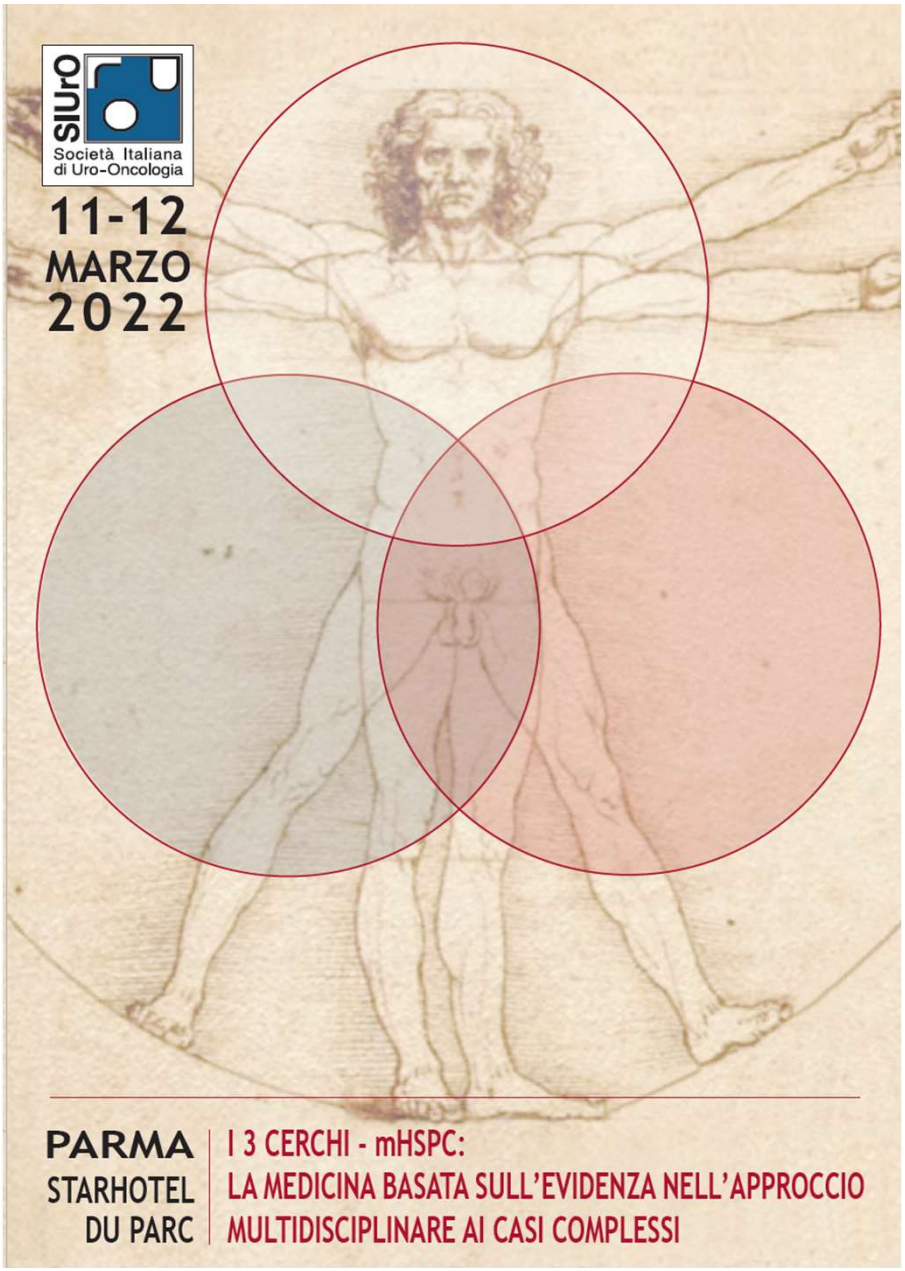


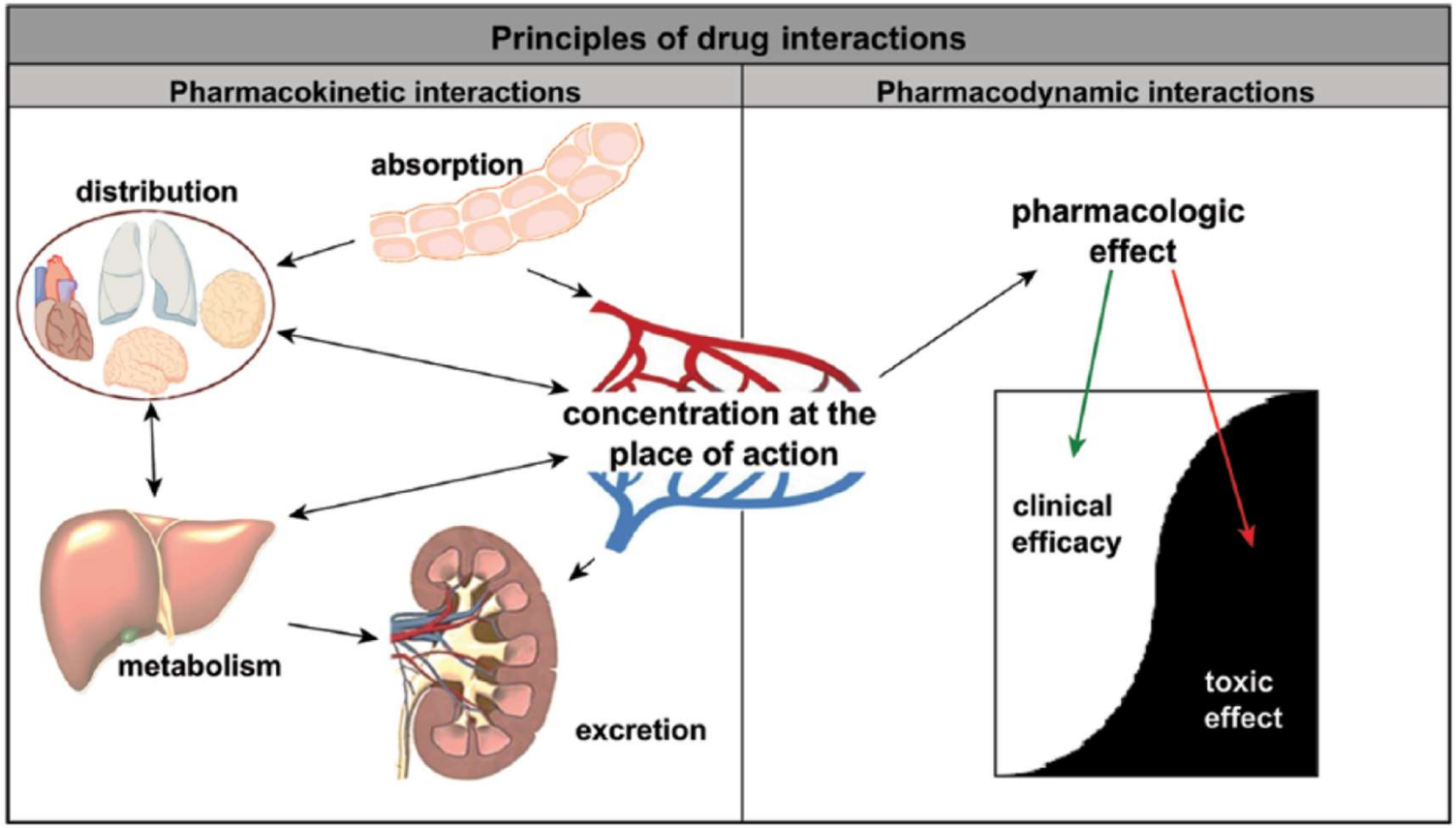
Le interazioni farmacologiche

Marzia Del Re

