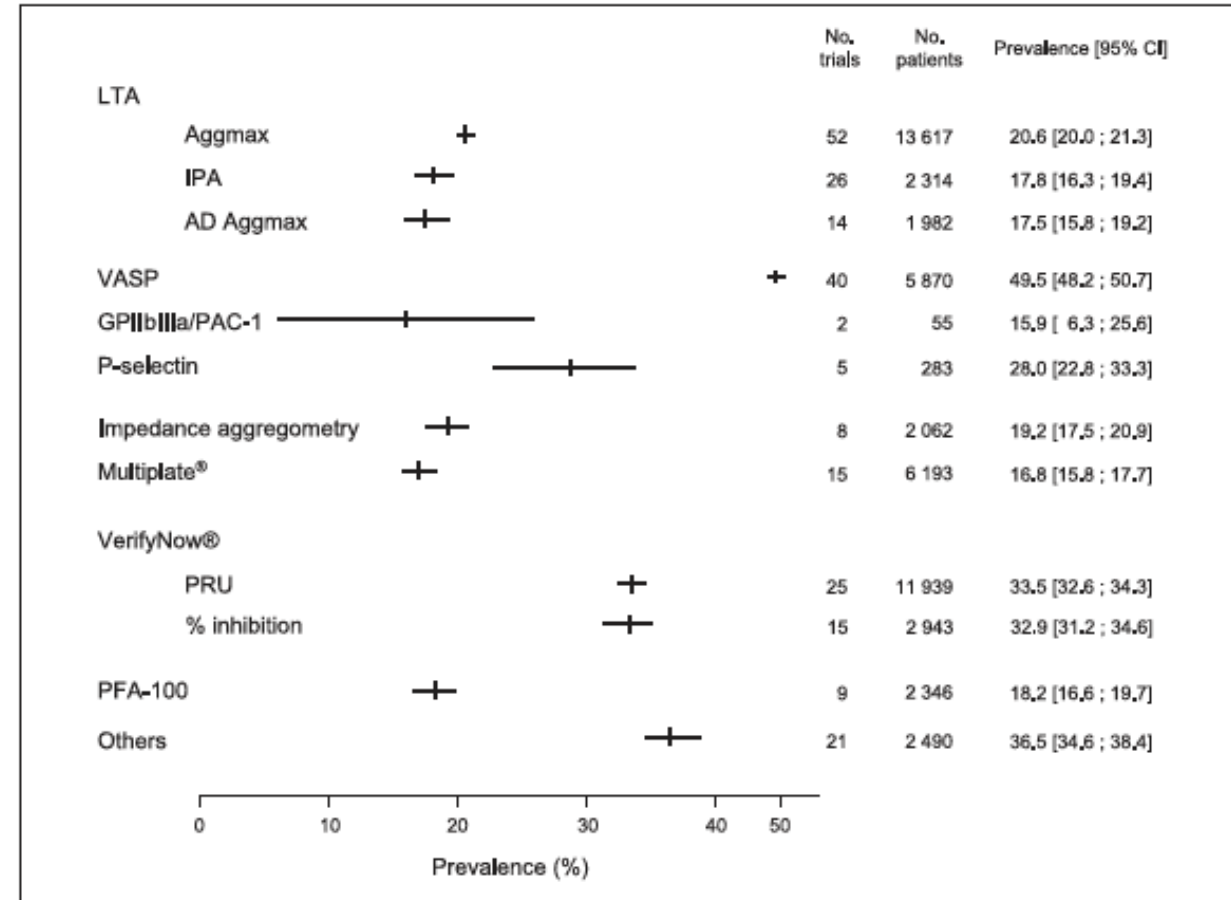
171 publications, 45,664 patients

Poor biological response to clopidogrel:

from 15.9% to 49.5%

according to the platelet function assay employed!

**No gold standard method
for clinical application
is yet identified, standardised and validated!**



Platelet function tests for modulation ?

