



ICT 2023

28th International
Congress on Thrombosis

Personalized medicine in thrombosis

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*Member of the ESC Committee for Practice
Guidelines*

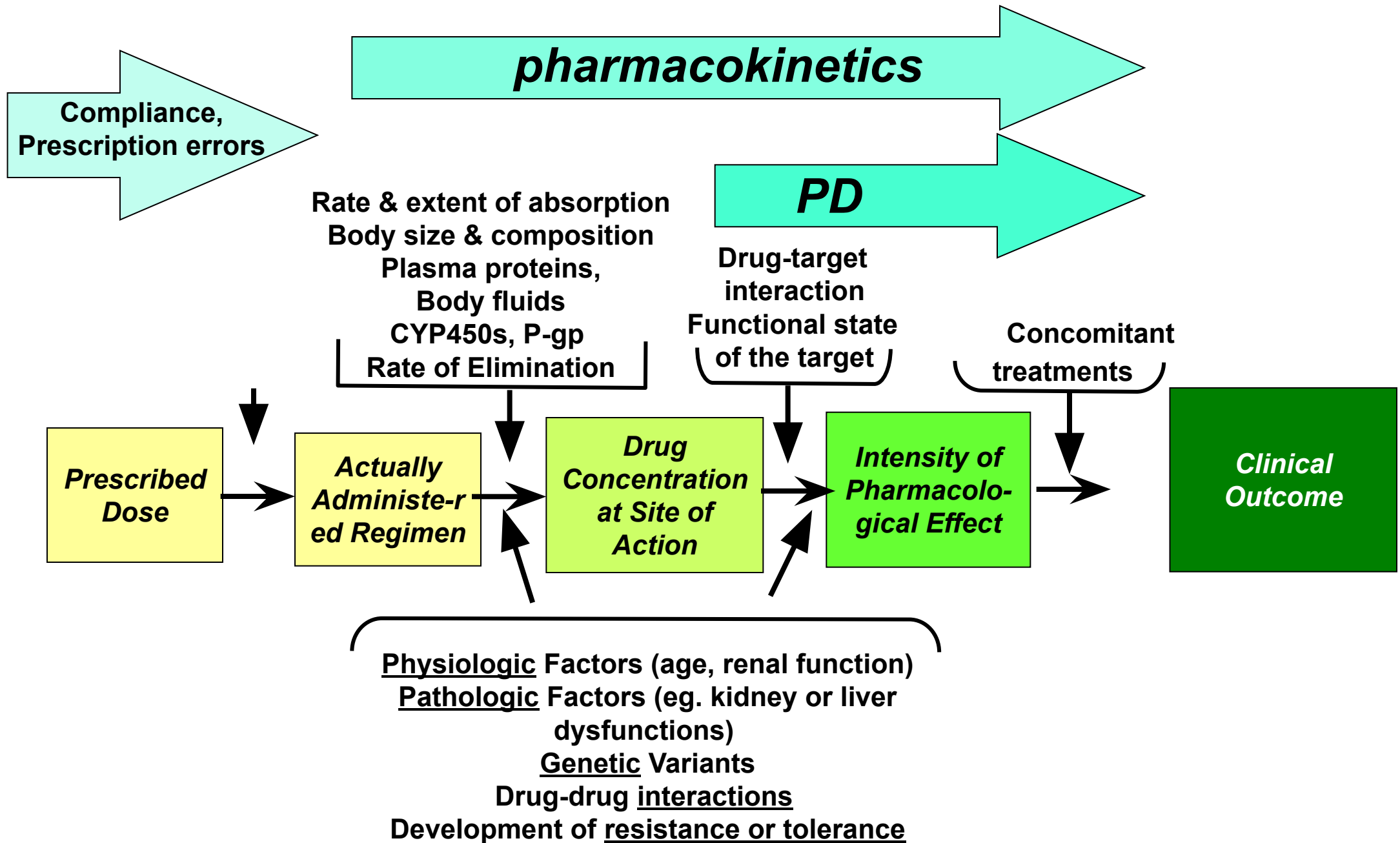
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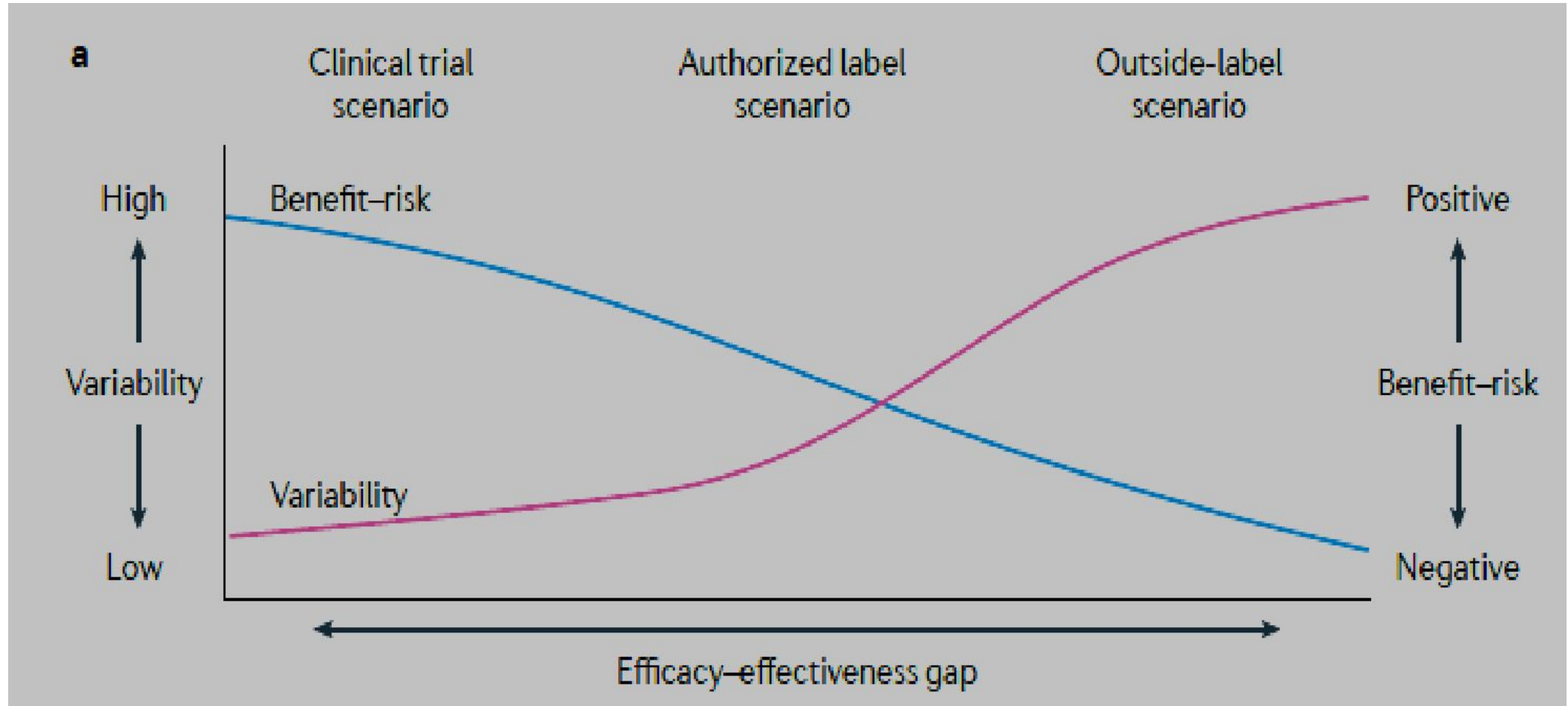


My Conflicts of Interest:

- Research grant from the Italian Medicines Agency (AIFA) for studies on acetylsalicylic acid in Essential Thrombocythemia
- Research grant from Cancer UK for studies on acetylsalicylic acid in cancer
- Investigator-initiated research grant from Bayer AG for rivaroxaban in diabetes
- Consulting fee from Aboca SRL for substance-based medical devices



Understanding the determinants of inter-individual variability in drug response and reducing variability can improve drug effectiveness in the real world



PRECISION DOSING



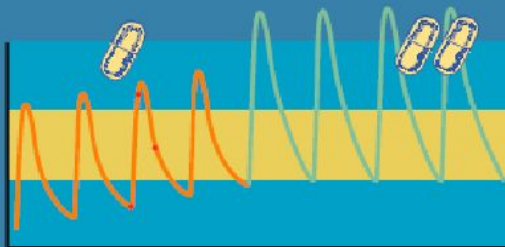
Too Little



Just Right



Too Much



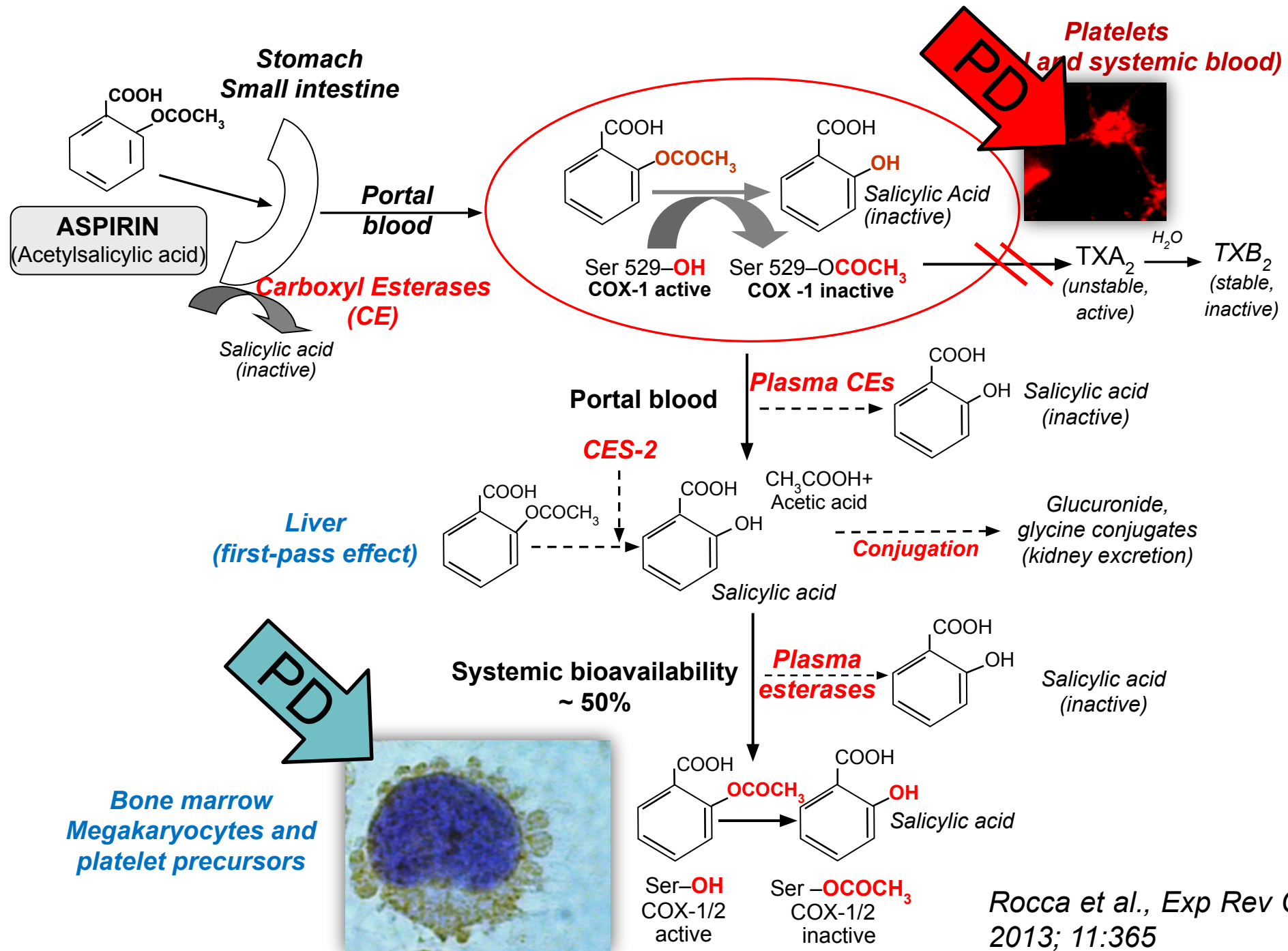
GOLDILOCKS PRINCIPLE

Identifying a **drug regimen** that **maximizes** the **benefit/risk** balance at the level of the **individual patient.**