UO Farmacologia clinica e Farmacogenetica

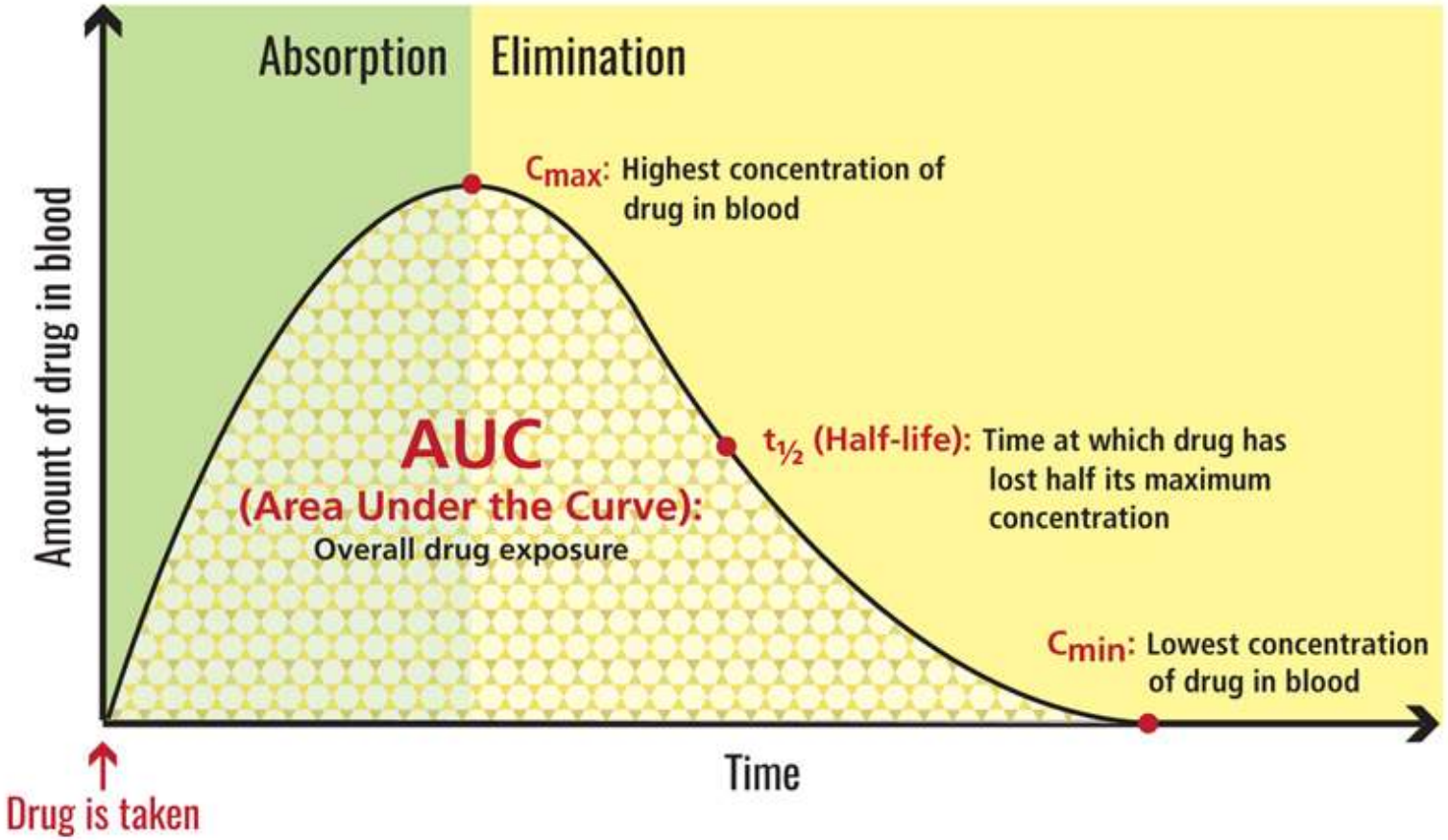
Università di Pisa

Potential mechanisms