14th Residential Course on Clinical Pharmacology of Antiretrovirals

Turin, 16-18 January 2019

SESSION I - MANAGEMENT OF POLYPHARMACY AND DDIs (Chair: D. Back, R. Garaffo)

15:30 Polypharmacy in HIV and HCV patients: not only drug interactions **(C. Marzolini)**

16:00 Before Liverpool site: how to evaluate a potential DDI **(M. Siccardi)**

16:30 Coffee break

17:00 Beyond Liverpool site: pharmacological support for the management of polypharmacy in HIV-positive patients **(D. Cattaneo)**

17:30 Beyond Liverpool site: how to evaluate the impact of a DDI in the clinical setting **(C. Alcantarini, S. Bonora)**

Alert from the pharmacy sheet

Potential DDIs, polypharmacy to manage

Alert from the Outpatient Service

Pharmacist

ID specialist

Pharmacist

Internal medicine

+/-

Others

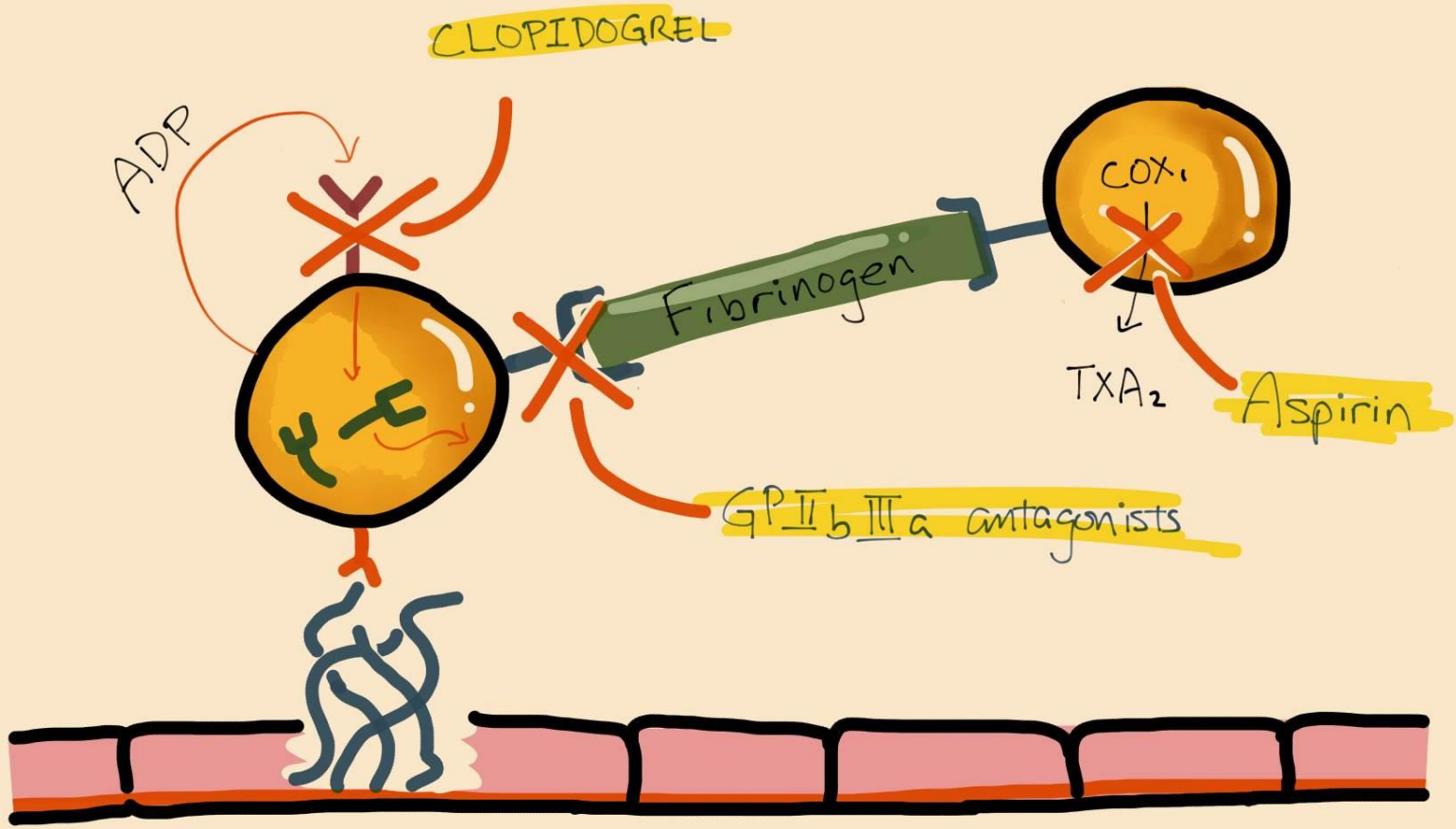
ID specialist(s)

PK Lab
TDM/genetics (ARVs and /or **non ARVs**)

