

# Impact of CYP2C19 and ABCB1 single nucleotide polymorphisms (SNPs) on outcomes with ticagrelor and clopidogrel in acute coronary syndromes

A PLATO genetic substudy

**Discussant**

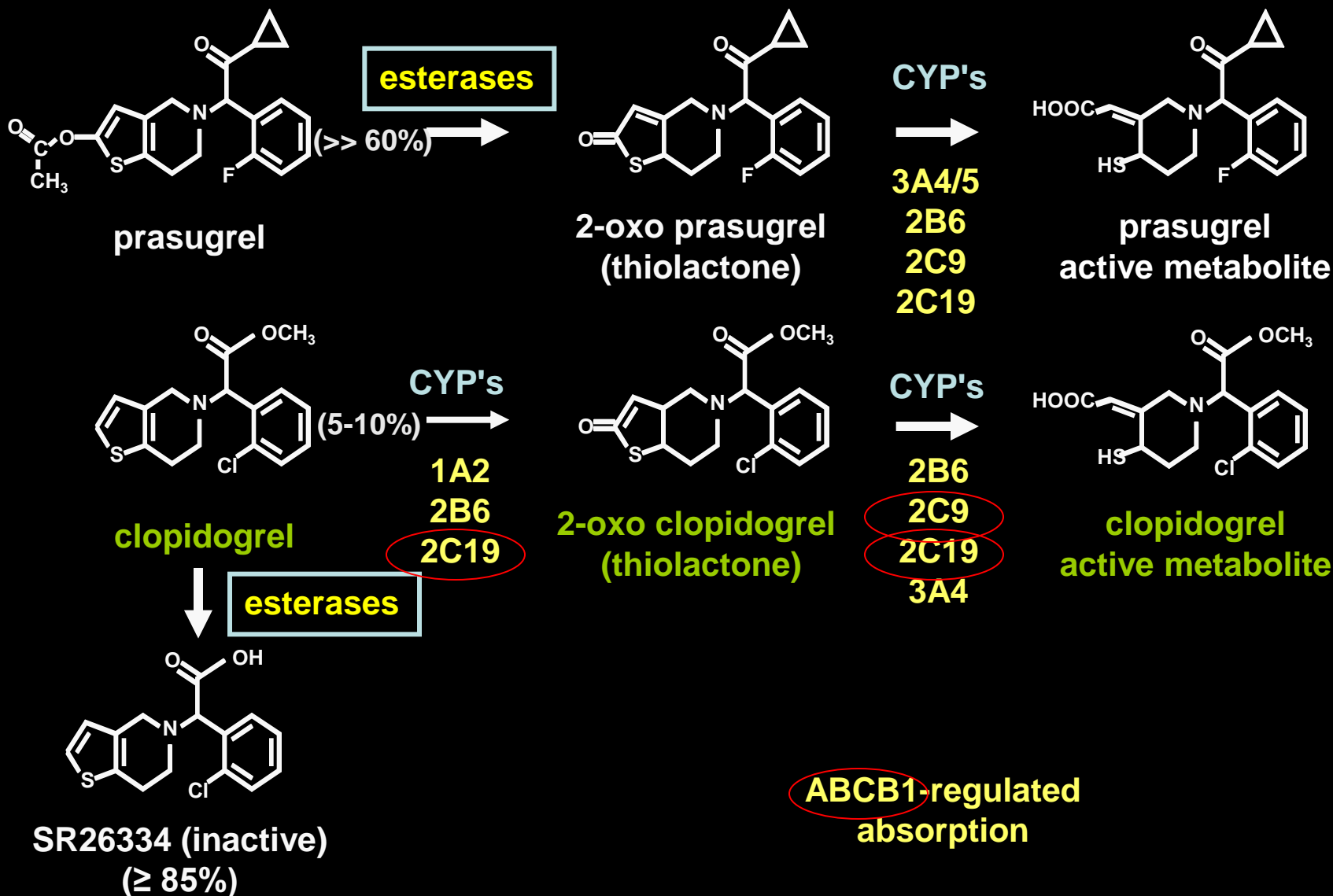