Strategy trials of modulation of antiplatelet therapy guided by platelet function testing in patients undergoing PCI

(treatment effect: investigational strategy vs. standard dual antiplatelet therapy)

Trial	Intervention	n	Population	Follow-up	Primary endpoint	Findings
Trials of PFT guidance						
ARCTIC ⁷⁴	PFT-guided escalation or de-escalation by switch or dose adjustment	2240	CCS or ACS	12 months	MACE	HR, 1.13; 95% CI, 0.98–1.29; <i>P</i> = 0.10
ANTARCTIC ⁷⁵	PFT-guided escalation or de-escalation by switch or dose adjustment	877	ACS	12 months	NACE	HR, 1.00, 95% CI 0.78–1.29; <i>P</i> = 0.98
TROPICAL ACS ⁷⁶	PFT-guided de-escalation by switch	2610	ACS	12 months	NACE	HR, 0.81; 95% CI, 0.62–1.06; <i>P</i> = 0.0004 for noninferiority
PATH-PCI ⁷⁷	PFT-guided escalation by switch	2237	CCS	6 months	NACE	HR, 0.68, 95% CI, 0.49–0.95; <i>P</i> = 0.023

Low-risk patients

High-risk patients

Multiplate

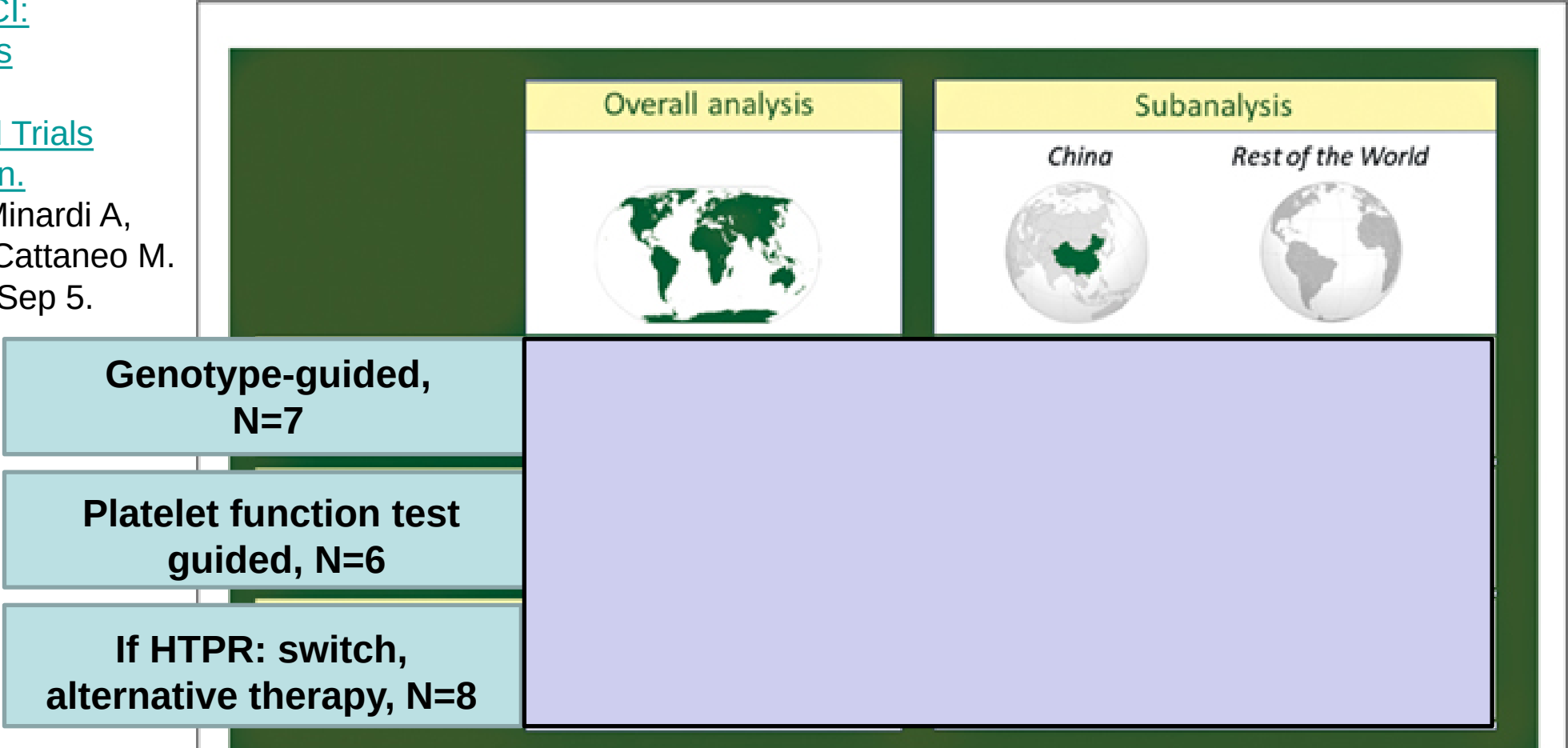
Chinese bedside device PL-12

ACS: acute coronary syndrome; ARD: absolute risk difference; HPR: high platelet reactivity; LOF: loss of function; MACE: major adverse cardiac events; NACE: net adverse cardiac events; PCI: percutaneous coronary intervention; PFT: platelet function testing.

Some promising results in high-risk patients?