ID specialist

ASL CITTÀ DI TORINO

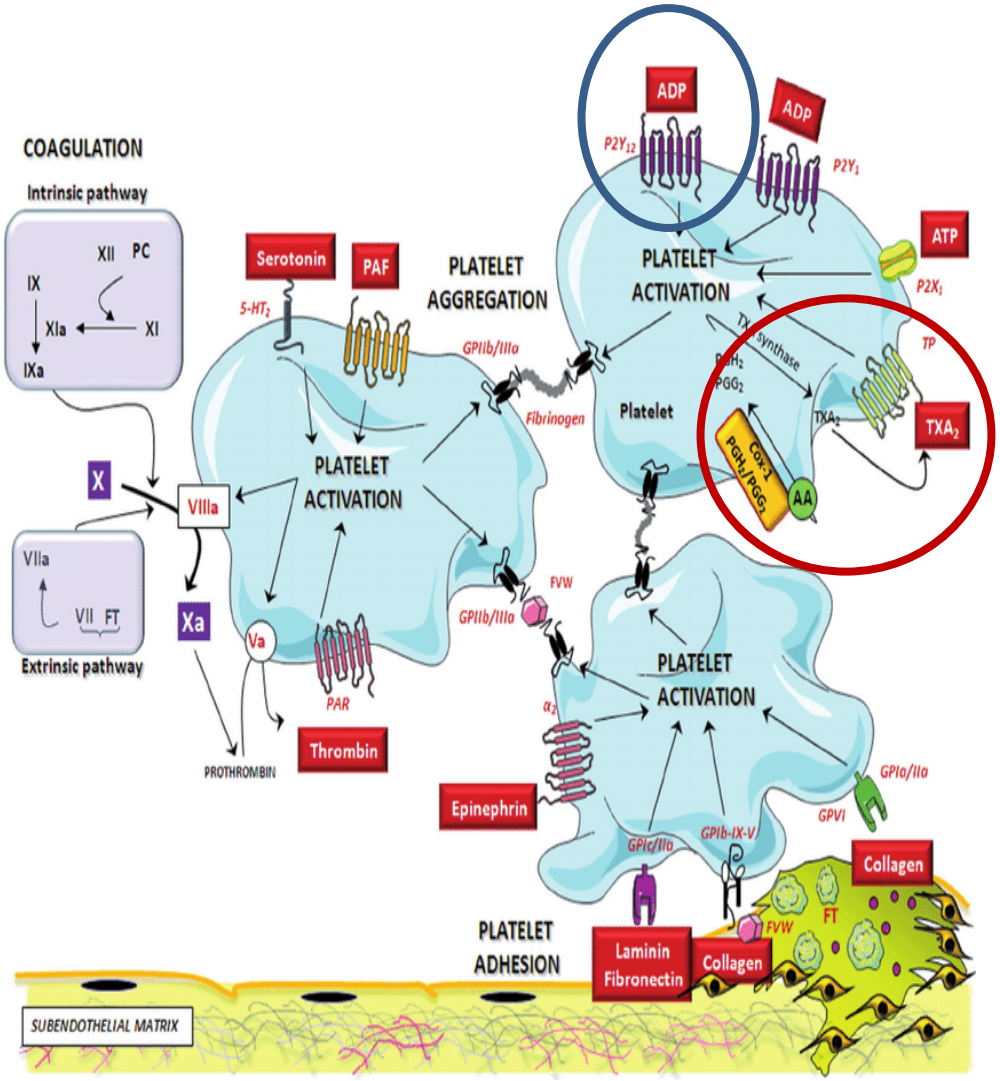
key ANTI-PLATELETS



QH

ANTIPLATELET THERAPY and MECHANISM of ACTION

TARGET	AGENTS	MECHANISMS OF ACTION
Thromboxane inhibitors	Aspirin ~~Triflusal~~	→ Platelet Cox-1 inhibitors
	Terutroban	→ Thromboxane receptor blockade
ADP P2Y receptor Antagonists	Thienopyidines - Ticlopidine - Clopidogrel - Prasugrel	→ •Prodrugs: Require hepatic metabolism. •Irreversibly bind the ADP receptor P2Y12
	Non-thienopyridines: - Ticagrelor - Cangrelor	→ •Active drugs: Do not require hepatic metabolism. •Reversibly block the ADP receptor P2Y12 •Cangrelor is intravenously administered
GPIIb/IIIa inhibitors	Abciximab	→ Monoclonal antibody that irreversibly block GPIIb/IIIa receptor
	Eptifibatide Tirofiban	→ Synthetic molecules that competitively and reversible block GPIIb/IIIa receptor
Thrombin receptor antagonists	Varopaxar Atopaxar	→ Oral antagonists of platelet thrombin receptor PAR-1
Agents under pre-clinical investigation	vWF-GPIb inhibitors	→ Inhibit platelet adhesion by preventing vWF-GPIb interaction.
	NCX-4016	→ Nitric-oxide donor + aspirin releaser
	Soluble CD39	→ ATP and ADP metabolization
	Nitric oxide donors	



Adapted from Badimon L et al. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease.

Table 2 – Comparison of the effects of the most important antiplatelet drugs.