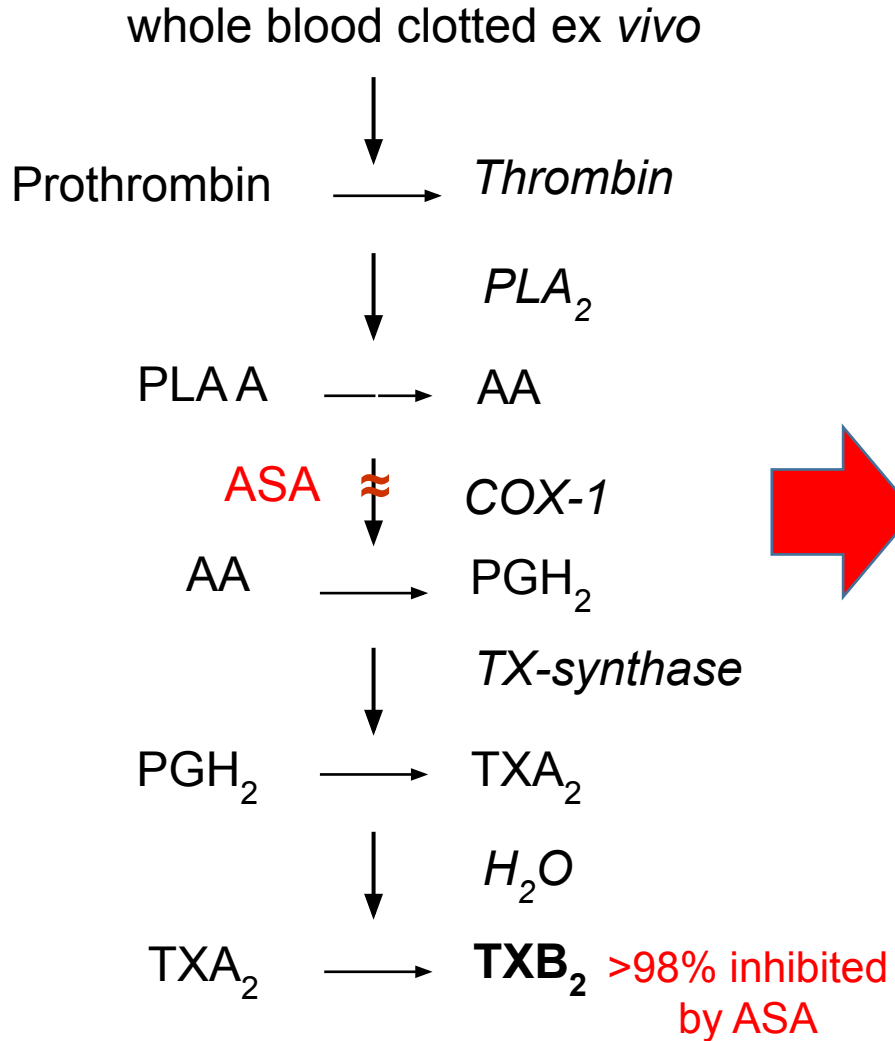
Maxfield et al., JAMA 2021;15:1505

Tools for identifying determinants of variability and develop precision dosing (pharmacomics)

- **Robust and reliable measure** of drug response (pharmacodynamics-PD) or pharmacogenetics, possibly **validated** as surrogate biomarker of clinical efficacy: the case of aspirin
- **Strong hypotheses on specific and identifiable** populations: the case of aspirin and clopidogrel
- *In silico* PK/PD drug **modelling & simulation** for precision dosing: the case of aspirin and clopidogrel

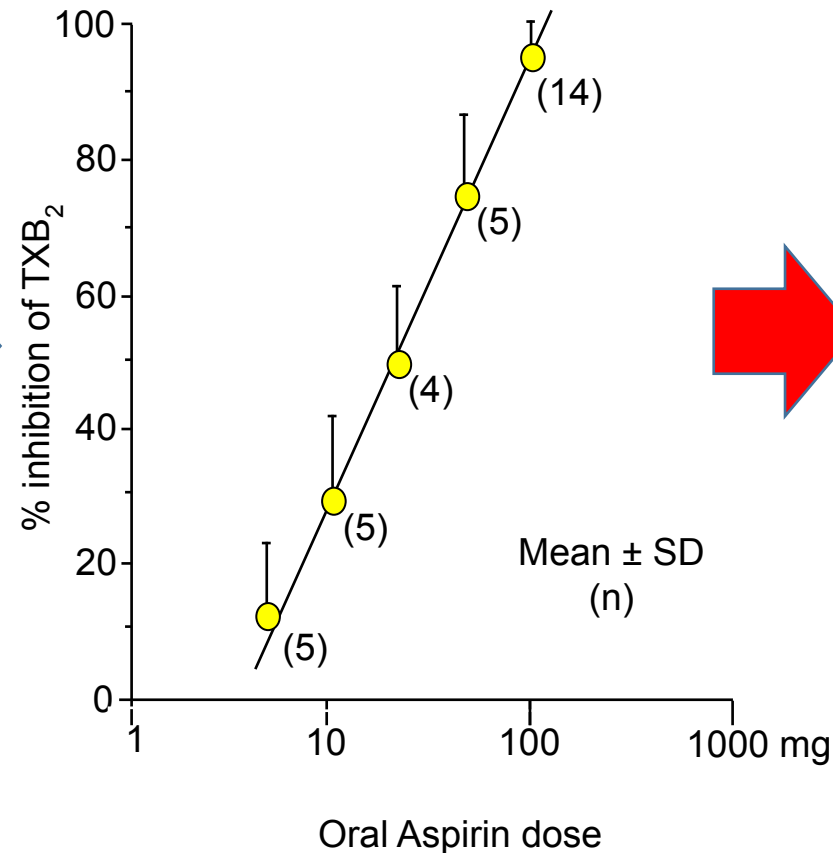


Serum thromboxane (TXB)₂: a biomarker of COX activity in platelets and aspirin PD



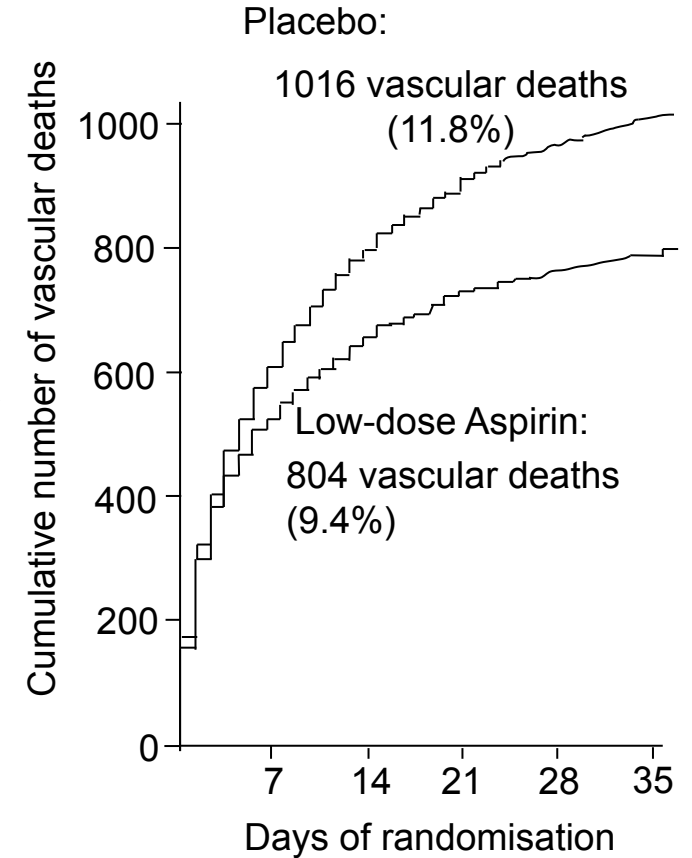
Patrino et al, Thromb Res 1980

Clinical Pharmacology of Platelet COX-1 and low-dose aspirin



Patrignani et al., J Clin Invest 1982

Validation in Clinical Trial of High Risk CV patients



ISIS-2, Lancet 1988

Serum TXB₂ *ex vivo*: a biomarker surrogate of ASA efficacy required for the approval of new aspirin formulations: a tool for precision dosing



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 25 July 2002

Doc. Ref: EMEA/CPMP/EWP/282/02/Final

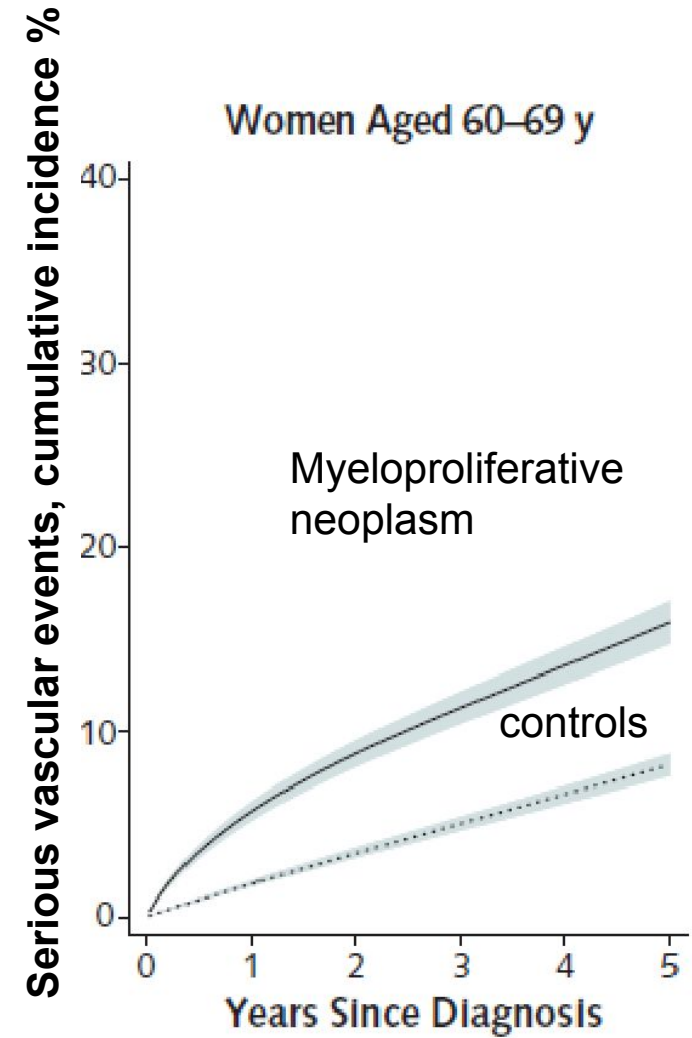
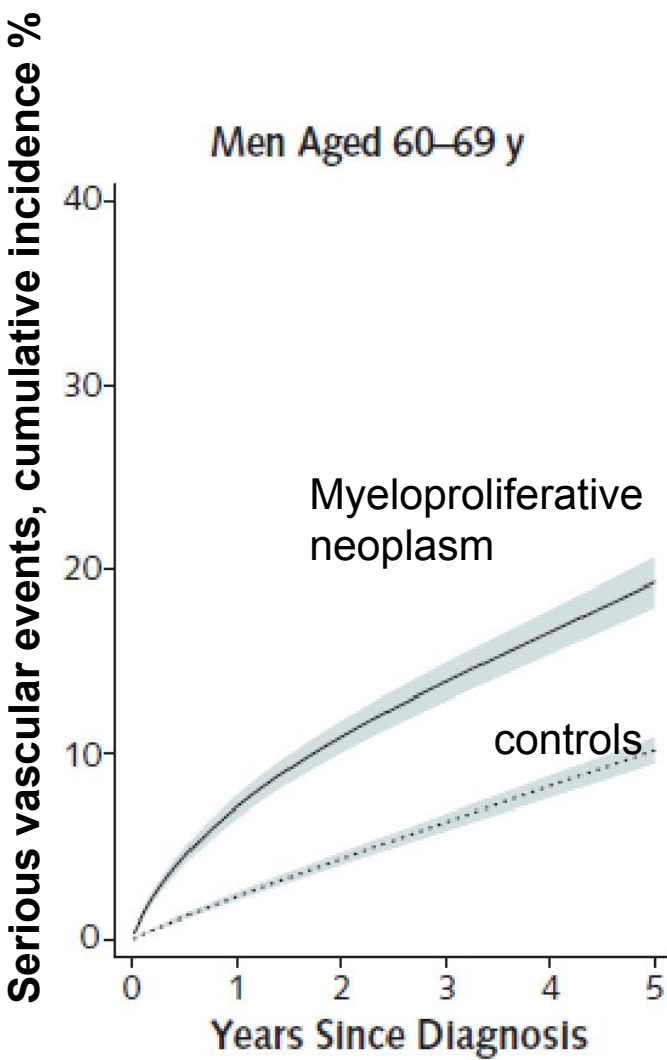
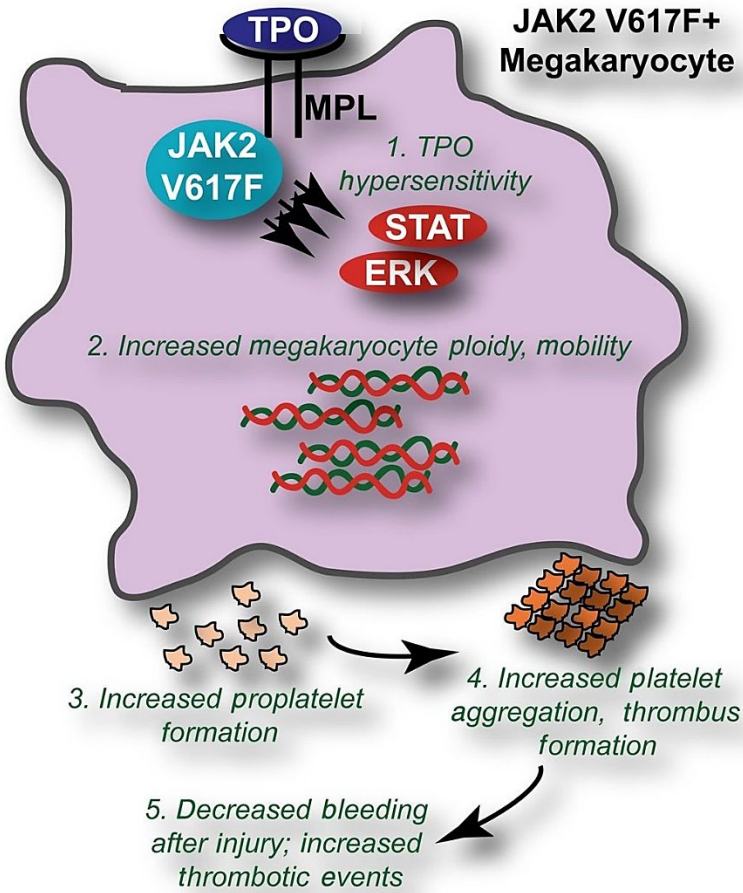
POSITION PAPER ON THE REGULATORY REQUIREMENTS FOR THE AUTHORISATION OF LOW-DOSE MODIFIED RELEASE ASA FORMULATIONS IN THE SECONDARY PREVENTION OF CARDIOVASCULAR EVENTS