of drug interactions



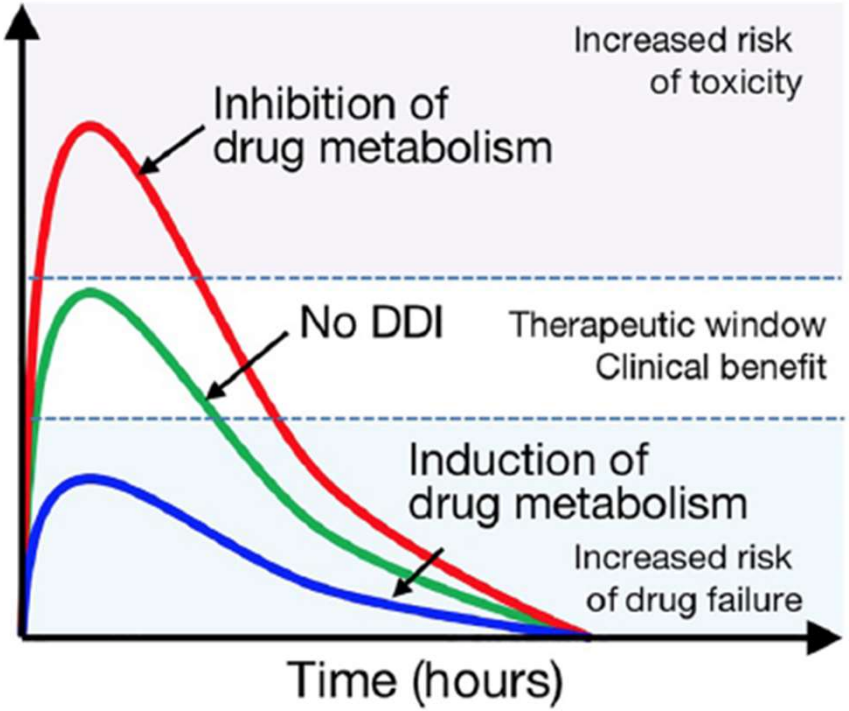
May M, et al. Ther Adv Endocrinol Metab. 2016 Apr; 7(2): 69–83