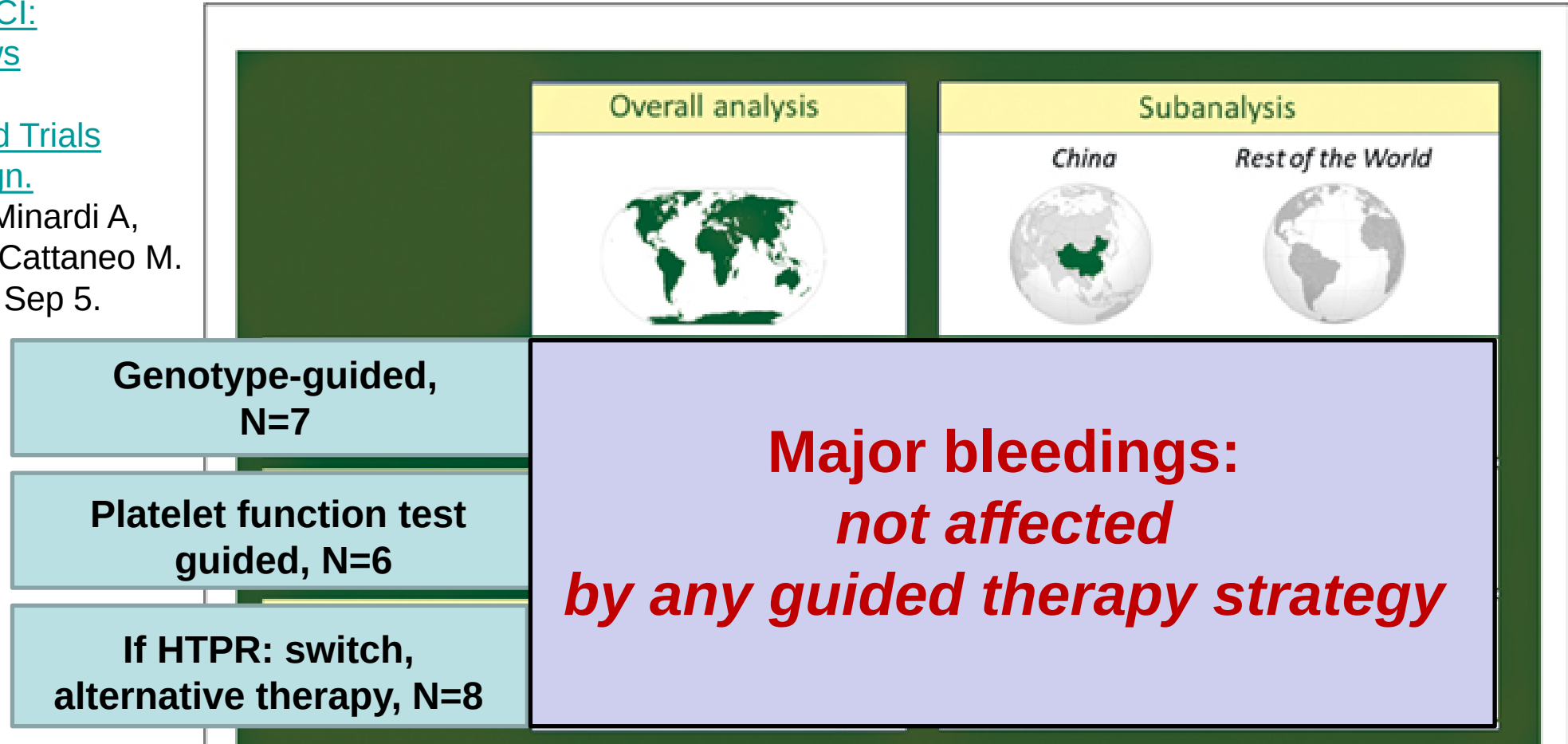
Guided Anti-P2Y12 Therapy
in Patients Undergoing PCI:
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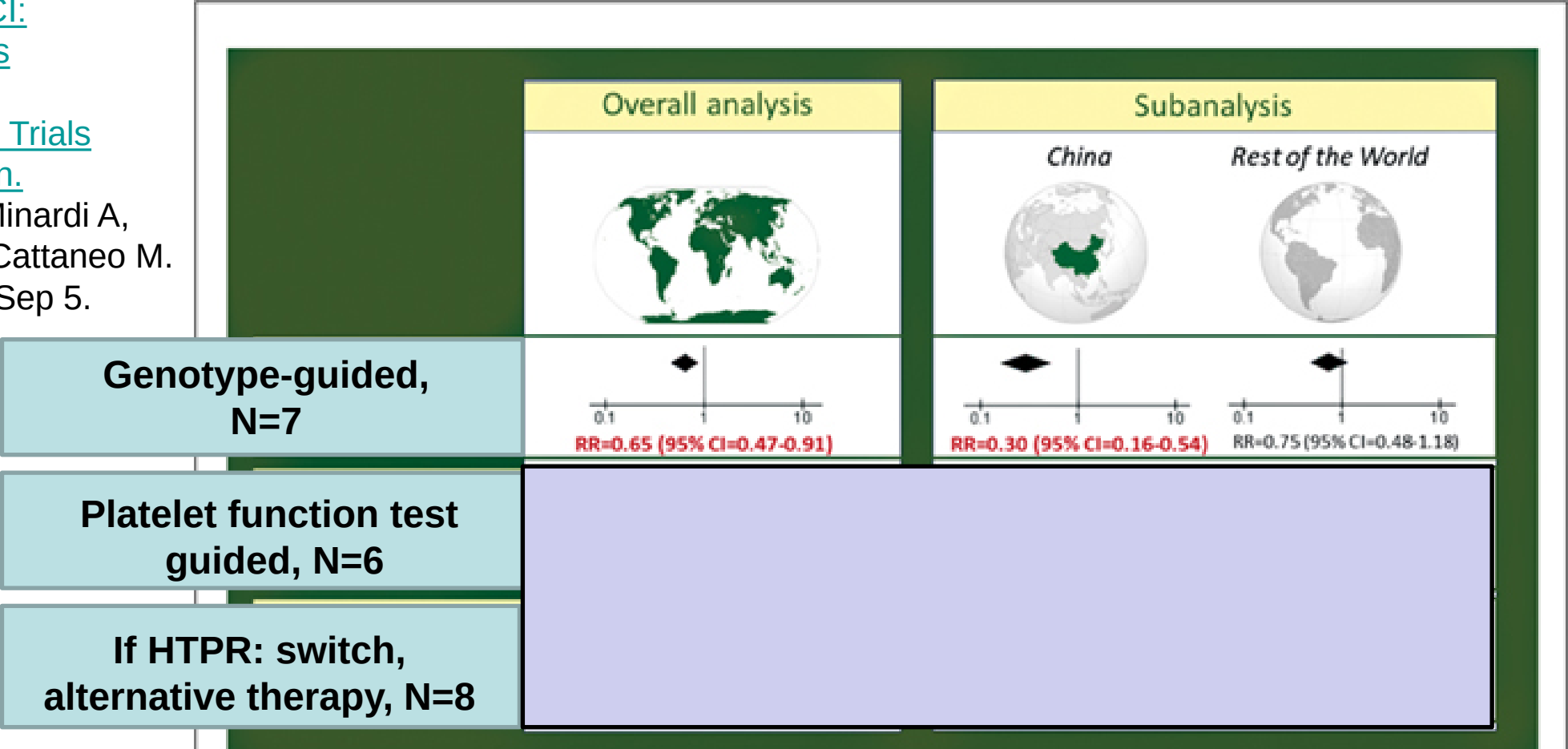
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