*[...] the reduction of TXB₂ levels **in serum (not in plasma)** can be considered as a widely accepted **surrogate** for platelet aggregation and **for efficacy** in secondary prevention of cardiovascular events [...]*

Tools for identifying determinants of variability and develop precision dosing

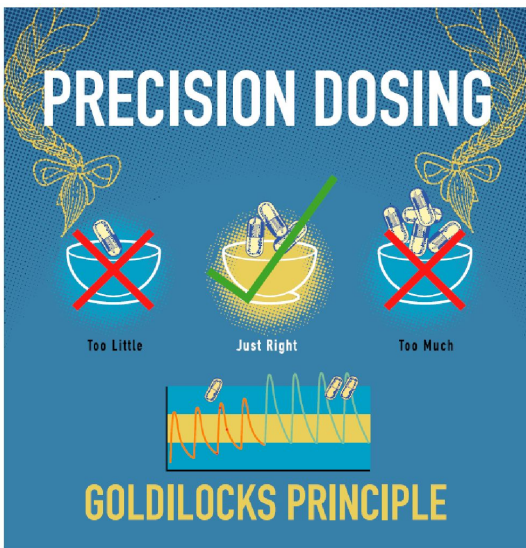
- Robust and reliable measure of drug response (pharmacodynamics-PD) or pharmacogenetics, possibly validated as surrogate biomarkers of clinical efficacy
- **Strong hypotheses on specific and identifiable populations with clear difference in drug response:**
 - Chronic and acute settings of high platelet turnover- aspirin
 - (Dys)Metabolic conditions: obesity- aspirin and clopidogrel
 - Genetic background- clopidogrel

Essential Thrombocythemia (ET): rare chronic status of high megakaryocyte and platelet turnover with increased major vascular events in spite of antiplatelet therapy



Fleischman and Tyner; Blood 2013;122:3705

Hultcrantz et al., Ann Int Med 2018



The 'Goldilocks Hypothesis':
too little ASA dosing for ET patients?

Newly released platelets with unacetylated COX-isozyme(s) released over the standard **dosing interval of 24 hours** might contribute to the **variable (poorer) aspirin responsiveness** in ET and need **more frequent** rather than higher daily dosing

A randomized trial of different **A**spirin **R**egimens to optimize antiplatelet therapy in **E**sSential thrombocythemia (**A**RES)



Part A: double blind, placebo controlled, randomized phase 2 trial

245 ET patients on chronic 100 mg once-daily ASA randomized to 2-week ASA:

100 mg *once-daily* 100 mg *twice-daily* 100 mg *three times daily*

Select the dosing regimen producing:

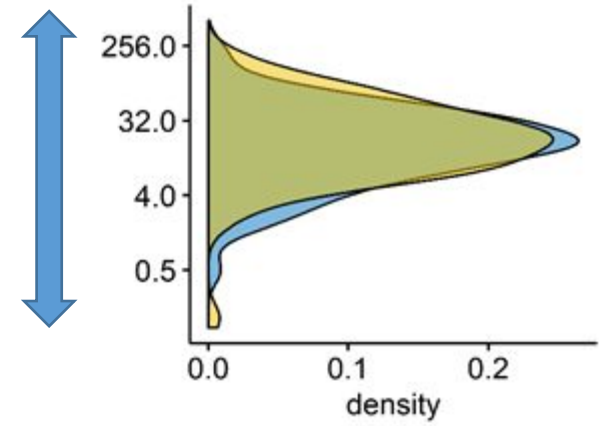
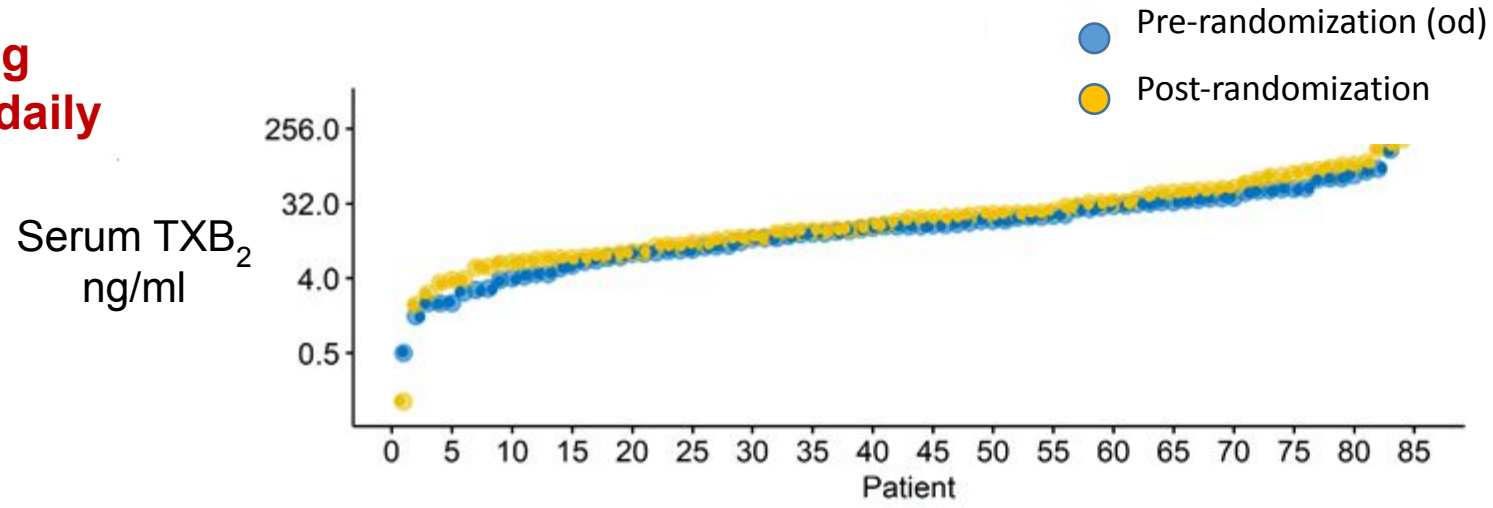
- 1) a significantly lower serum TXB₂ (biomarker surrogate of efficacy) and
- 2) non-inferior prostacyclin excretion (biomarker surrogate of safety) vs. 100 mg od

Part B: open label, randomized phase 2 trial

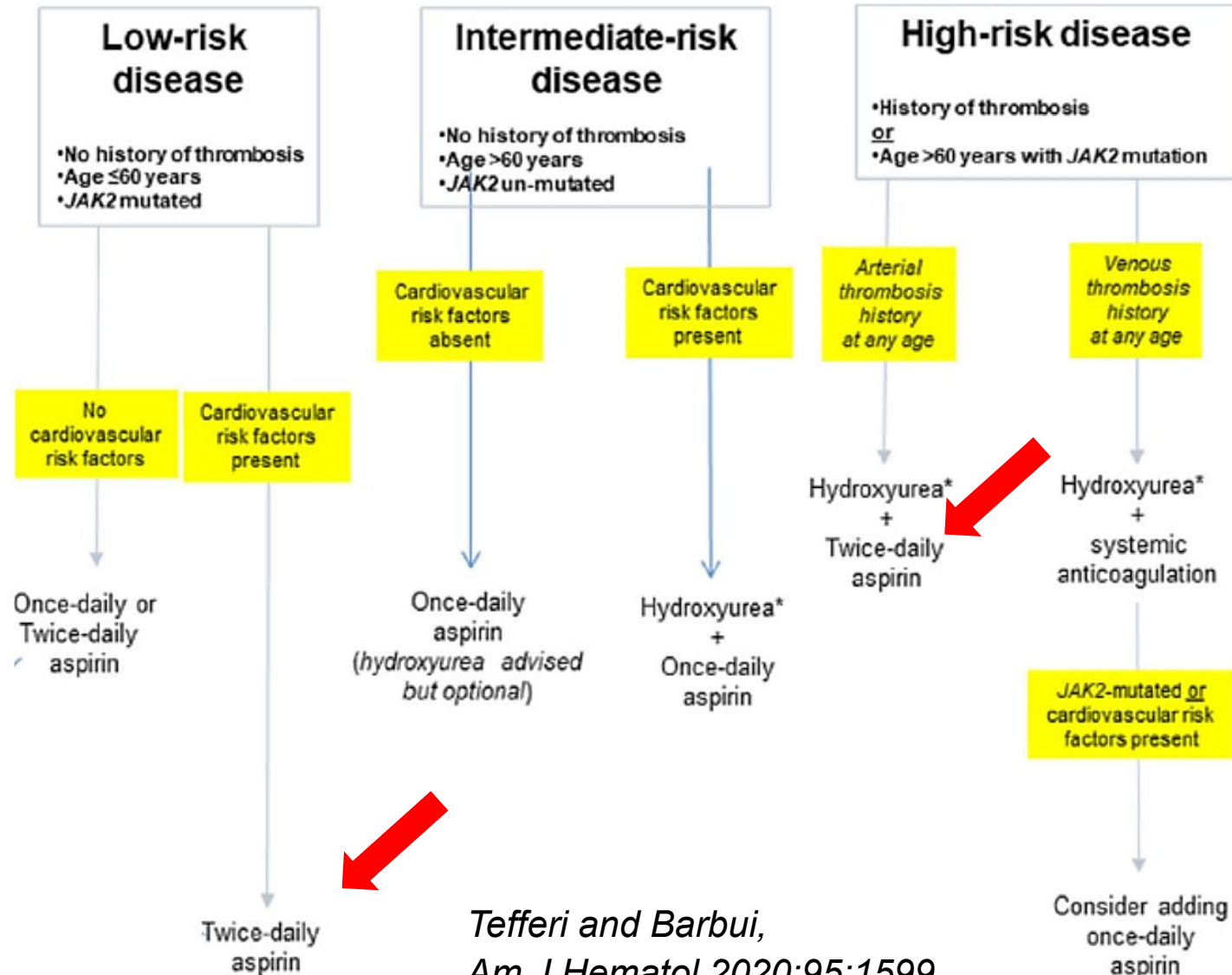
250 ET patients randomized to 20 months of:
100 mg od vs. the optimized regimen identified in Part A

Repeated serum TXB₂ measures every 3 months to assess the **long term persistence** of superior biochemical efficacy and **safety** of the optimized regimen

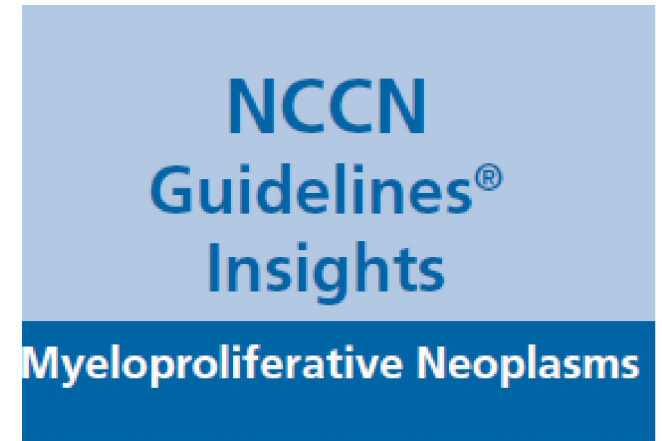
**100 mg
once-daily**



Current therapeutic recommendations for primary and secondary thrombosis prevention in essential thrombocythemia



Tefferi and Barbui,
Am J Hematol 2020;95:1599.



In carefully selected patients, **twice-daily** aspirin at a 100 mg dose has been found to be superior to once-daily aspirin (100 mg), a finding that is yet to be confirmed in randomized controlled studies.

https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf V3.2022



Obesity: the pharmacokinetic challenge!