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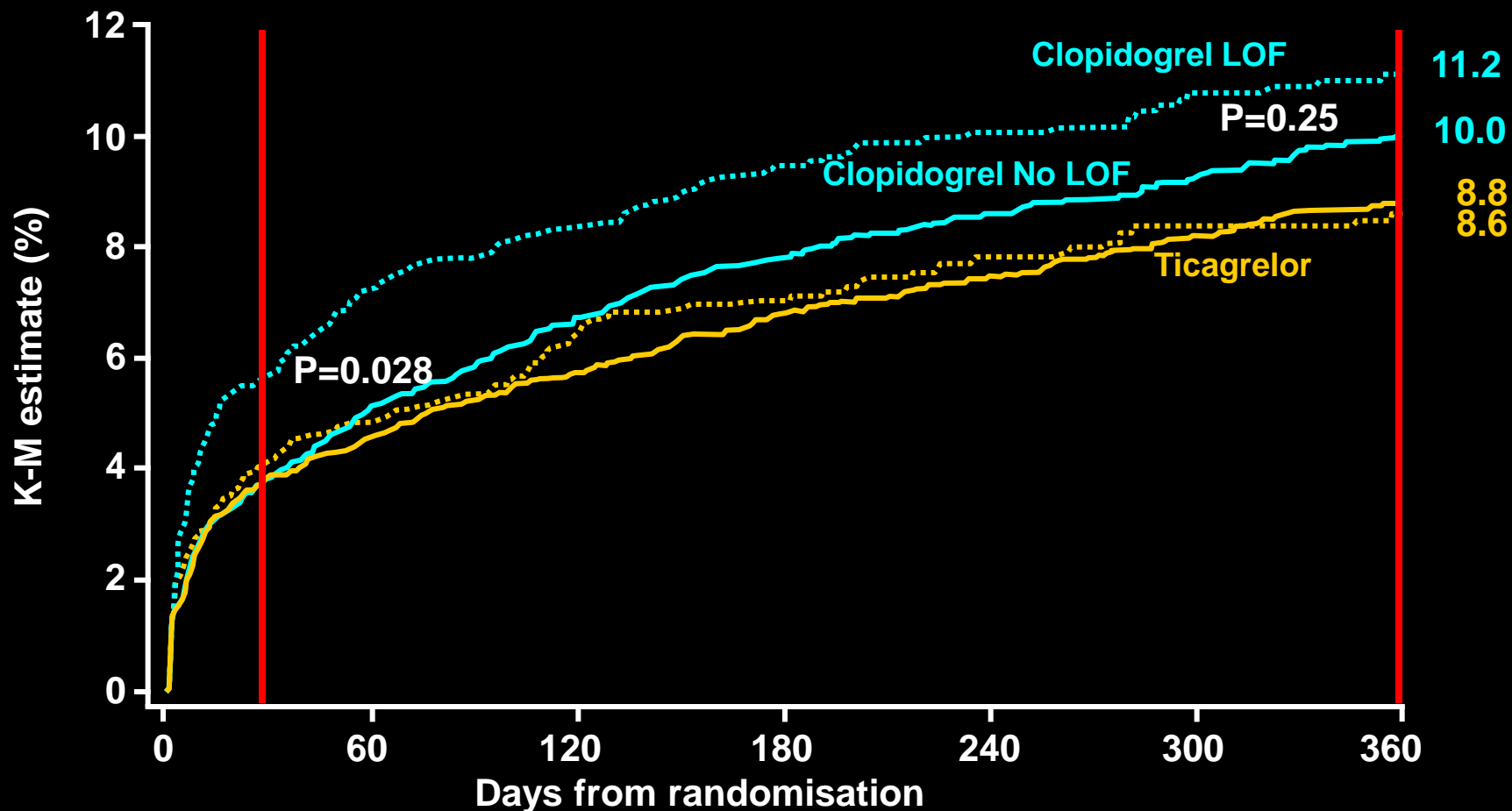
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# Clopidogrel and prasugrel: formation of the active metabolite