Drug	Mechanism of action/type of bond	Route of administration	Metabolic activation	Plasma half-life	Onset of effect	Peak effect achieved	Effect wears off within
Clopidogrel	$P2Y_{12}$ rec. inhibition/ irreversible	Oral	CYP2C19 (sensitive to CYP2C19 inhibition of type of polymorphism)	≈6 h (active metabolite)	1–4 h (loding dose 600 mg)	4–5 h (loding dose 600 mg)	≈week
Ticlopidine	$P2Y_{12}$ rec. inhibition/ irreversible	Oral	CYP2C19 (sensitive to CYP2C19 inhibition of type of polymorphism)	7–13 h (active metabolite)	1–2 days	3–4 days	≈week
Prasugrel	$P2Y_{12}$ rec. inhibition/ irreversible	Oral	CYP3A4 and 2B6 (resistant to inhibition or CYP isoenzyme polymorphism)	≈7 h (2–15) (active metabolite)	30 min	1–2 h in fasting state, 2–3 h post-prandially	≈week
Ticagrelor	$P2Y_{12}$ rec. inhibition/ reversible	Oral	Not necessary, active metabolite involved in the effect by 1/4	6–13 h (parent drug and active metabolite)	30–60 min	1–2 h	1–2 days
Cangrelor (being evaluated)	$P2Y_{12}$ rec. inhibition/ reversible	Parenteral	Not necessary	10–15 min	Minutes	15 min	1 h
Vorapaxar (being evaluated)	PAR-1 rec. inhibitor/ reversible	Oral	Not necessary	165–310 h	30 min	2 h	>8 weeks
Acetylsalicylic acid (*non-entero-solvent tablets*)	Irreversible COX_1 blockade (inhibition of TXA_2 synth.)	Oral and parenteral	Not necessary	2–3 h	<10 min with i.v. admin, 20–30 min with oral route	1 h	≈week

Bultas eta la. Cor and Vasa 2018

Aspirin and Clopidogrel Resistance in Coronary Artery Disease

Table 2. Prevalence of clopidogrel resistance based on laboratory assay[7]

Table 3. Summary of laboratory tests reporting clopidogrel resistance.

Study	n	Condition studied	Loading dose clopidogrel	Maintenance dose clopidogrel	Platelet function test	Prevalence of resistance
Gurbel et al[54]	92	PCI	300 mg	75 mg	LTA	31%–35%
Angiolillo et al[55]	52	Diabetes	300 mg	75 mg	LTA and Flow cytometry	38% in DM, 8% in non-DM
Angiolillo et al[56]	48	PCI	300 mg	75 mg	LTA	44%
Lepantalo et al[57]	50	PCI	300 mg	75 mg	LTA and PFA 100	40%
Jaremo et al[58]	18	PCI	300 mg	75 mg	LTA	28%
Lev El et al[59]	150	PCI	300 mg	–	LTA	24%
Mobely et al[60]	50	PCI	300 mg	75 mg	LTA	30%
Muller et al[61]	115	PCI	600 mg	75 mg	LTA	5%–11%
Barragan et al[62]	48	ISR[16] vs no ISR[32]		Clop 75 mg B.I.D. vs. Ticlopidine 250 mg B.I.D.	Flow cytometry	63% (ISR) vs. 40% (no ISR)
Bounamici et al[32]	804	ISR	600 mg	75 mg	ADP induced platelet aggregation	13%
Ajzenberg et al[63]	32	ISR[10] vs. no ISR[22]	300 mg	75 mg	Shear induced platelet aggregation (SIPA)	41% (cases) vs. 18% (controls) at shear rate of 200/s 57% (cases) vs. 23% (controls) at shear rate of 4000/s
Matetzky et al[29]	60	STEMI	300 mg	75 mg	LTA	25%
Dziewierz et al[64]	31	CAD	300 mg	–	LTA	23%

Source of table: Saraf et al. (2009)[7]

Factors influence variability of CLOPIDOGREL response	
Bioavailability	• Nonadherence patient • Drug interaction (lipophilic statins, omeprazole) • Poor absorption • Underdosing
Cellular factor	• Enhanced platelet turnover • Increased platelet sensitivity to ADP and collagen • Reduced activity CYP3A • Increased exposure ADP • Upregulation of P2Y12 pathways • Upregulation of P2Y-independent pathways: collagen, thrombin, epinephrin, TXA2
Genetic factor	• Polymorphisms of P450 (CYP2C19681G>A[*2,*3,*4, and *5] • Polymorphisms of P2Y1 • Polymorphism of P2Y12 • Polymorphism GPIa • Polymorphism GP IIIa
Other factors	• Increased body mass index • Diabetes • Hyperinsulinemia • Hypercholesterolemia • Smoking

Saraf S., Bensalha I., Gorog D.A. 2009. Antiplatelet resistance-does it exist and how to measure it? Clin Med Cardiol, 3(3):77-91

Aspirin and Clopidogrel Resistance in Coronary Artery Disease

Table 1. Prevalence of aspirin resistance based on laboratory assay[7]

Table 2. Summary of laboratory tests reporting Aspirin resistance.

Study	n	Type of subjects	Aspirin dose	Platelet function test	Prevalence of resistance (%)
Gum et al[50]	325	Stable CAD	325 mg	ADP and AA induced optical aggregation	5.2
Mueller et al[38]	100	PAD	100 mg	Corrected whole blood aggregometry	60
Grotemeyer et al[35]	180	CVA	1500 mg	Platelet reactivity	33
Chen et al[24]	151	Elective PCI	80–325 mg	RPFA	19
Andersen et al[23]	202	Post MI	160 mg Aspirin vs. 75 mg Apirin plus warfarin	PFA-100	35% in patients taking aspirin only, vs. 40% in patients taking aspirin and warfarin
Macchi et al[21]	98	Stable CAD	160 mg	PFA-100	29%
Helgason et al[51]	306	CVA	300–325 mg	ADP induced platelet aggregation	25%
Hobikoglu et al[22]	204	ACS: 104 Stable CAD: 100	80–300 mg	PFA-100	40% in ACS 27% in Stable CAD
Grundmann et al[52]	53	CVA/TIA in prev 3 days 35	100 mg	PFA-100	34% in symptomatic 0% in asymptomatic patients
Alberts et al[53]	129	CVA	81 mg vs. 325 mg	PFA-100	37% overall, with 56% in patients on 81 mg vs. 28% in those on 325 mg aspirin.