Drug Distribution

- adipose tissue mass and Volume of distribution for lipophilic drugs
- lean body mass, and Volume of distribution for hydrophilic drugs
- modified lean/total mass ratio
- tissue perfusion
- changes in plasma protein binding
- cardiac output
- splanchnic blood flow
- hepatic function

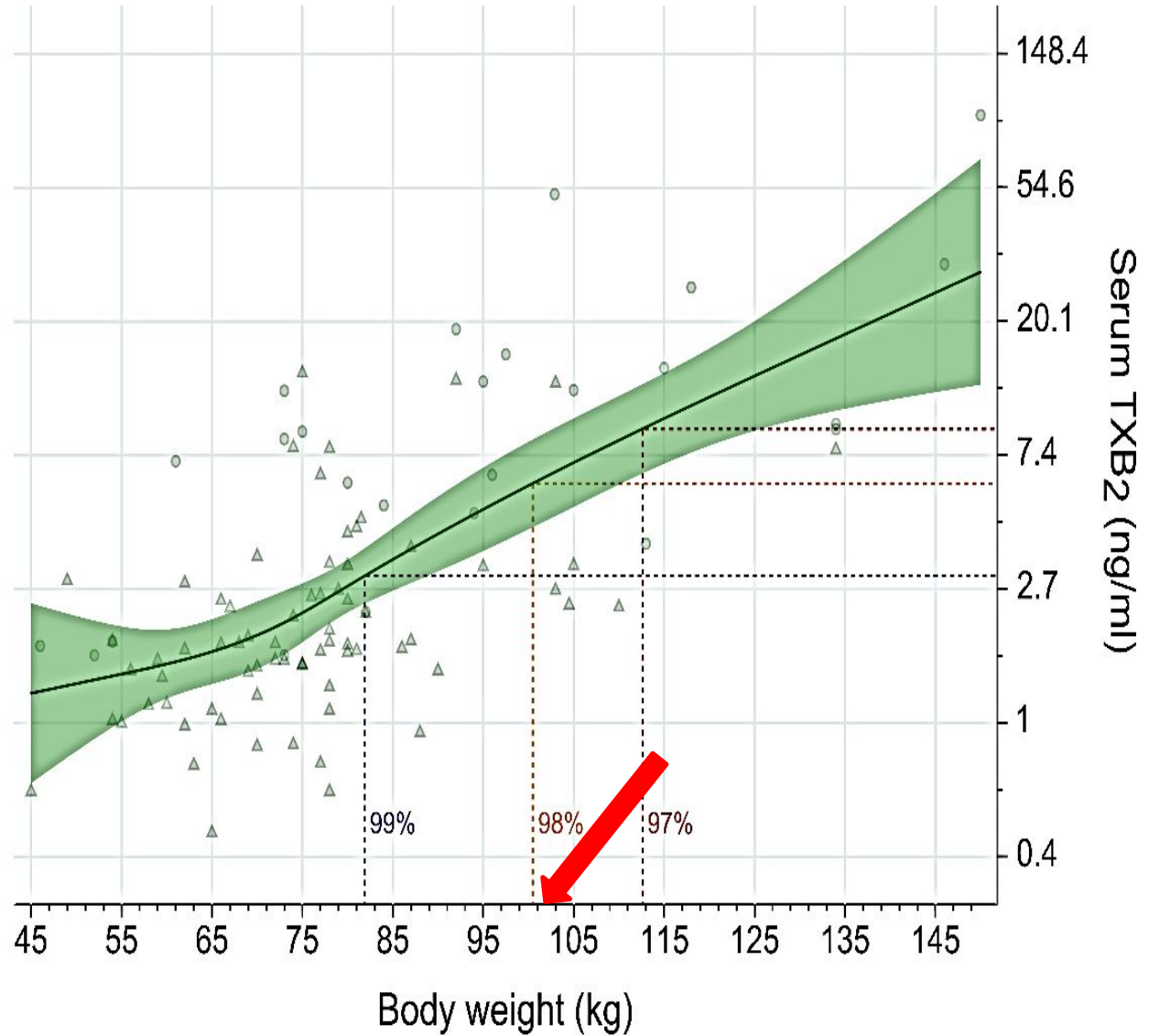
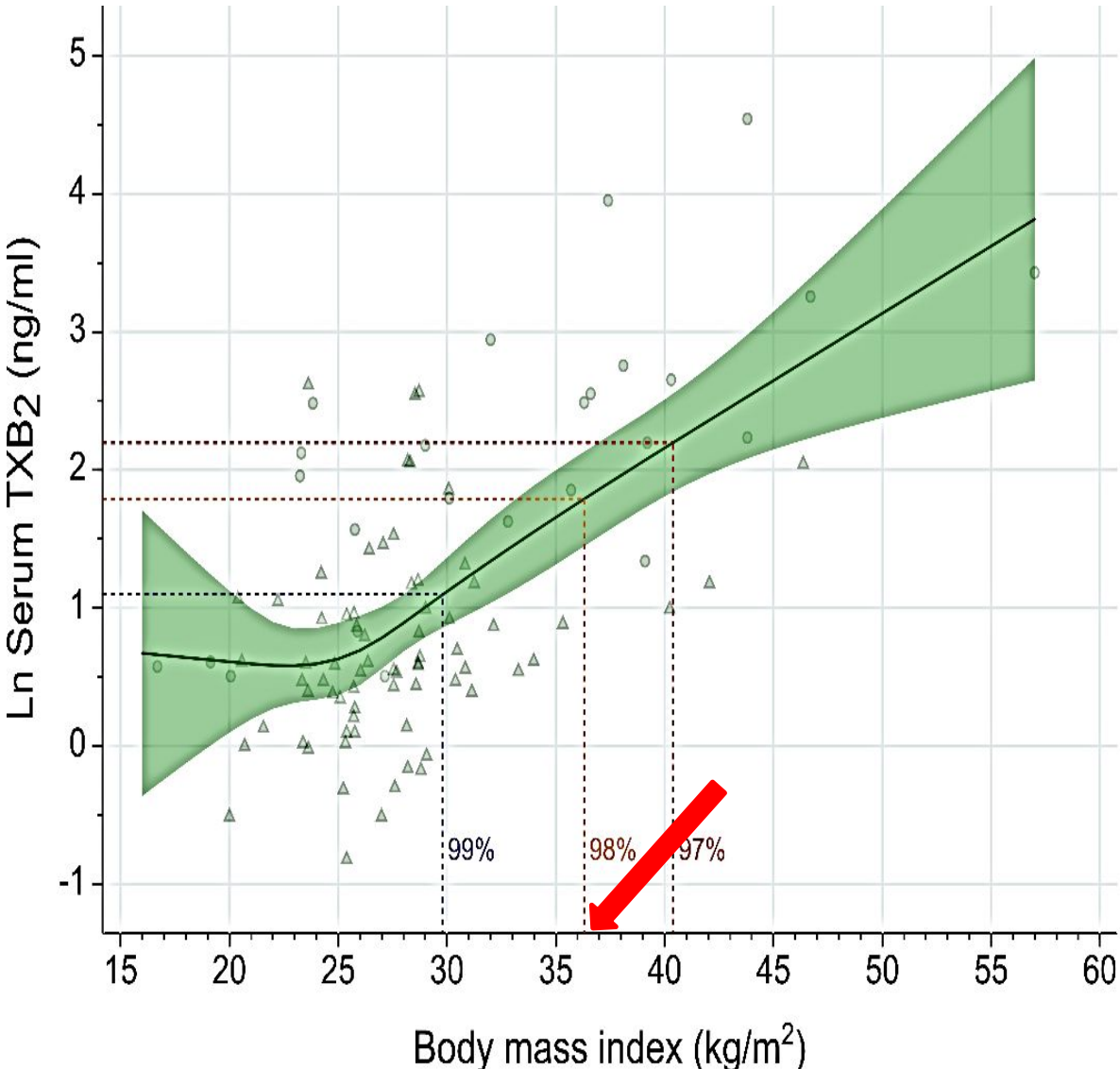
Biotransformation

- activity of CYP2E1
- glucuronidation and sulfation phase II enzymes
- 3A4 activity, 2C9, 2C19, 2D6, 1A2

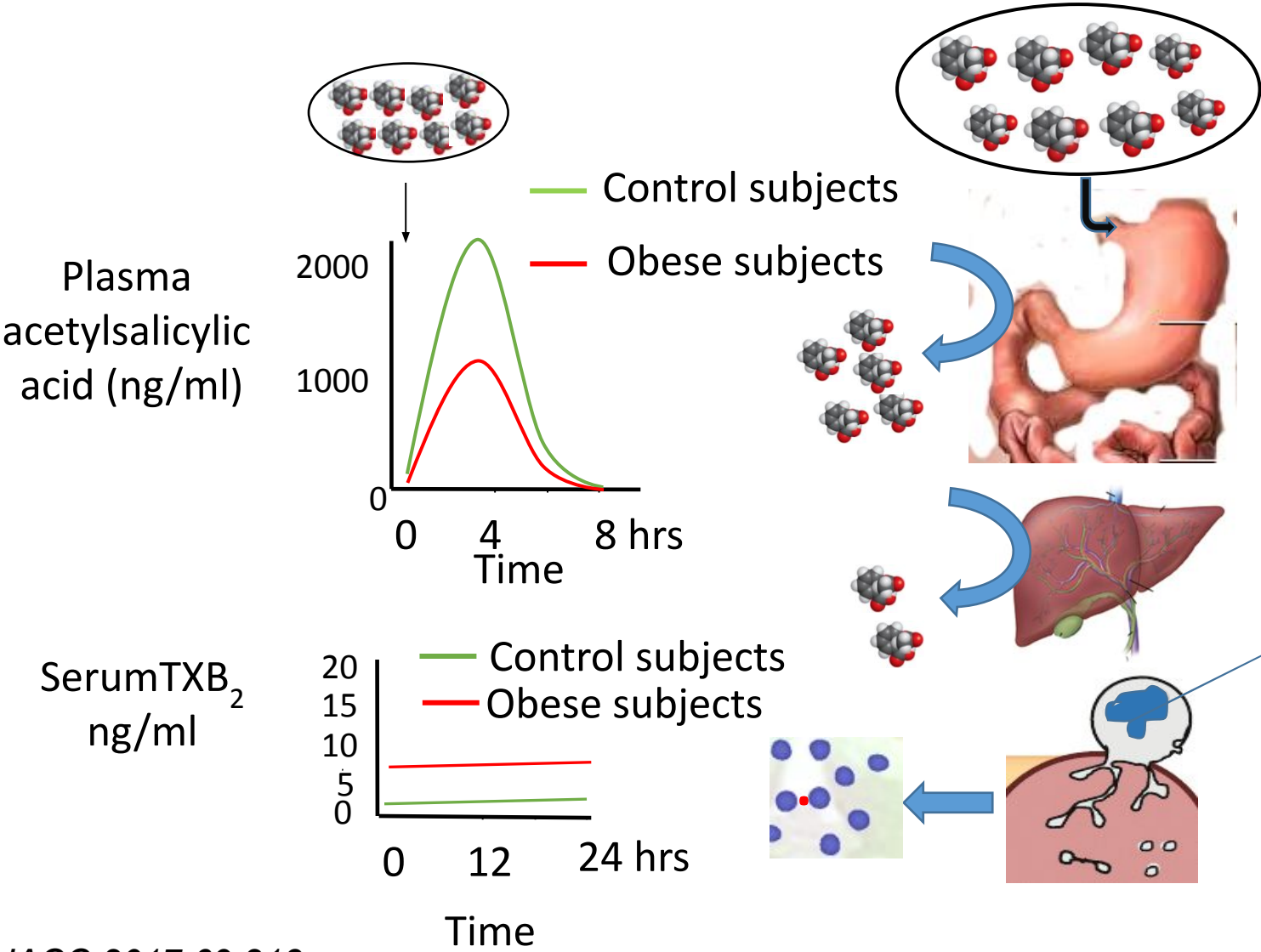
Excretion

- estimation of glomerular filtration rate depends on diverse body size descriptors
- GFR due to increased kidney weight (in the absence of co-morbidities)
- changes in tubular secretion and reabsorption

High residual serum TXB₂ at 24 hours is exponentially correlated with body size in 100 subjects on standard low-dose aspirin (100 mg/od)