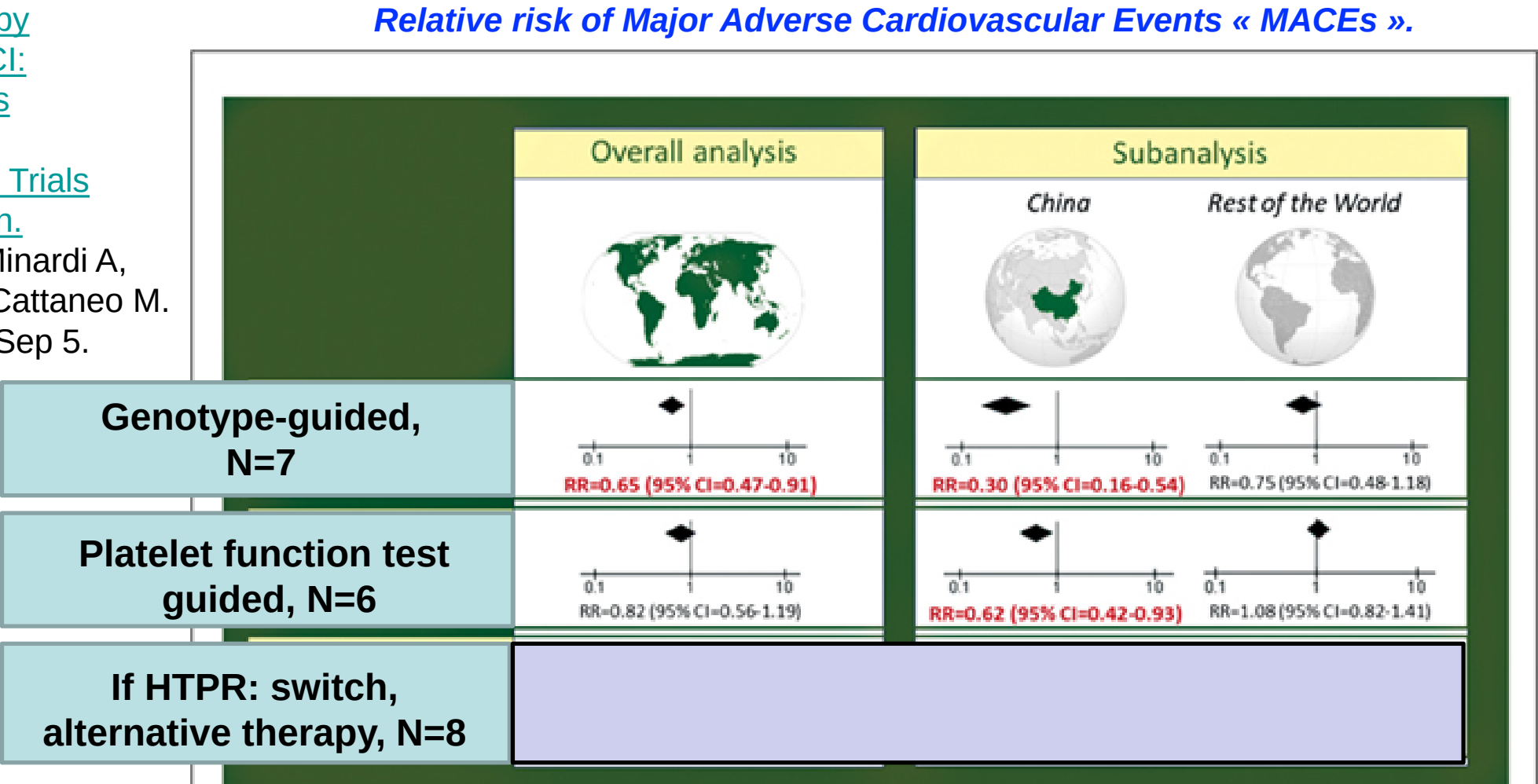
Relative risk of Major Adverse Cardiovascular Events « MACEs ».