Source of table: Saraf et al. (2009)[7]

5 to 60% of patients on chronic treatment with aspirin don't respond properly

Hankey G.J., Eikelboom J.W. Aspirin resistance. Lancet 2006

Factors influence variability of ACETYLSALICYLIC ACID response

Bioavailability decrement	• Poor compliance • Inadequate dosage • Low absorption (enteric coated aspirin) • Increased metabolism • Other drug interaction (NSAIDs)
Genetics Variations	• Gene COX1 mutation • MRP4 transporter overexpression
Enhanced platelet turnover	• Increment of bone marrow's platelet production • Unexposed aspirin new platelets (i.e. transfusion) • Platelet activation induced by cigars • Platelet activation induced by erythrocyte increment.
Platelet activation from alternative pathway	• TXA2 synthesis induced by cytokines, oxidative stress or nucleated cells • Platelet activation induced by cathecolamine • High incidence of shear stress, collagen, thrombin and other platelet activation pathway
Individual variation	• Diabetes or insulin-resistance • Hypercholesterolaemia • Hypertension • Old age • Obesity • Sex

Saraf S., Bensalha I., Gorog D.A. 2009. Antiplatelet resistance-does it exist and how to measure it? Clin Med Cardiol, 3(3):77-91

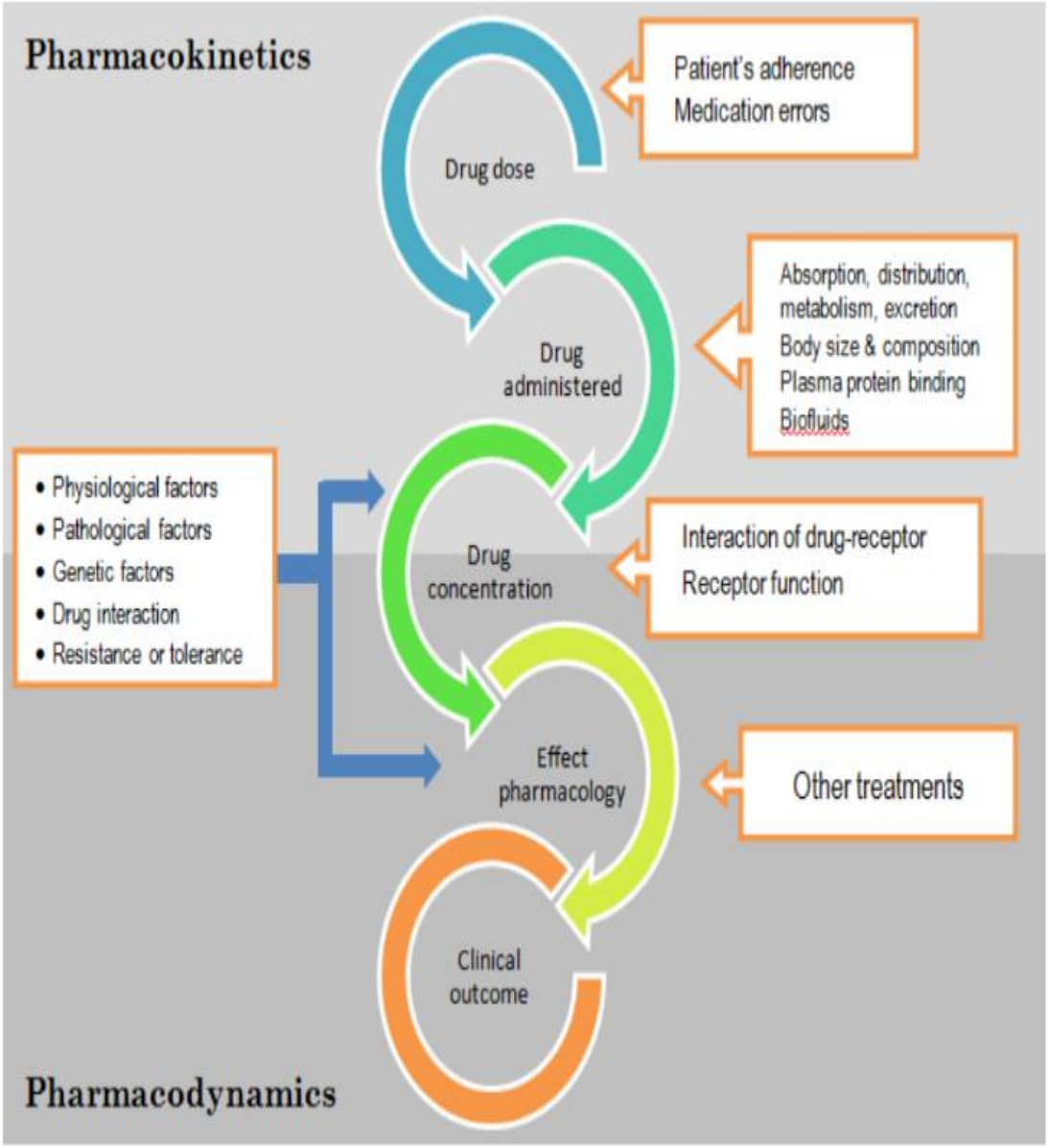


Figure 2. Pharmacokinetics and pharmacodynacis which influenced drug clinical outcome.