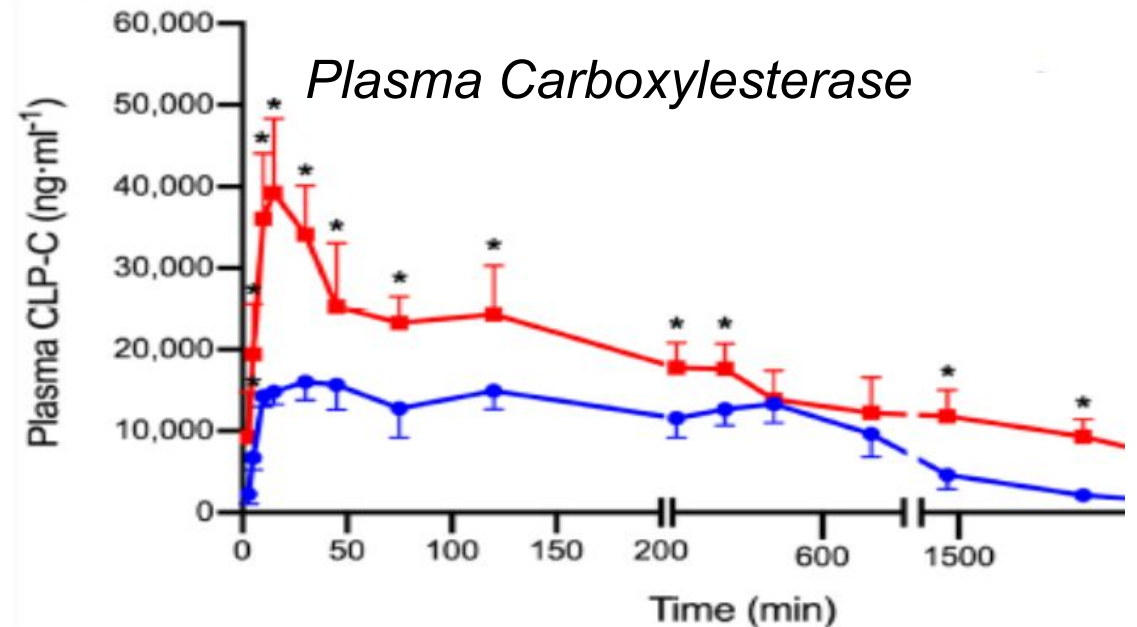
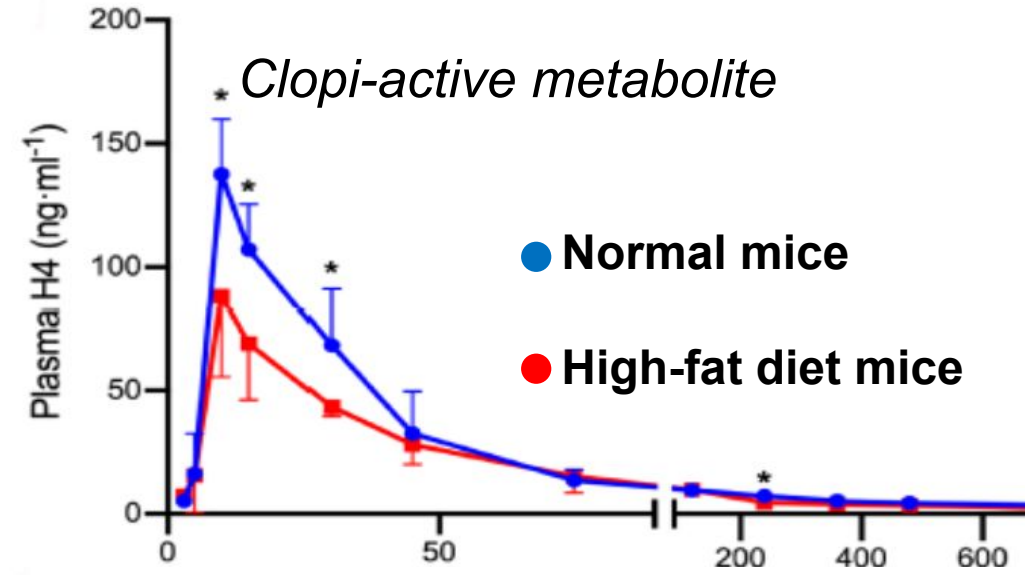
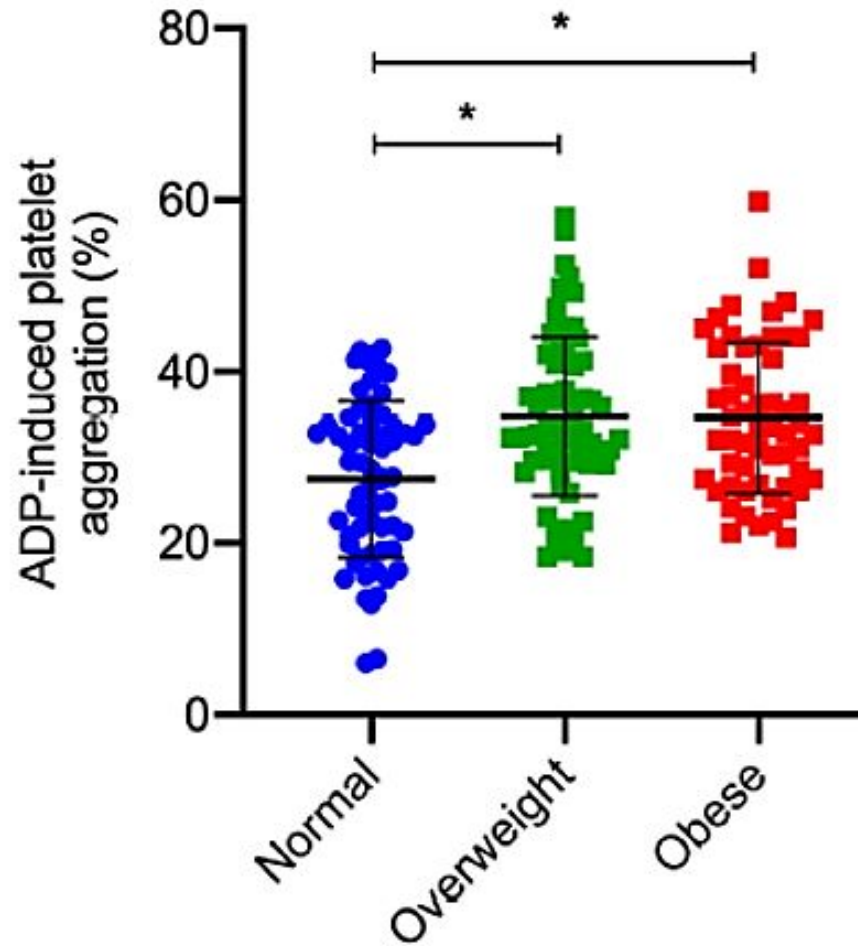


High degree obesity and altered aspirin pharmacokinetics



Clopidogrel: high residual ADP-induced platelet aggregation in obese subjects and poor PK biotransformation in obese mouse models

191 CAD patients on clopidogrel (75 mg once-daily)

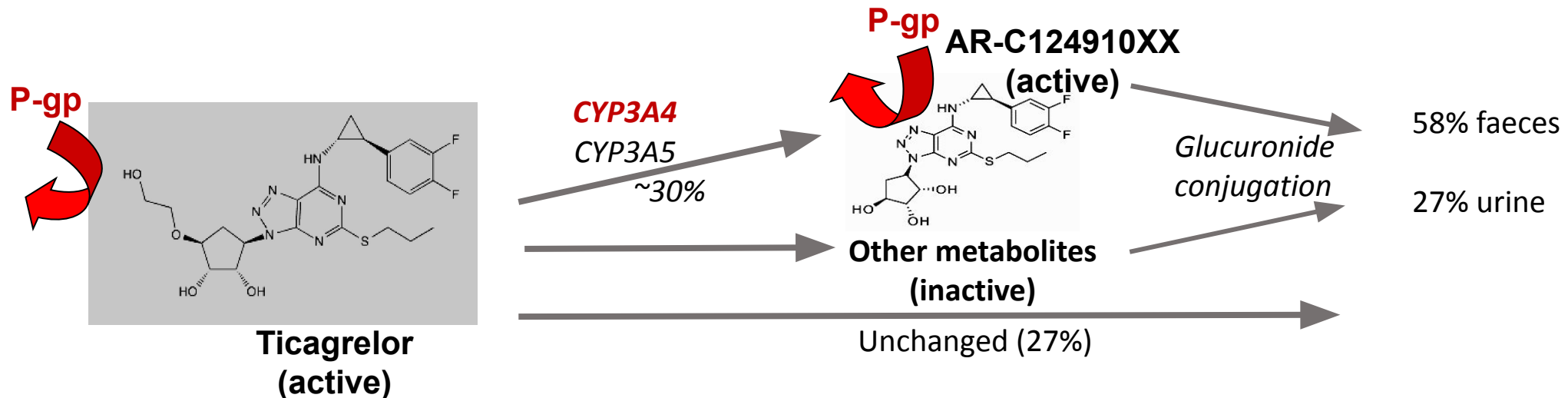
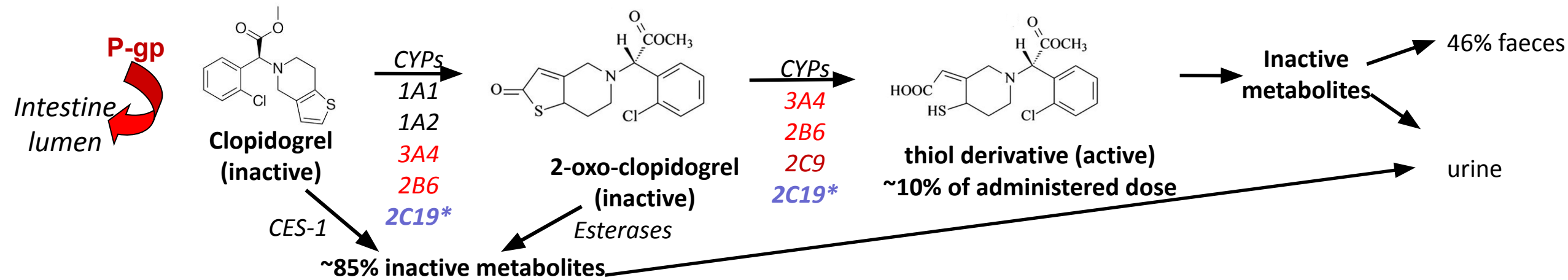


Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis

gery. It is reasonable to double the daily dose or shorten the dosing interval (twice-daily) for BMI ≥ 40 kg/m². Long-term adherence to low-dose aspirin treatment must be an important treatment goal, especially in the obese population. LoE 3

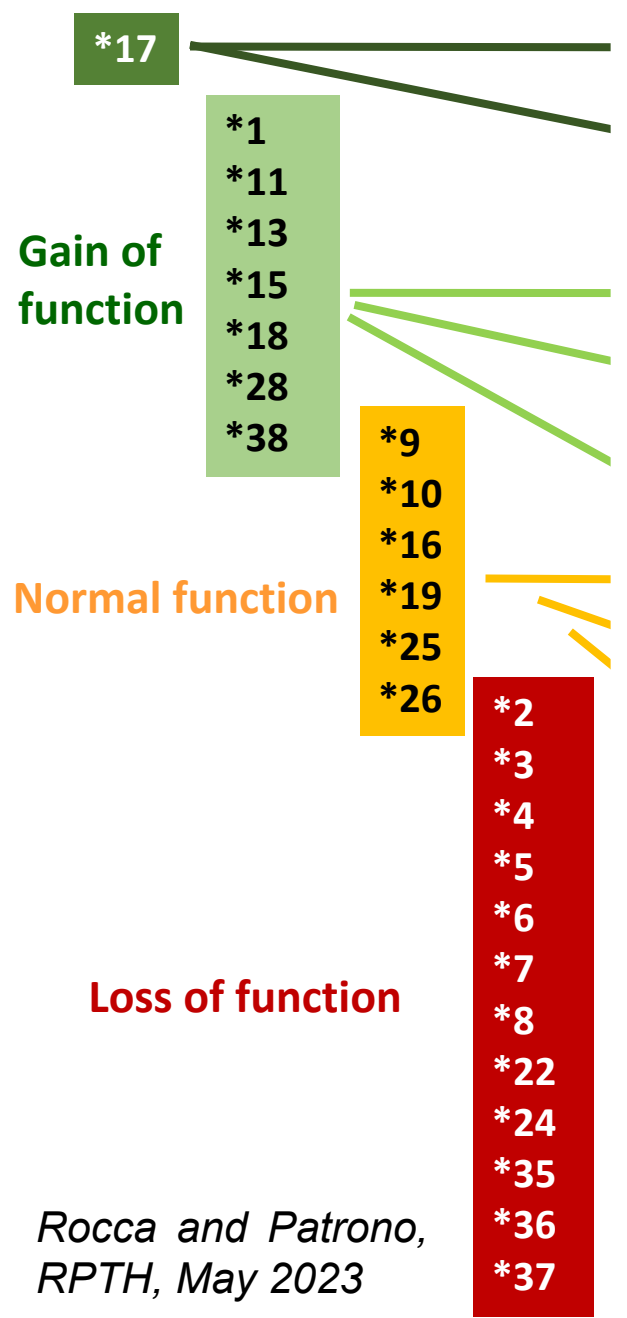
BW. However, significantly less clopidogrel active metabolite and lower degree of platelet inhibition are associated with class ≥ 2 obesity, especially in those with a poor or intermediate metabolizer genotype. ESC guidelines recommend a more potent P2Y₁₂ inhibitor in ACS patients without contraindication or requirement for oral anti-coagulant therapy. LoE 3

Drug's pharmacokinetics or pharmacogenomics as sources of variability and target of precision pharmacology in P2Y₁₂ inhibitors