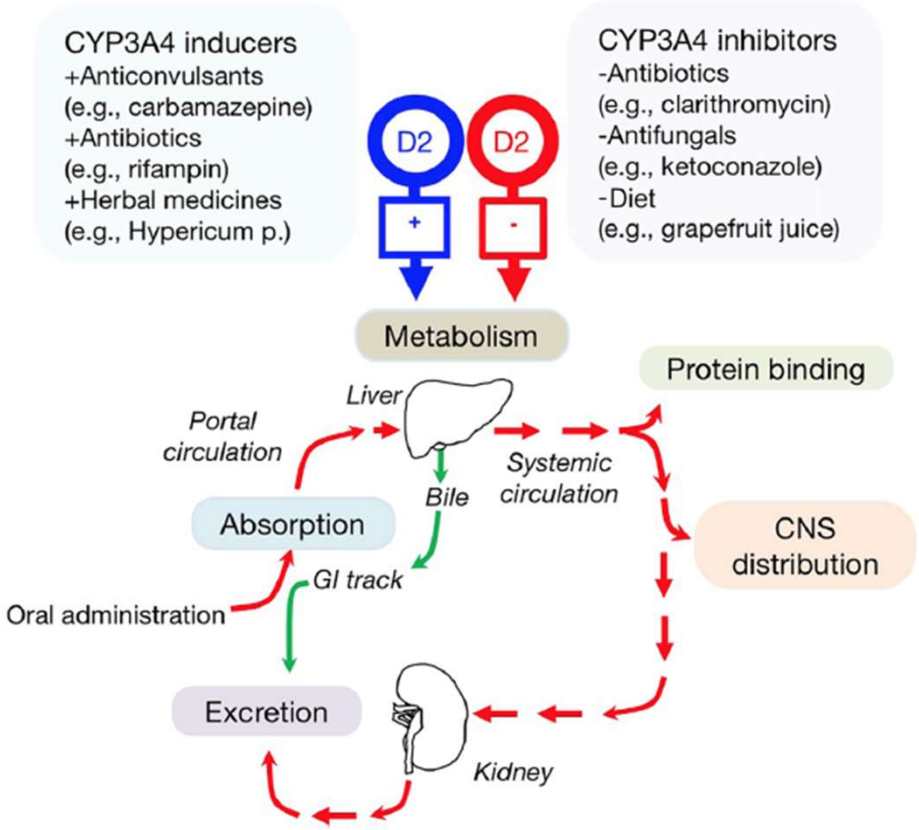
Pharmacokinetics (PK): Vocabulary



- AUC, area under the curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; PK, pharmacokinetics; $t_{1/2}$, half life.
- Clinical Info. Available at: https://clinicalinfo.hiv.gov/en/glossary/pharmacokinetics. Accessed September 2021.