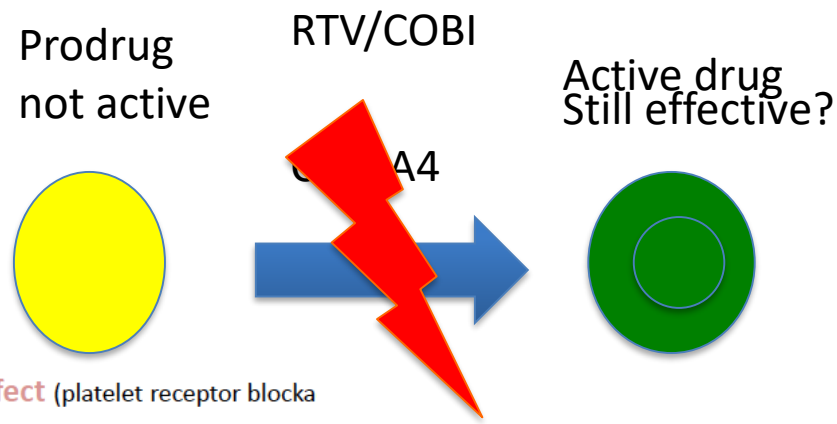
Rocca B., Petrucci G. 2012. Variability in the responsiveness to low-dose aspirin: pharmacological and disease-related mechanisms. Thrombosis, 376721;1-11.

	Bictegravir/FTC/TAF	Cobicistat (with ATV or DRV)	Darunavir/Cobi/FTC/TAF	Darunavir/cobicistat	Dolutegravir
Aspirin (Anti-platelet)	◆	◆	◆	◆	◆
Clopidogrel	◆	●	●	●	◆
Prasugrel	◆	◆	◆	◆	◆
Ticagrelor	◆	●	●	●	◆

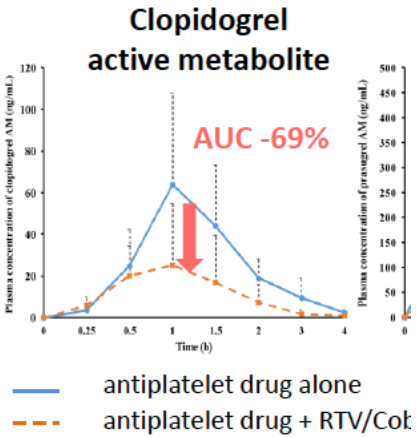
Clopidogrel

Clopidogrel is a prodrug and is converted to its active metabolite via CYPs **3A4**, 2B6, **2C19** and 1A2.

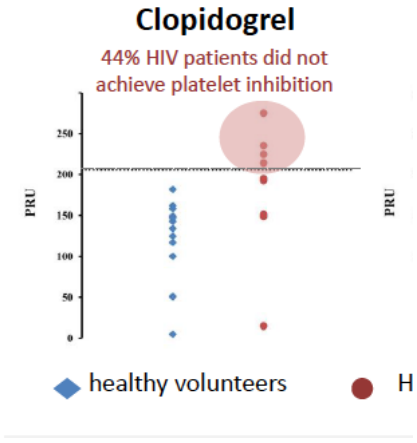
- The effect of induction of CYP2C19 and inhibition of CYP3A4 by ritonavir or inhibition of CYP3A4 by cobicistat are likely to **decrease exposure of the active metabolite leading to non-responsiveness to clopidogrel**. .



PK effect



PD effect (platelet receptor blocka



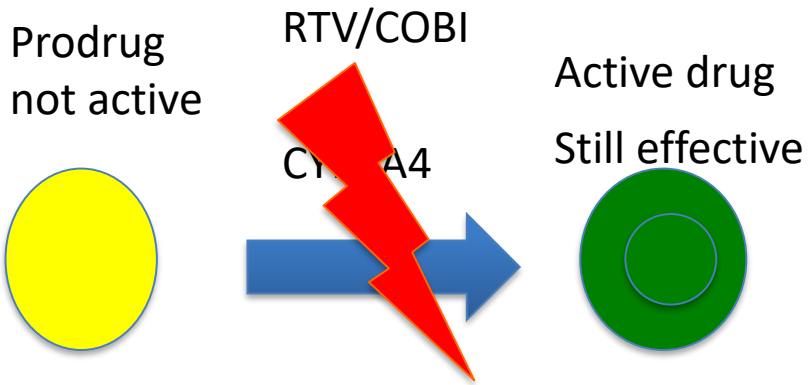
Probably not!!

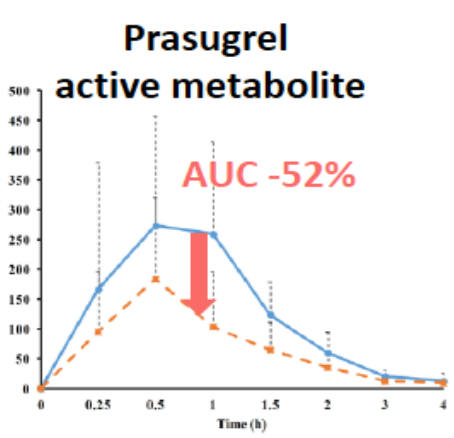
	Bictegravir/FTC/TAF	Cobicistat (with ATV or DRV)	Darunavir/Cobi/FTC/TAF	Darunavir/cobicistat	Dolutegravir
Aspirin (Anti-platelet)	◆	◆	◆	◆	◆
Clopidogrel	◆	●	●	●	◆
Prasugrel	◆	◆	◆	◆	◆
Ticagrelor	◆	●	●	●	◆

Prasugrel

Prasugrel is a prodrug and is converted to its active metabolite by CYP3A4 and CYP2B6.