Red: drug interaction sites
 2C19* relevant allelic variants

CYP2C19 Allele type

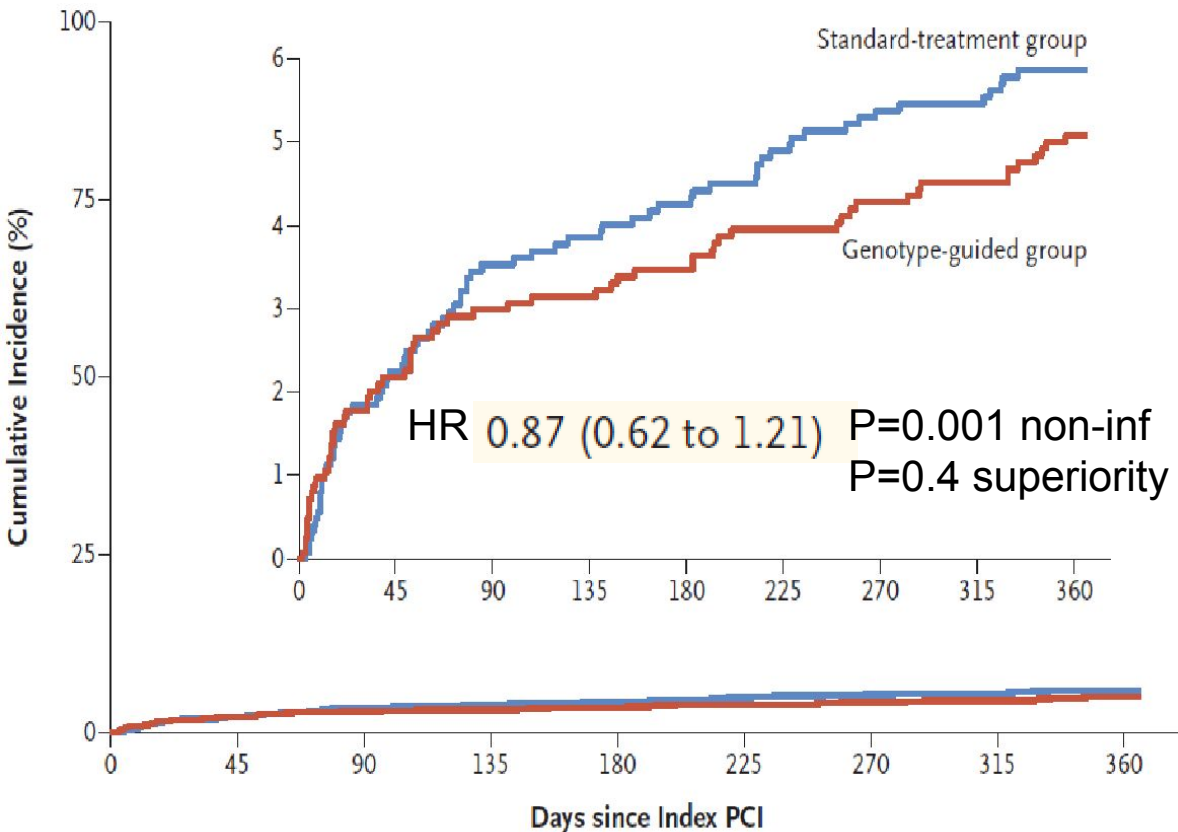


*Rocca and Patrono,
RPTH, May 2023*

Genotype-guided clopidogrel choice in DAPT: do we have strong evidence?

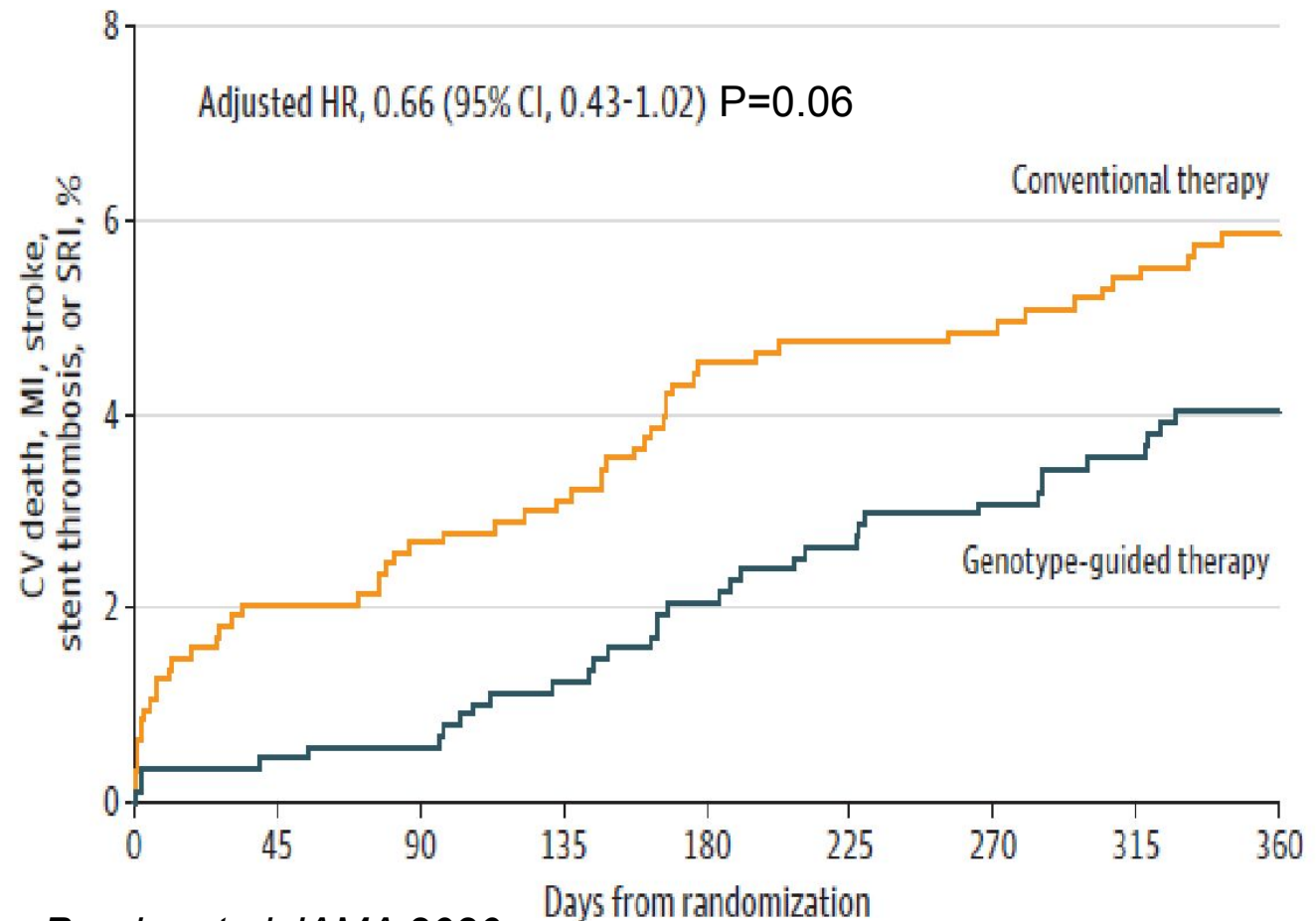
POPular Genetics vs TAYLOR-PCI randomized trials

MACE, all death, stent thrombosis, major bleeding



Claassens et al NEJM 2019

MACE, CV death, stent thrombosis



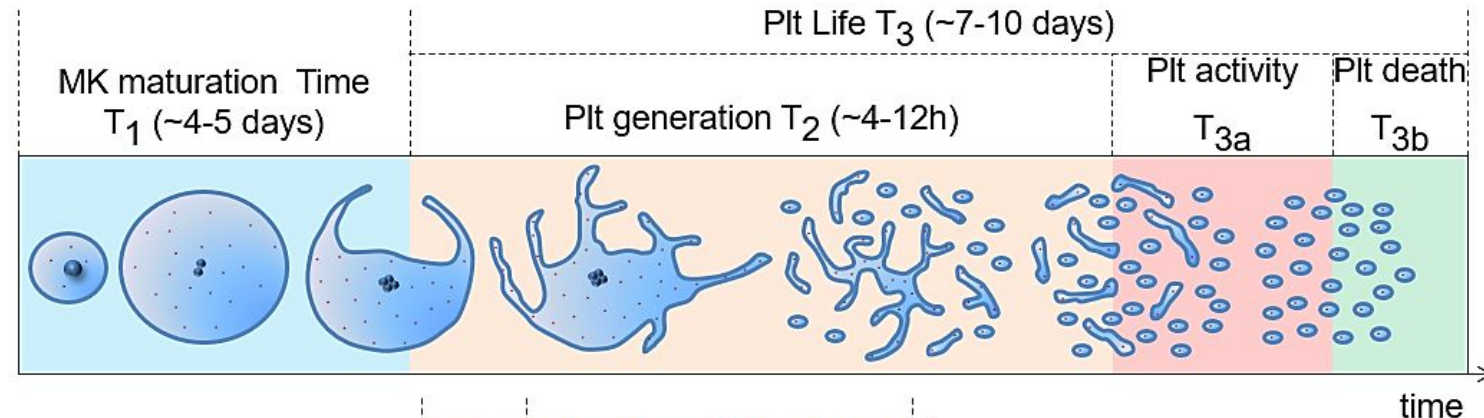
Pereira et al JAMA 2020

Organization	Antiplatelet therapy recommendations
EMA	The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, RCT. No study was adequately sized to detect differences in outcome in poor metabolizers.
FDA	Consider use of other anti-platelet medications or alternative dosing strategies in patients identified as poor metabolizers. An appropriate dose regimen for poor metabolizers has not been established in outcome trial.
Dutch PGx WG	Intermediate Metabolizers in PCI, stroke or TIA: alternative drug or double the dose to 150 mg/day (600 mg loading dose). Poor Metabolizers in PCI, stroke or TIA: avoid clopidogrel.
Clinical PGx Implementaition Consortium	Intermediate and Poor Metabolizers: avoid standard dose clopidogrel if possible, Use prasugrel or ticagrelor at standard dose if no contraindication (LoE strong for ACS and/or PCI patients, moderate for non-ACS, non-PCI patients)
French National Network on PGx	For patients carrying at least one deficiency allele, recommended using an alternative treatment that is not a CYP2C19 substrate (prasugrel, ticagrelor) Patients with at least one CYP2C19*2 and *3 alleles who have a high risk of thromboembolic recurrence, an alternative antiaggregant that is not a CYP2C19 substrate (prasugrel,ticagrelor, acetylsalicylic acid) is preferable. Based on current knowledge, it is not recommended to increase the clopidogrel dose in these patients.
IGNITE	Avoid clopidogrel in patients carrying a LOF allele due to the increased risk of major atherothrombotic events.

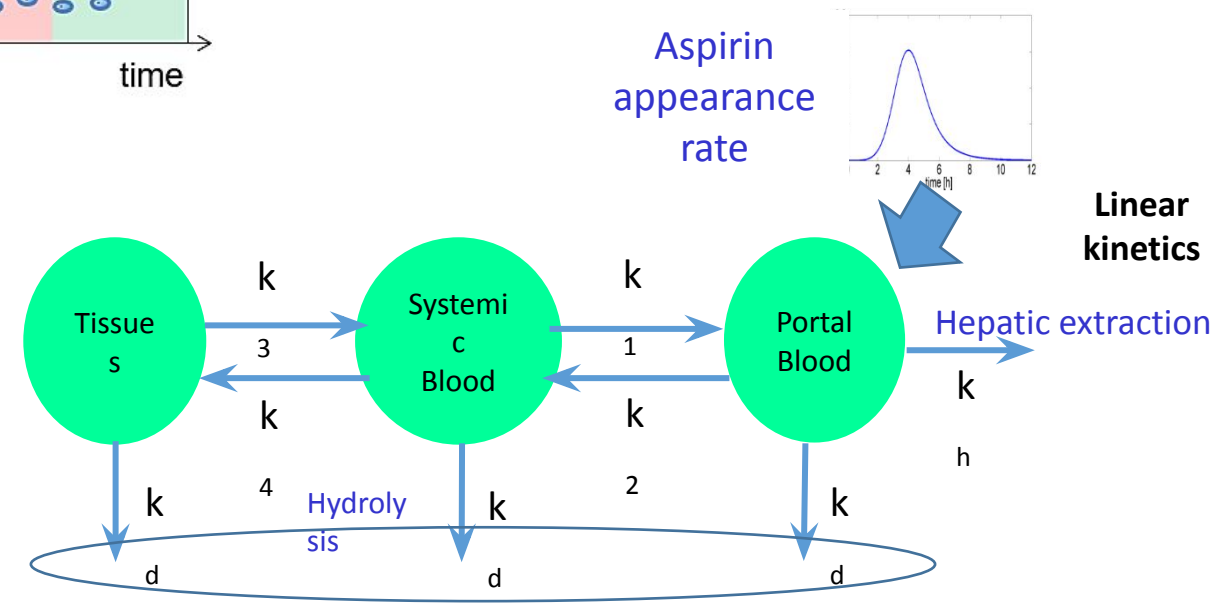
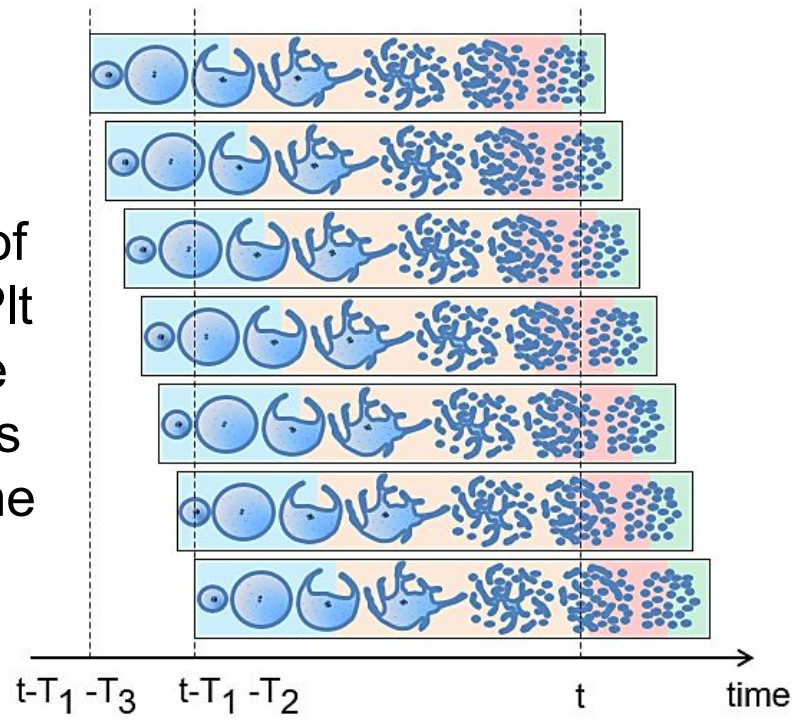
Tools for identifying determinants of variability and develop precision dosing