PK overview of DDIs effect





Fogli S, et al. Cancer Treatment Reviews 74 (2019) 21–28

Abiraterone

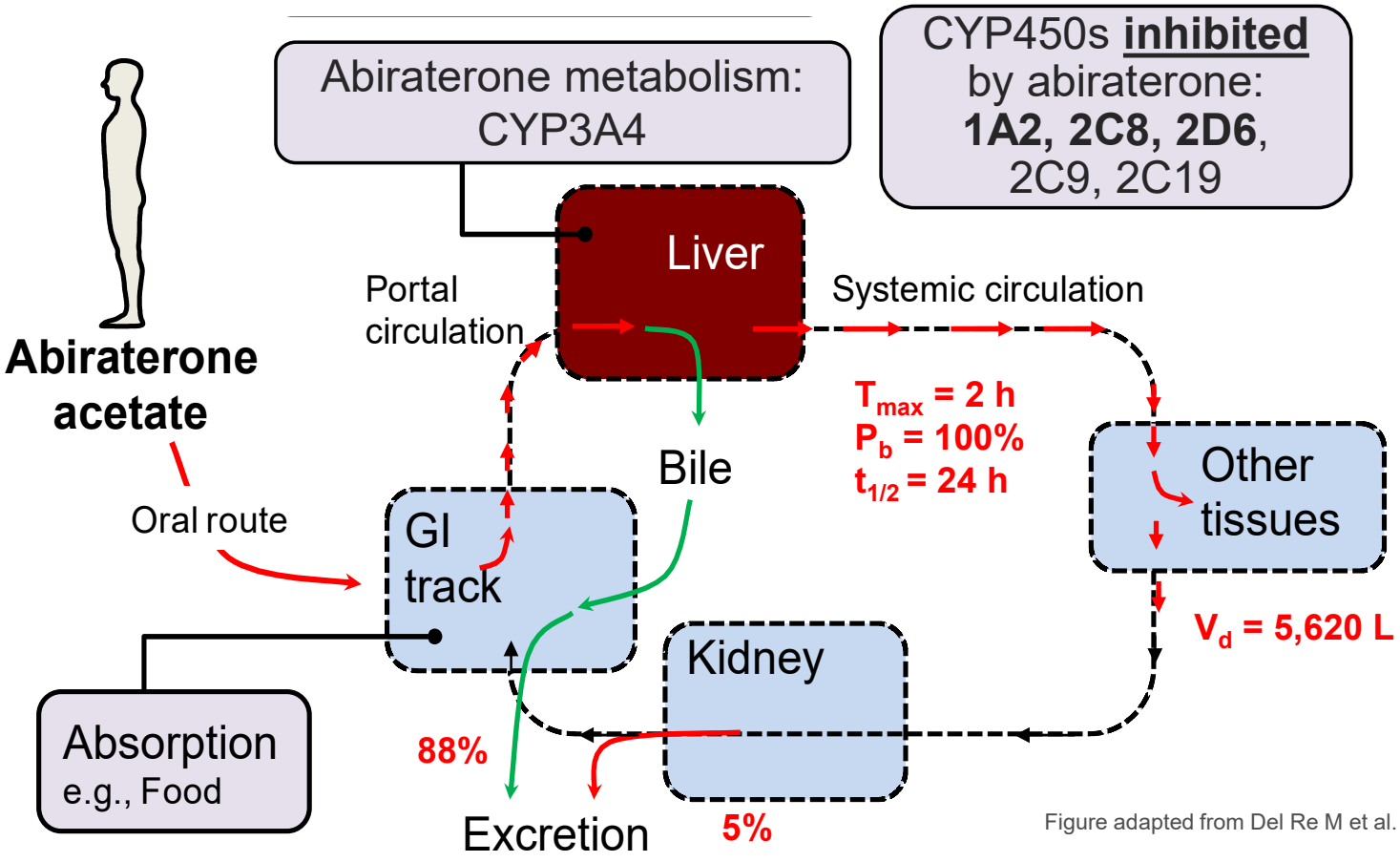


Figure adapted from Del Re M et al. 2017[1]

- GI, gastrointestinal; P_b, plasma protein binding; $t_{1/2}$, half life; T_{max}, time of maximum plasma concentration; V_d, mean apparent distribution volume.
- Del Re M et al. *Cancer Treat Rev* 2017;55:71–82.