MACEs:
overall, reduced by Genotype-Guided Therapy, but only in China

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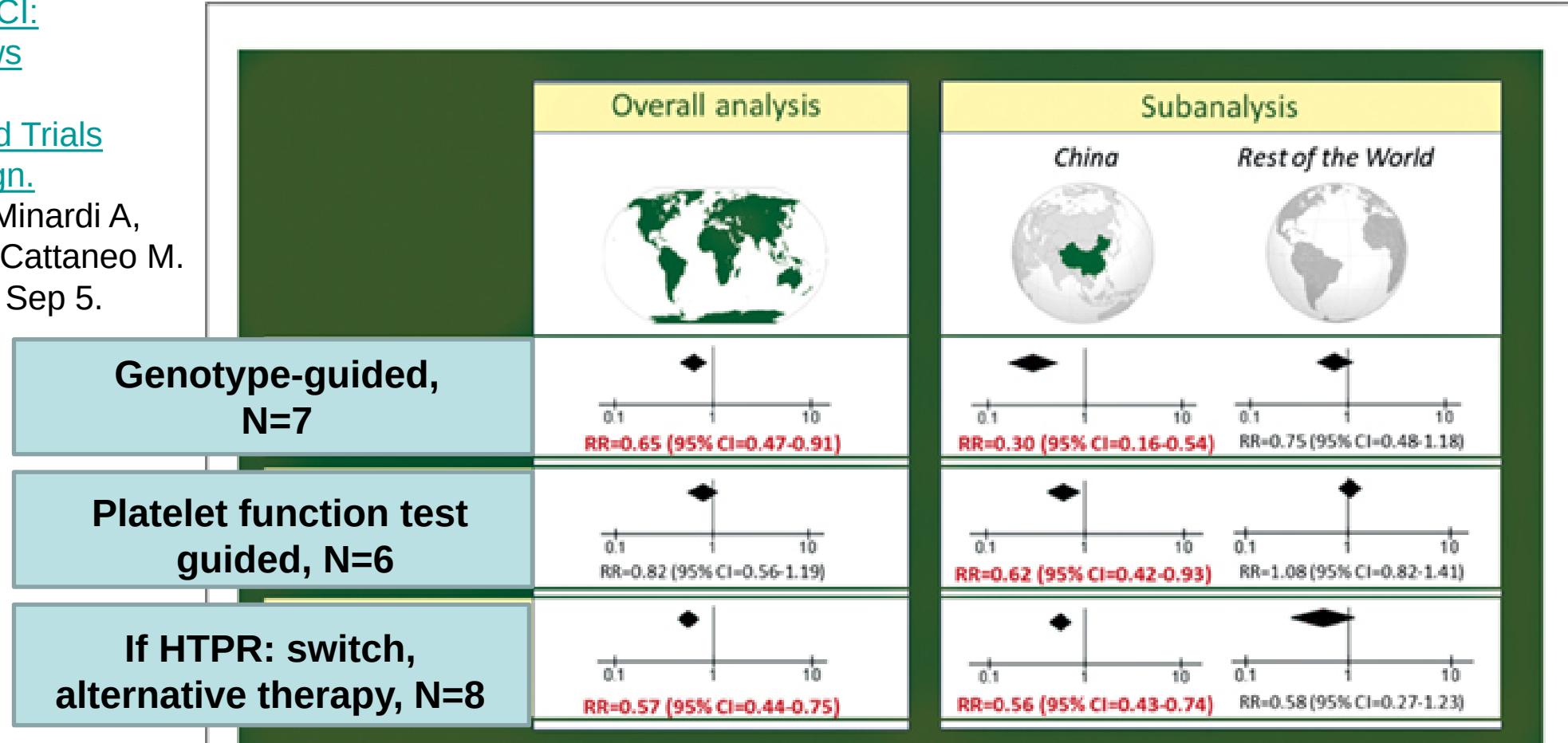