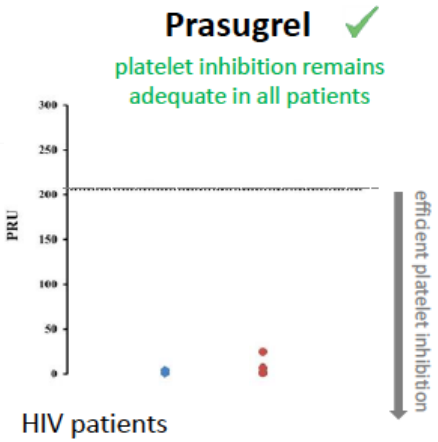
- Ritonavir (100 mg) has been shown to reduce prasugrel active metabolite Cmax and AUC by 45% and 38%, respectively, **but without a significant reduction in prasugrel efficacy** .





Cobicistat boosted regimen

ckade measured with VerifyNow®)

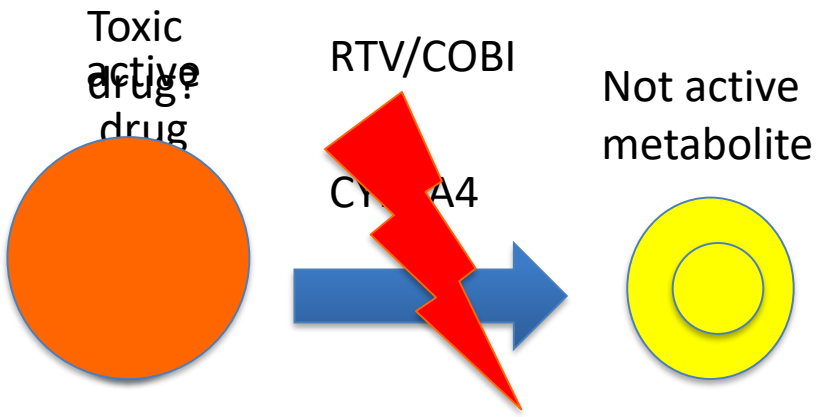


HIV patients

	Bictegravir/FTC/TAF	Cobicistat (with ATV or DRV)	Darunavir/Cobi/FTC/TAF	Darunavir/cobicistat	Dolutegravir
Aspirin (Anti-platelet)	◆	◆	◆	◆	◆
Clopidogrel	◆	●	●	●	◆
Prasugrel	◆	◆	◆	◆	◆
Ticagrelor	◆	●	●	●	◆

Ticagrelor

➢Coadministration of ticagrelor with strong inhibitors of CYP3A4 is contraindicated, as it may **lead to a substantial increase in exposure to ticagrelor**.



Pharmacokinetic drug interactions with clopidogrel: updated review and risk management in combination therapy