Enzalutamide

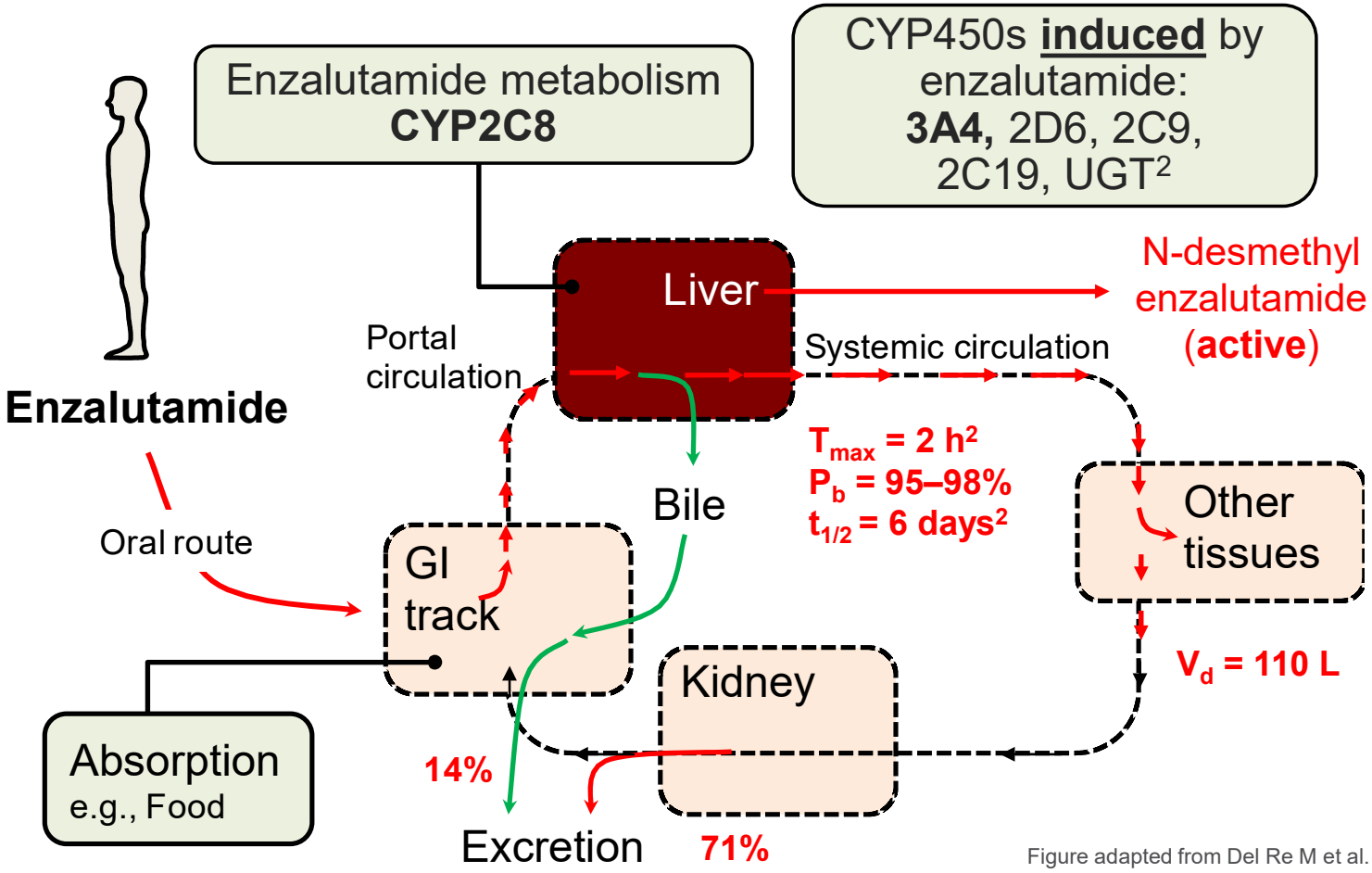
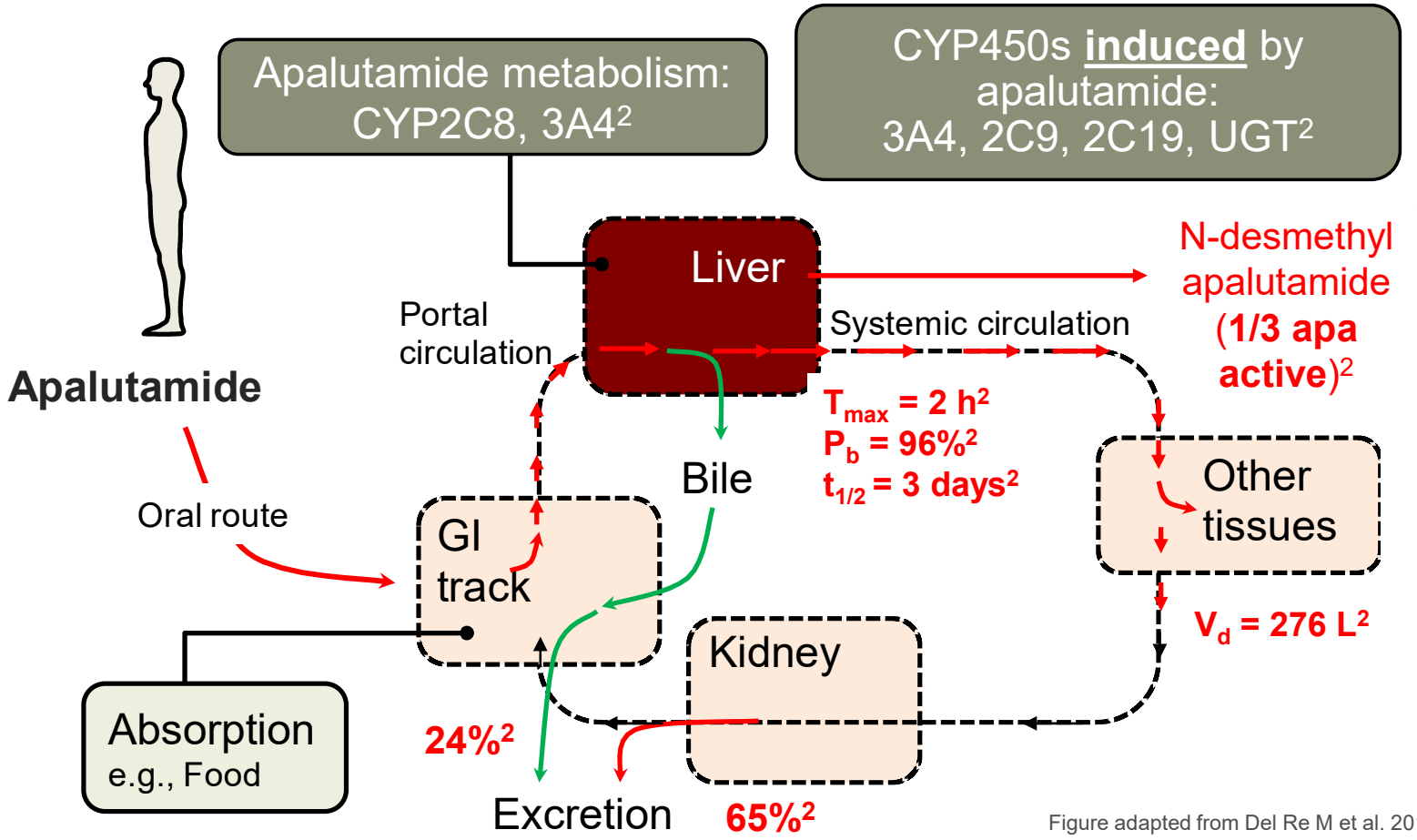