MACEs:
overall, not reduced by Platelet Function Test-guided Therapy, *but in China*

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Relative risk of Major Adverse Cardiovascular Events « MACEs ».



MACEs:

Platelet Function Test-Guided therapy performed poorly compared to HTPR-Therapy, likely due to inaccurate identification of HTPR patients by platelet function tests.

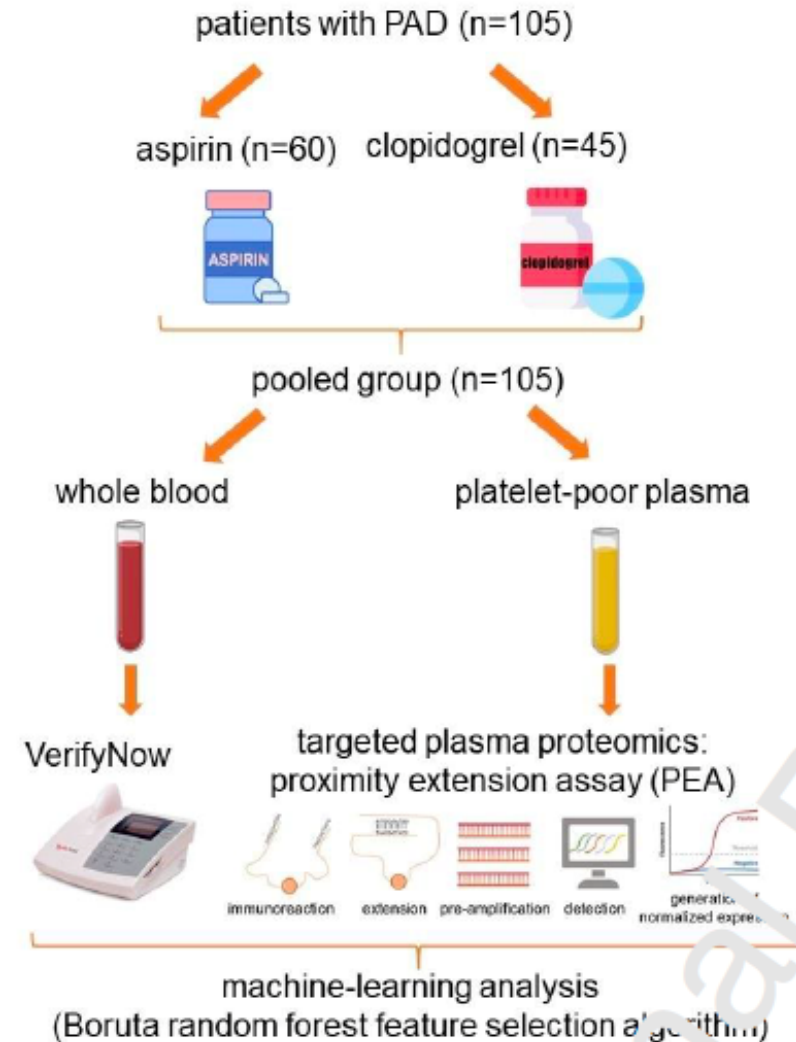
Plasma protein signatures ?