- **Robust and reliable measure** of drug response (pharmacodynamics-PD) or pharmacogenetics, possibly validated as surrogate biomarkers of clinical efficacy
- **Strong hypotheses on specific and identifiable populations:**
Chronic and acute settings of high platelet turnover
- ***In silico* PK/PD drug modelling & simulation for precision dosing:**
aspirin and clopidogrel

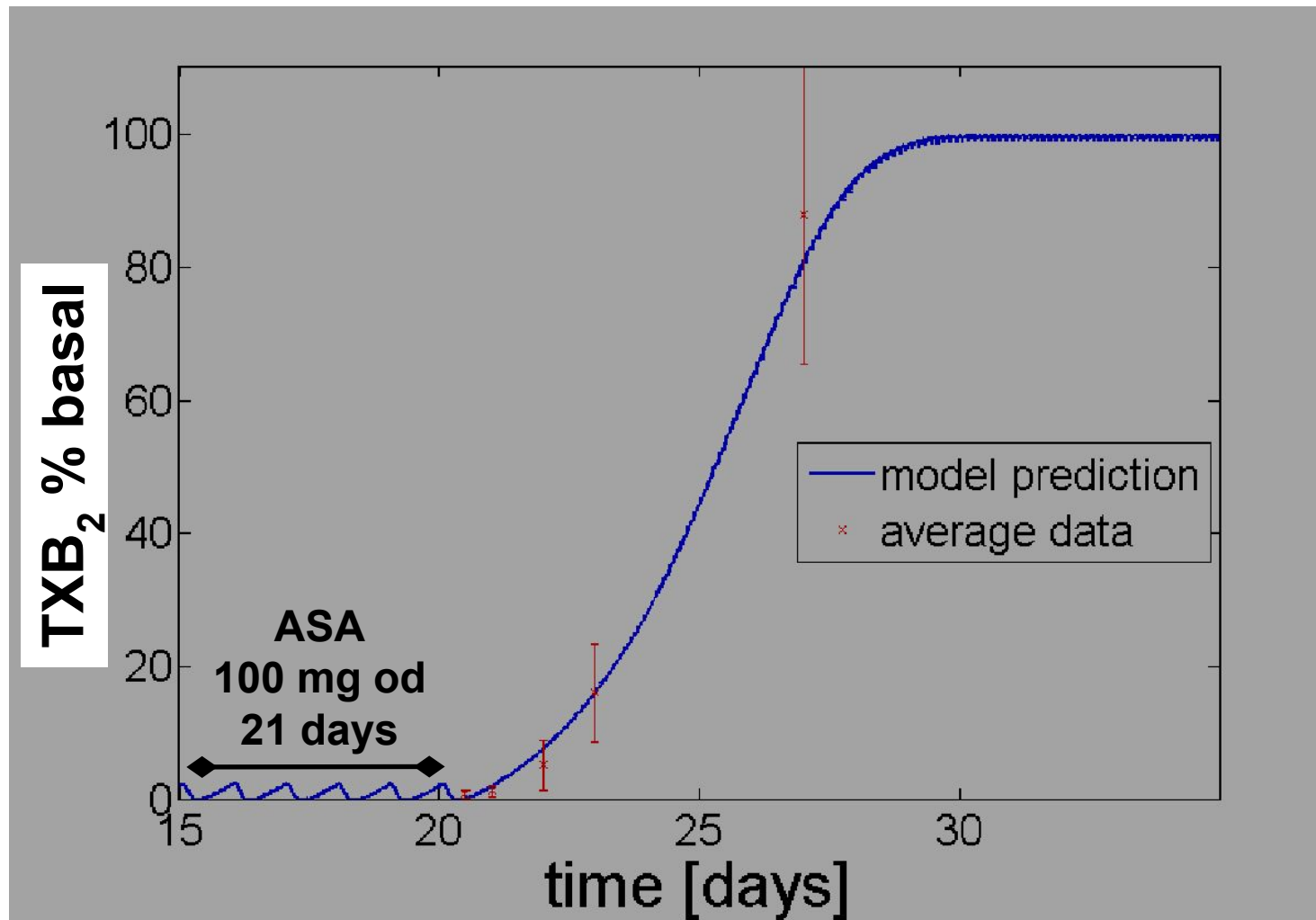
In silico PK/PD modelling for low-dose ASA to guide precision dosing



Population of MK-ProPlt-Plt units: same mechanisms shifted in time

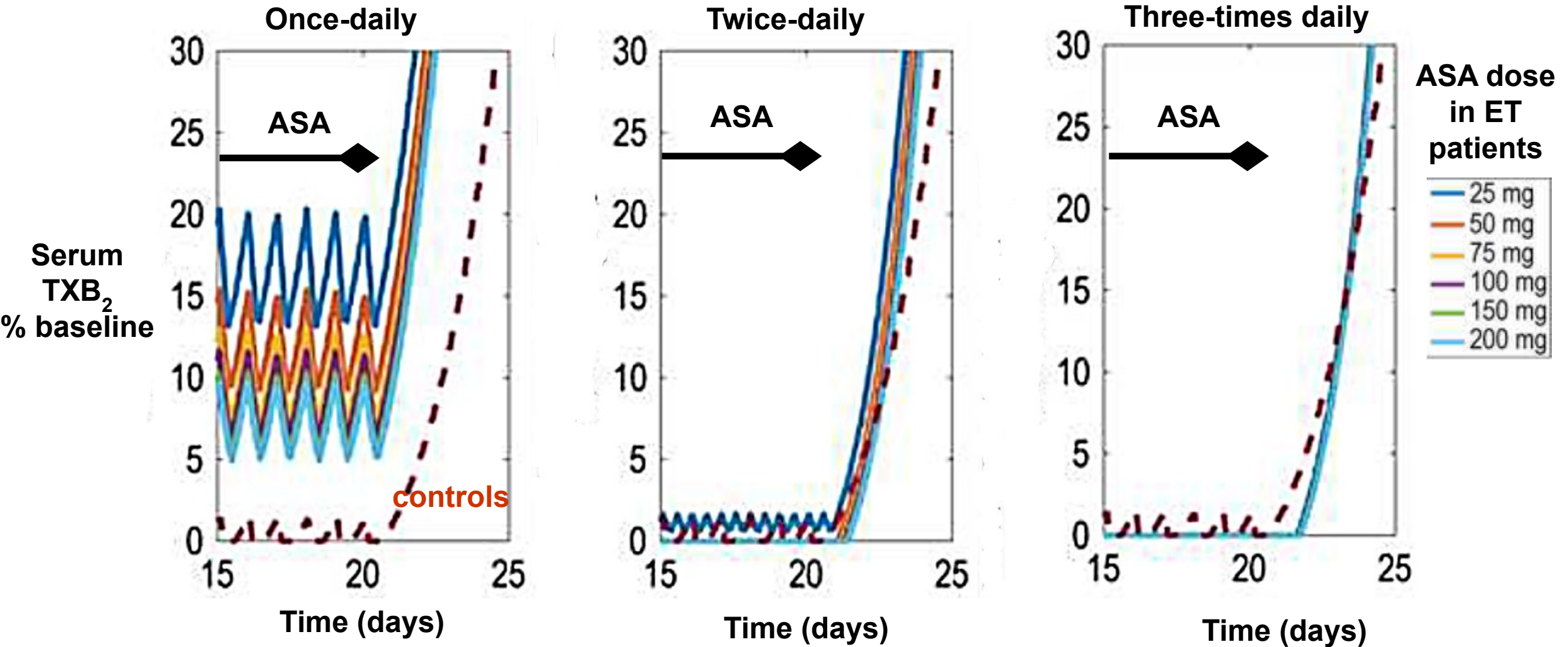


The *in silico* model could reproduce the experimental data of TXB₂ in healthy subjects on and off of low-dose aspirin