Zhu W,et al, Therapeutics and Clinical Risk Management 2018

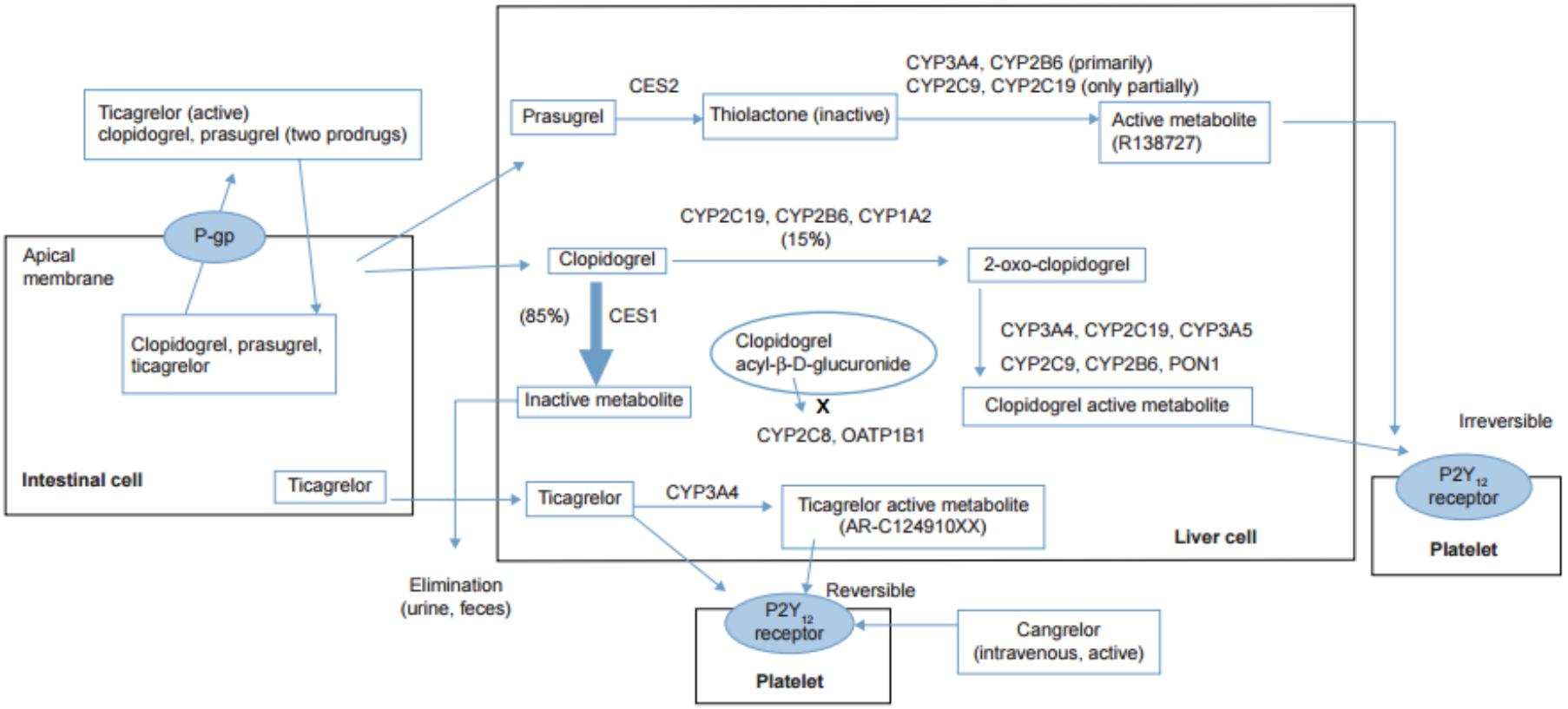
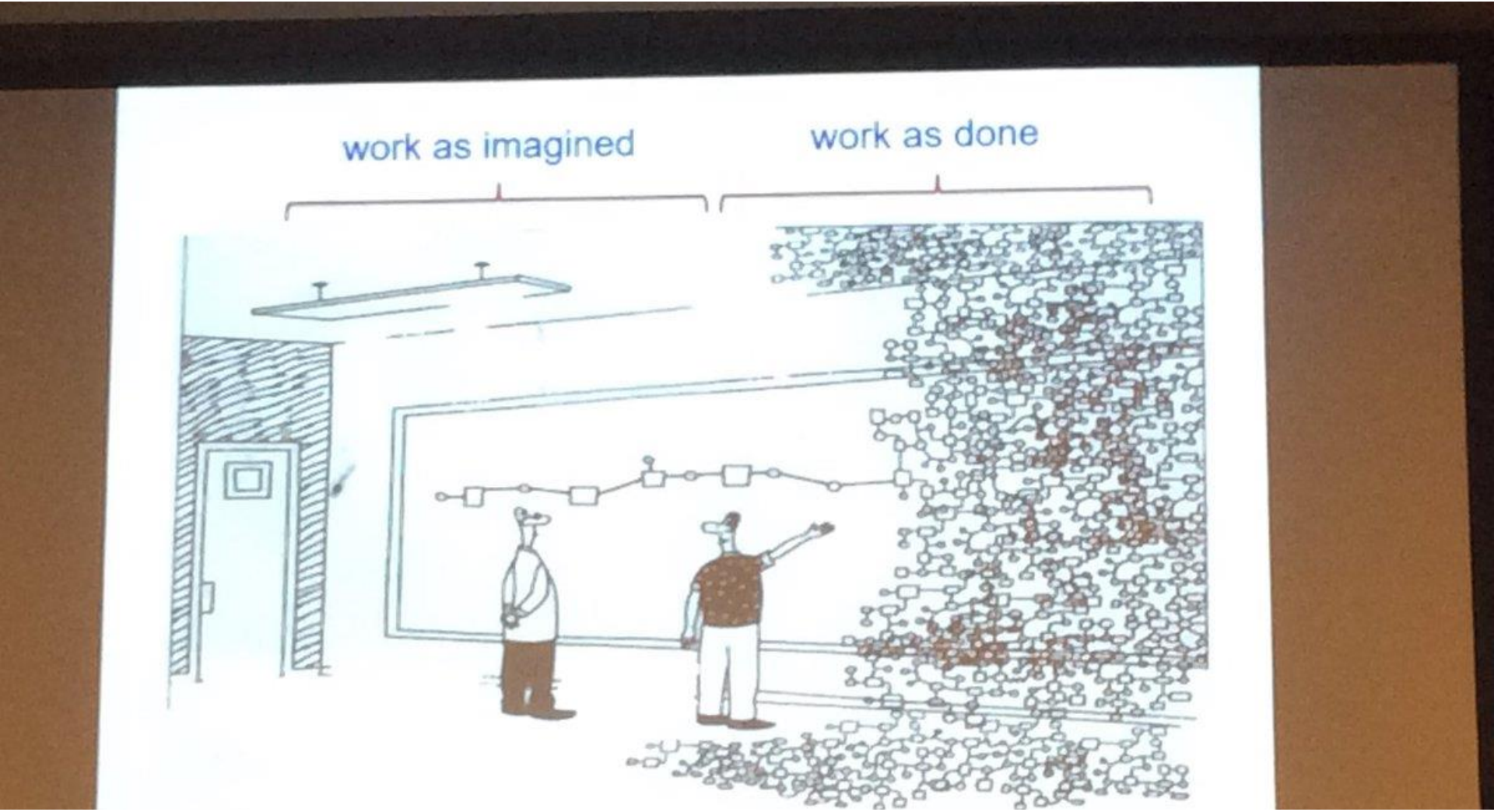


Figure 2 Metabolic profiles of $P2Y_{12}$ inhibitors.
Abbreviations: CES1, carboxylesterase 1; CES2, carboxylesterase 2; CYP, cytochrome P450; OATP1B1, organic anion transporter family 1B1; P-gp, P-glycoprotein; PON1, Paraoxonase-1.