# K-M estimate of the primary endpoint in relation to any CYP2C19 LOF allele



No. at risk	0	60	120	180	240	300	360
Clopidogrel LOF	1,388	1,275	1,259	1,226	1,027	801	658
Clopidogrel No LOF	3,516	3,321	3,256	3,186	2,691	2,123	1,757
Ticagrelor LOF	1,384	1,305	1,274	1,250	1,053	834	683
Ticagrelor No LOF	3,554	3,352	3,301	3,222	2,718	2,127	1,761

# Studies demonstrating influence of CYP 450 SNPs on clopidogrel metabolism and clinical outcome

Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, Stratz C, Schmiebusch P, Bestehorn HP, Buttner HJ, Neumann F: Cytochrome P450 2C19 681G>A polymorphism and high on clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. . J Am Coll Cardiol 2008;51:1925-1934.

Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, Sabatine MS: Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009;360:354-362.

Varenhorst C, James S, Erlinge D, Brandt JT, Braun OO, Man M, Siegbahn A, Walker JR, Wallentin L, Winters KJ, Close SL: Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. Eur Heart J 2009;30:1744-1752.

Harmsze A, Van Werkum J, ten Berg J, Zwart B, Bouman H, Breet N, van 't Hoff A, Ruven H, Hackeng C, Klungel O, de Boer A, Deneer V: CYP2C19\*2 and CYP2C9\*3 alleles are associated with stent thrombosis - a case-control study. Eur Heart J 2010.

# What is known, what is not known

CYP2C19 polymorphisms account for only approximately 12% of variability in clopidogrel platelet response

Shuldiner et al. JAMA 2009

The positive predictive value of CYP2C19 loss-of function polymorphisms for cardiovascular events in patients with ACS undergoing PCI is low, approximately 12% to 20%

Shuldiner et al. JAMA 2009, Mega et al. Circulation 2009

Retrospective analyses, meta-analyses

No prospective RCT combining genetic profiling with individual treatment

It is unknown, whether a specific genetic polymorphism is capable of influencing outcome for the individual patient

# What are the consequences ?

Routine determination of SNPs ?

- which single SNP is important for the individual patient?
- point-of-care assays are not available
- genetic profiling is frequently not refunded

Should we tailor clopidogrel treatment (dosage) or the use of other new ADP receptor blockers (prasugrel, ticagrelor) based on genetic profiling?

- studies are ongoing, but most of these trials investigate for pharmacodynamics (SPICE (2 trials), ACCEL-2C19, ACCELAMI2C19, ACCEL2C19, GeCCO, PAPI-2) and not for clinical outcome

Should we use more potent agents than clopidogrel in medium-to-high risk patients (STEMI, high risk NSTEMI, stent thrombosis) without genetic profiling ?

- no known influence of SNPs on pharmacodynamics of prasugrel
- ticagrelor has different pharmacokinetics and is not affected

# Summary

Certain SNPs (CYP 2 C19) play a role for low-response to clopidogrel by influencing pharmacokinetics (metabolism), pharmacodynamics (platelet function testing) as well as clinical outcome

Genetic disorders explain only a part of „clopidogrel resistance“

Based on the current data and missing outcome results of prospective intervention trials, genetic profiling should not be recommended for routine use at present but will remain of increased scientific interest

The use of more efficient antiplatelet agents, especially in patients with a medium-to-high risk profile for thrombotic complications after stenting (STEMI, NSTEMI, prior stent thrombosis) has been shown to be effective and safe and makes genetic profiling less important