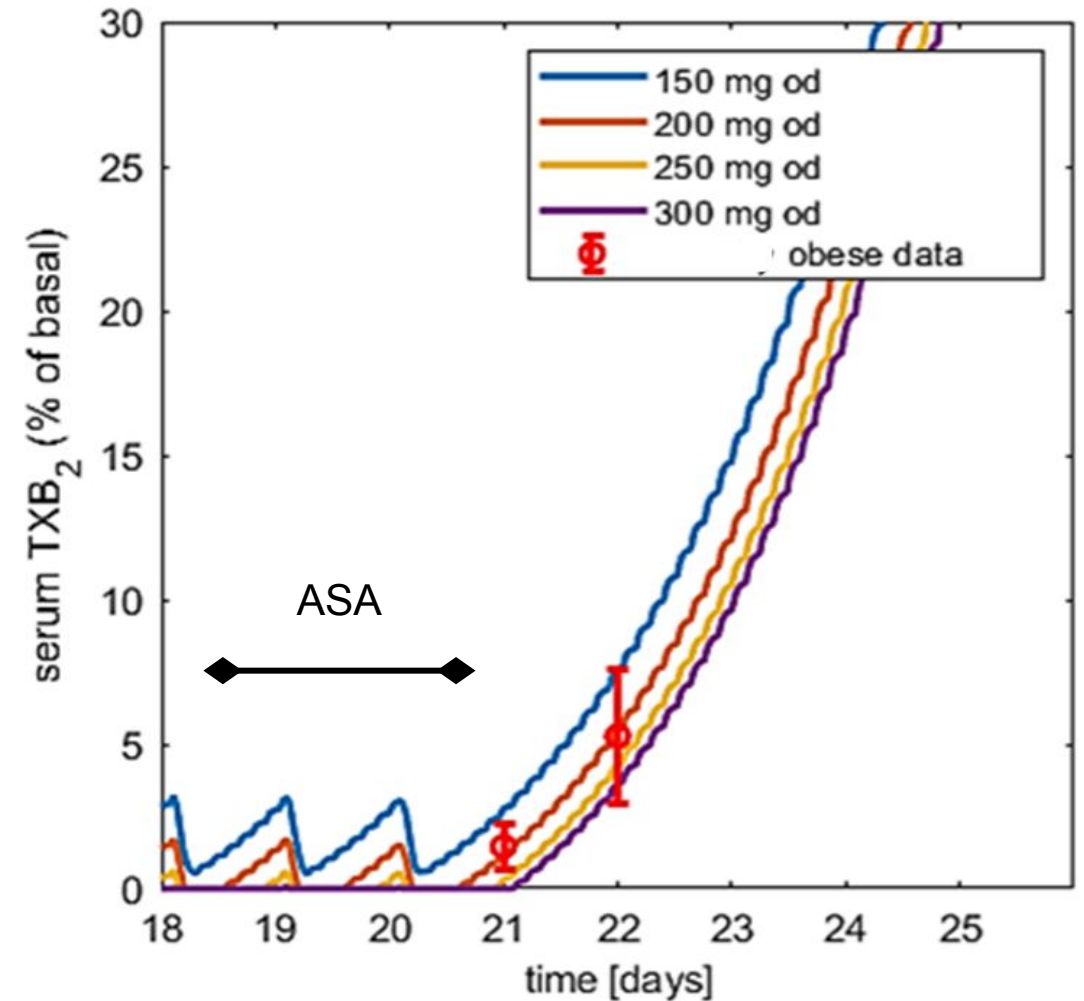
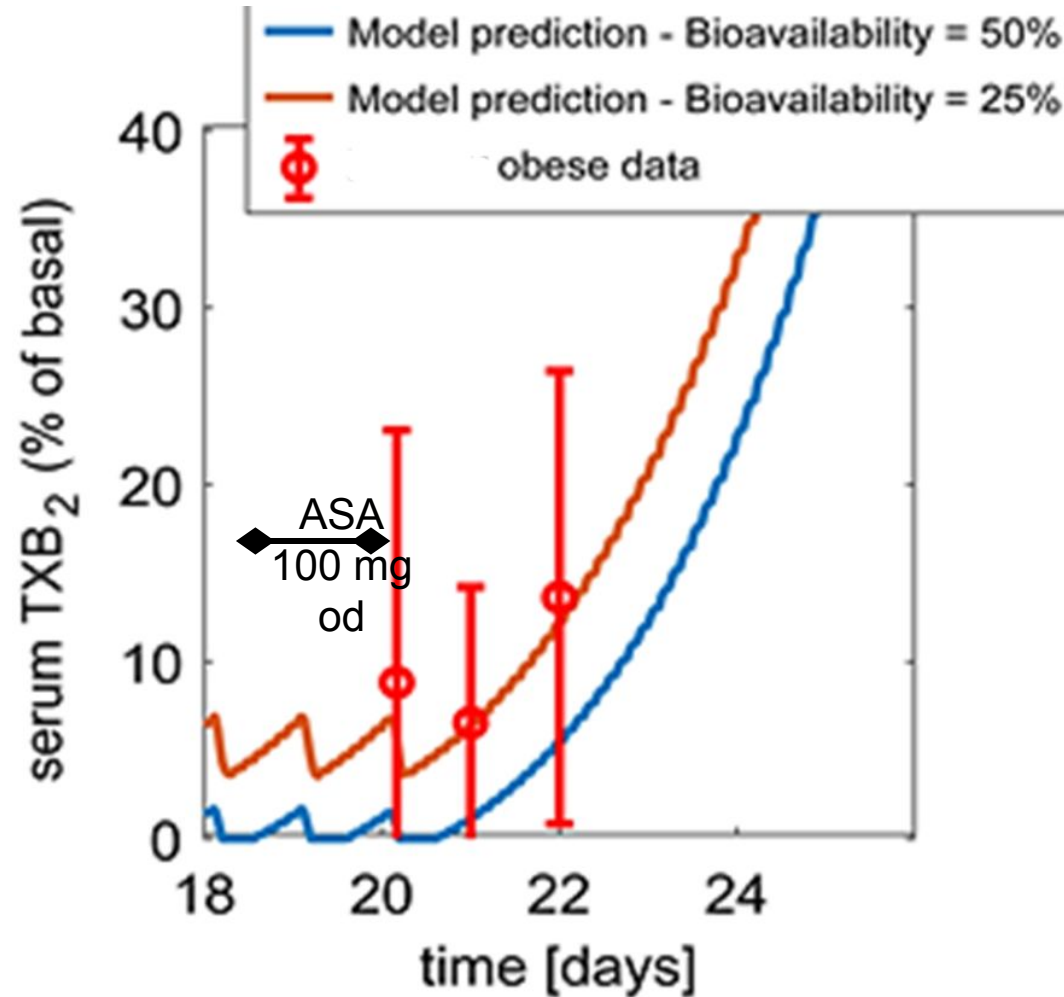


Best simulation: MK lifespan: 4 days; platelet lifespan: 7 days

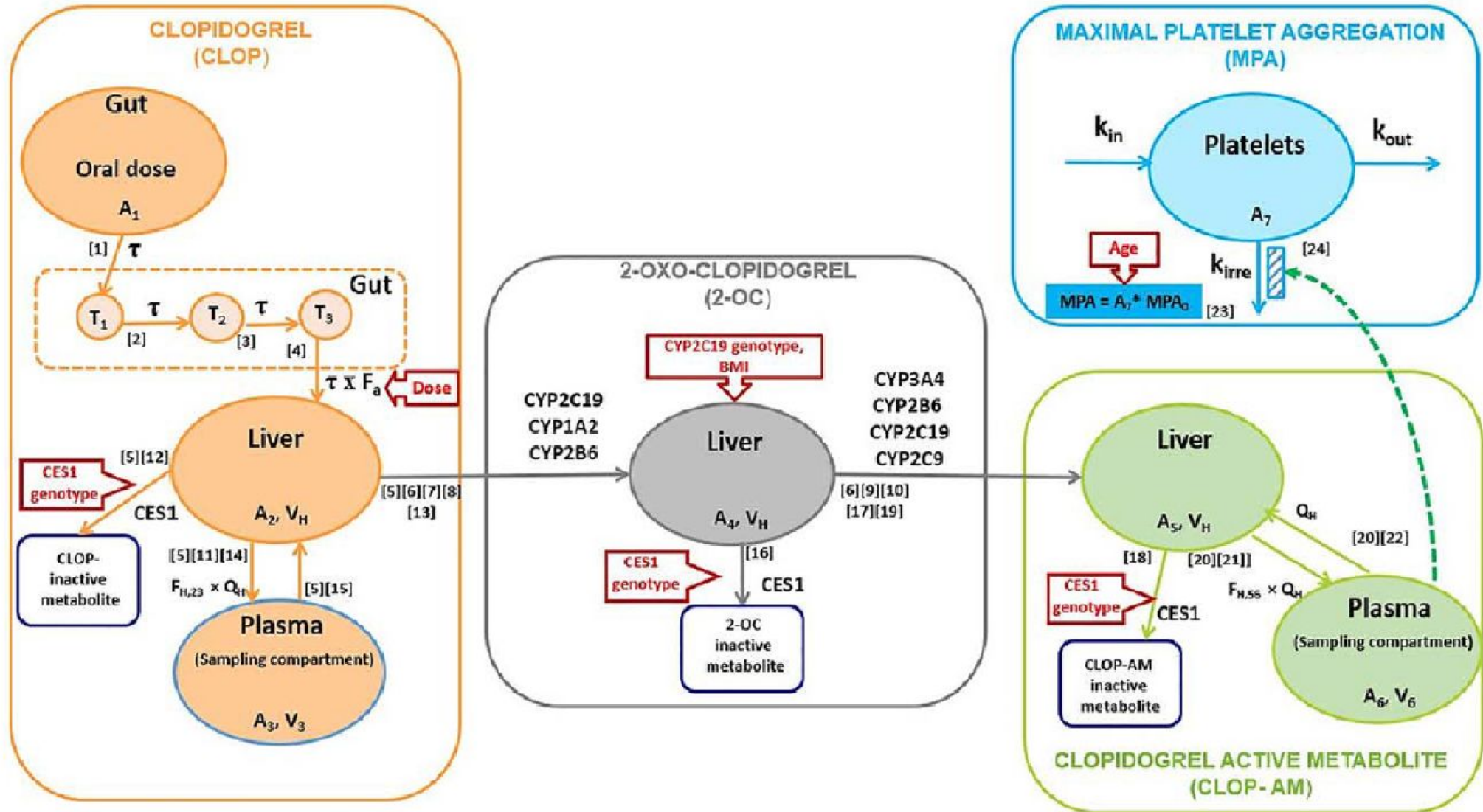
The *in silico* model could predict twice-daily dosing as the best low-dose ASA regimen in conditions of high platelet turnover



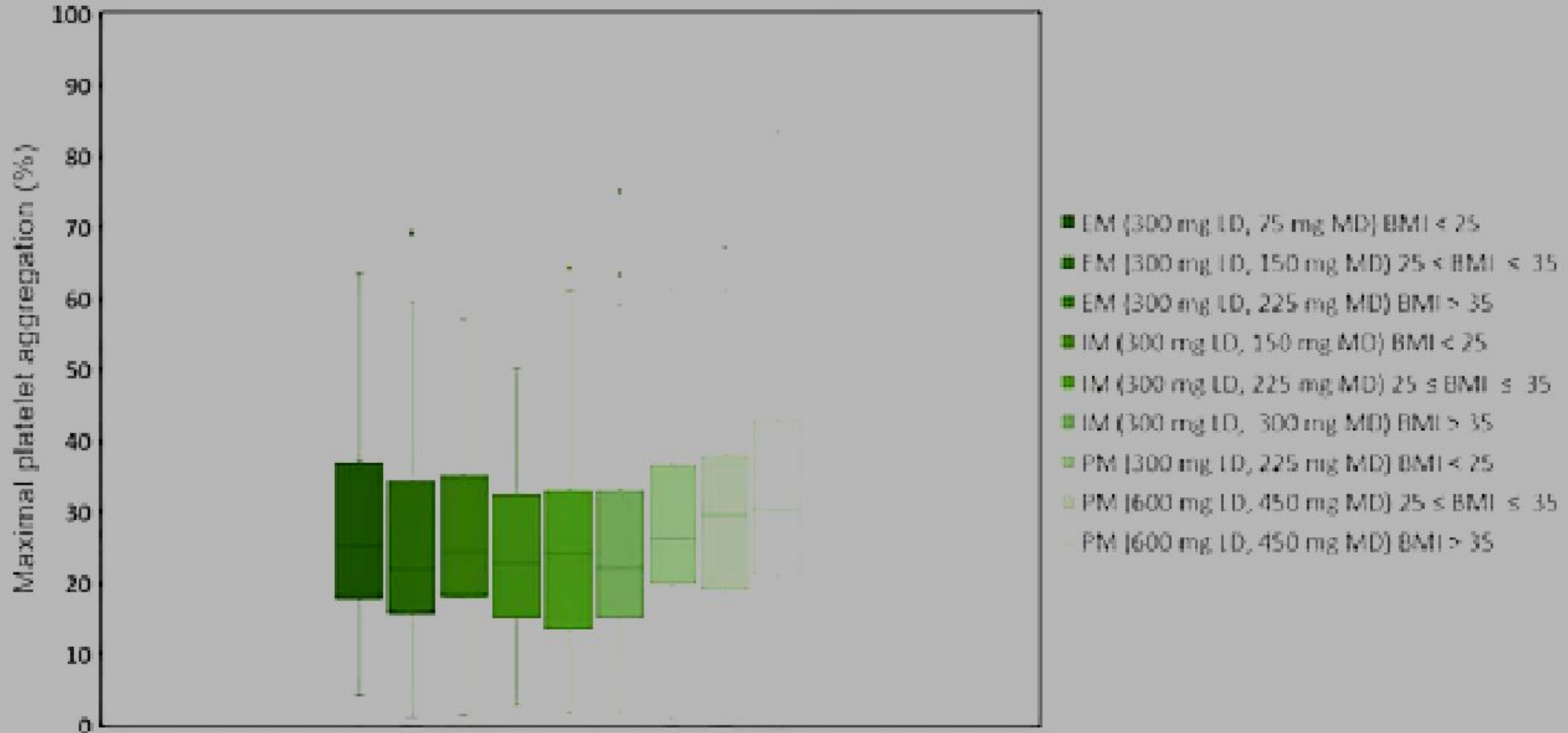
The model reproduced data from severely obese subjects on ASA 100 mg od by halving drug bioavailability and predicts need for higher once-daily dosing



Clopidogrel PK/PD modelling and simulation: relevance of body size, age, CES1 and CYP2C19 genotype



Clopidogrel modeling and simulation of drug dosing as a function of CYP2C19 metabolizer status and BMI as co-variates



Platetet Turn-Over
Diabetes
Body Size

Liver & Kidney Function
Drug-Drug Interactions
Platetet Turn-Over

Platetet Turn-Over
Body Size

Liver & Kidney Function
Drug-Drug Interactions
Diabetes



Aspirin

Clopidogrel

Prasugrel

Ticagrelor

Validated PK/PD biomarkers (all)

Genotyping (clopidogrel)

In silico models in rare and complex settings (clopidogrel, prasugrel, aspirin)

Check for and avoid drug-drug interactions (ticagrelor, clopidogrel)

Consider relevant co-morbidities (all)



Right Drug & Dosing Regimen For The Individual Patient

Acknowledgments

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All the Physicians from 26 ARES Centers across Italy

Dedicated patients and healthy volunteers participating to these studies

AIFA Ricerca Indipendente, Grant Agreement FARM12Y8H

Conclusions

- ✓ Identifying determinants of variability in antiplatelet drug response is central to hypothesize **new regimens of precision pharmacology for personalized medicine.**
- ✓ A **bid regimen** of low-dose aspirin restores an adequate platelet's COX inhibition in conditions of chronically- or acutely-enhanced **platelet turnover.**
- ✓ A **higher daily dose** may improve effectiveness of aspirin and clopidogrel in moderate-to-high degree of obesity.
- ✓ **Drug modeling and simulation generated** by PK/PD data can instruct decision algorithms of precision dosing **in complex or rare clinical settings under-represented or excluded from phase III trials** as well as adequately-sized **randomized trials** of precision vs conventional antiplatelet regimens.