Journal Pre-proof

Plasma protein signatures for high on-treatment platelet reactivity to aspirin and clopidogrel in peripheral artery disease

Baidildinova G^{1,2}, Pallares Robles A^{1,2}, ten Cate V^{2,3,4}, Kremers BMM⁵, Heitmeier S⁶, ten Cate H^{1,2,7}, Mees BME⁸, Spronk HMH^{1,7}, Wild PS^{2,3,4,9}, ten Cate-Hoek AJ^{5,7*}, Jurk K^{2,3,4*}.

Thromb Res 2023; 230:105-118.



Plasma protein signatures ?

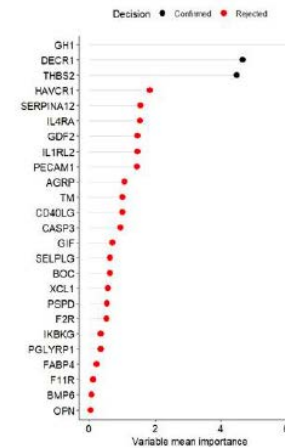
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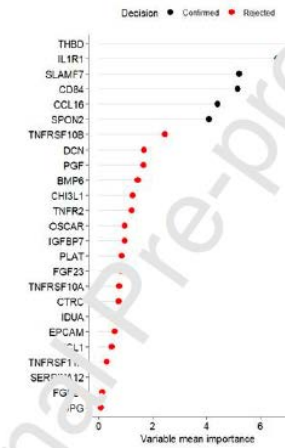
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<https://doi.org/10.1016/j.thromres.2023.08.017>

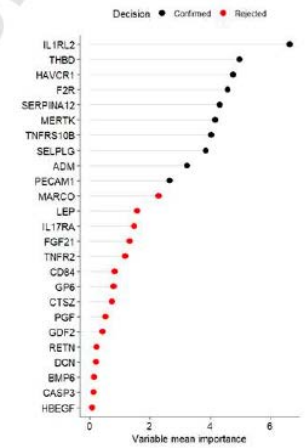
A – aspirin



B – clopidogrel



C – pooled



Associated with increased VerifyNow ASPI-test value:

Aspirin:

Growth hormone-1 (GH)
2,4-dienol-CoA-reductase, mitochondrail (DECR1)
Thrombospondin 2 (TSP-2)

Clopidogrel:

Thrombomodulin (TM)
Interleukin-1 receptor antagonist protein (IL1RT1)
SLAM family number 7 (SLAM7)
CD84 (SLAMF5)
C-C motif chemokine 16 (CCL16)
Spondin-2 (SPON2)

It was a dark
and stormy night.



Conclusion

- **Many areas of development deserve further investigation**

- Safer drugs in the pipeline
- Development of effective and safe reversal compounds
- The optimal, cost-effective use of laboratory facilities
 - Pharmacogenomics
 - If it applies...
 - Platelet function testing
 - If we can validate a robust and easy-to-apply clinically-relevant one
 - Proteomics?
 - to be prospectively confirmed on clinical outcomes



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- **The move towards patient-centered precision medicine**

- risk stratification for both bleeding and thrombosis
 - Prospectively-validated tool(s)?
- Validated linkage with the selection of appropriate agents
 - Drug, optimal dose, therapy duration

University
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- Haematology
- UMR UA11 INSERM
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