Table 1 Summary of clopidogrel-associated drug-drug interactions

Circumstances	Comedications	Implications and risk management
1. Clopidogrel comedicated as a precipitant drug	Statins	Clopidogrel has a clinically relevant and significant DDI with cerivastatin instead of other statins. Simvastatin doses greater than 40 mg should be avoided in patients receiving ticagrelor.[14–21]
	Insulinotropic agents	Clopidogrel should not be comedicated with repaglinide in order to avoid occurrence of potential hypoglycemic events. Ticagrelor may be an alternative to clopidogrel in patients on repaglinide therapy. Nateglinide and mitiglinide may be alternatives to repaglinide when patients are concomitantly using clopidogrel.[15,22,23]
	Ferulic acid	Close monitoring for potential drug interactions may be necessary in patients who are receiving combined therapy with clopidogrel and ferulic acid-containing herbs, eg, Danggui (*Angelicae sinensis*) and Chuangxiong (*Rhizoma chuanxiong*).[25]
	Sibutramine	Careful treatment planning is required when clopidogrel is comedicated with sibutramine, especially in patients with a CYP2B6 functional deficit genotype.[28,29]
	Efavirenz	Clopidogrel may decrease elimination of efavirenz in HIV patients and therefore increase adverse effects of efavirenz, especially in patients with the *CYP2B6*6* genotype. Combinations like efavirenz-ticagrelor may be a better choice.[33,34]
	CYP2C19 substrates	Clinicians should pay more attention to the possible interactions of clopidogrel and substrate drugs of CYP2C19 because the prevalence of extensive metabolizers of CYP2C19 exceeds 50% in the population. Prasugrel and ticagrelor would not cause a clinically relevant interaction with CYP2C19 substrates.[27,36]
2. Clopidogrel comedicated as an object drug		
• Low efficacy of clopidogrel treatment would be anticipated	Omeprazole, esomeprazole	Clinicians should avoid prescribing omeprazole and esomeprazole in patients taking clopidogrel. The potential of PPIs to attenuate the efficacy of clopidogrel could be minimized by using pantoprazole, dexlansoprazole, or rabeprazole. Clopidogrel-esomeprazole DDI can be diminished by increasing the clopidogrel dose to 150 mg or replacing esomeprazole with ranitidine or famotidine. Prasugrel may be an alternative that can escape the adverse DDIs induced by PPIs.[37–47]
	Morphine	Coadministration of morphine is best avoided. Caution should be exercised in STEMI patients receiving morphine. Cangrelor, an intravenously administered direct-acting $P2Y_{12}$ receptor inhibitor, might be an ideal choice in STEMI patients receiving morphine.[49,50]
	Grapefruit juice	Use of grapefruit juice is best avoided during clopidogrel therapy, and both clinicians and patients should know the enhanced antiplatelet effect of ticagrelor in the presence of grapefruit juice to avoid the risk of potential bleeding events.[93,94]
	Scutellarin	Potential herb-drug interaction between scutellarin and clopidogrel should be borne in mind in clinical use to avoid a reduced antiplatelet effect.[51]
	Fluoxetine	Combination use of fluoxetine and clopidogrel should be avoided. Venlafaxine may be an alternative antidepressant comedicated with clopidogrel. Combination therapy of ticagrelor and venlafaxine is an alternative regimen.[52,53]
• Low efficacy of clopidogrel would be anticipated	Azole antifungal agents	Combination of clopidogrel and azole antifungal agents like ketoconazole and itraconazole should be avoided. Prasugrel is an alternative when comedicating with azole antifungal agents. Pharmacogenetic screening of *CYP3A5*3* should be performed prior to initiating combination therapy with clopidogrel and CYP3A inhibitors.[54–56]
	Some CCBs	Combination use of clopidogrel and amlodipine should be avoided. When concurrent treatment with clopidogrel and a CCB is initiated, close therapeutic monitoring is needed to prevent a potentially poor response to clopidogrel, especially in patients with a mutant *CYP3A4*1G* gene.[57–59]
	Sulfonylureas	Ticagrelor should be considered and clopidogrel should be avoided when initiating combination therapy of sulfonylureas and $P2Y_{12}$ receptor inhibitors.[61,62]
	Ritonavir	Avoid combinations such as ritonavir-clopidogrel and ritonavir-prasugrel (CYP3A4-mediated inhibition by ritonavir and a potentially lower antiplatelet effect) and clopidogrel-efavirenz (CYP2B6-mediated inhibition by clopidogrel and potentially increased efavirenz toxicity); choose combinations such as efavirenz-ticagrelor and ritonavir-ticagrelor since ticagrelor does not require metabolic activation; theoretically, nevirapine may enhance the metabolic activation of clopidogrel and offset the adverse DDI between clopidogrel and antiretroviral medications with inhibitory effects on CYP3A4.[7,34,63,64]



17:30 Beyond Liverpool site: how to evaluate the impact of a DDI in the clinical setting **(C. Alcantarini, S. Bonora)**