Figure adapted from Del Re M et al. 2017[1]

- GI, gastrointestinal; P_b, plasma protein binding; $t_{1/2}$, half life; T_{max}, time of maximum plasma concentration; UGT, uridine 5'-diphospho-glucuronosyltransferase; V_d, mean apparent distribution volume.
- 1. Del Re M et al. *Cancer Treat Rev* 2017;55:71–82; 2. Astellas Pharma Ltd. XTANDI (enzalutamide). Summary of Product Characteristics.

Apalutamide



The contribution of CYP2C8 and CYP3A4 in the metabolism of apalutamide is estimated to be 58% and 13% following single dose[2,3] but changes to 40% and 37%, respectively at steady-state[3]

Figure adapted from Del Re M et al. 2017[1]

- apa, apalutamide; GI, gastrointestinal; P_b, plasma protein binding; $t_{1/2}$, half life; T_{max}, time of maximum plasma concentration; UGT, uridine 5'-diphospho-glucuronosyltransferase; V_d, mean apparent distribution volume.

- 1. Del Re M et al. *Cancer Treat Rev* 2017;55:71–82; 2. Janssen-Cilag Ltd. ERLEADA (apalutamide) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/9832. Accessed September 2021; 3. Janssen-Cilag Ltd. ERLEADA (apalutamide) US Prescribing Information. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ERLEADA-pi.pdf. Accessed September 2021.

Darolutamide

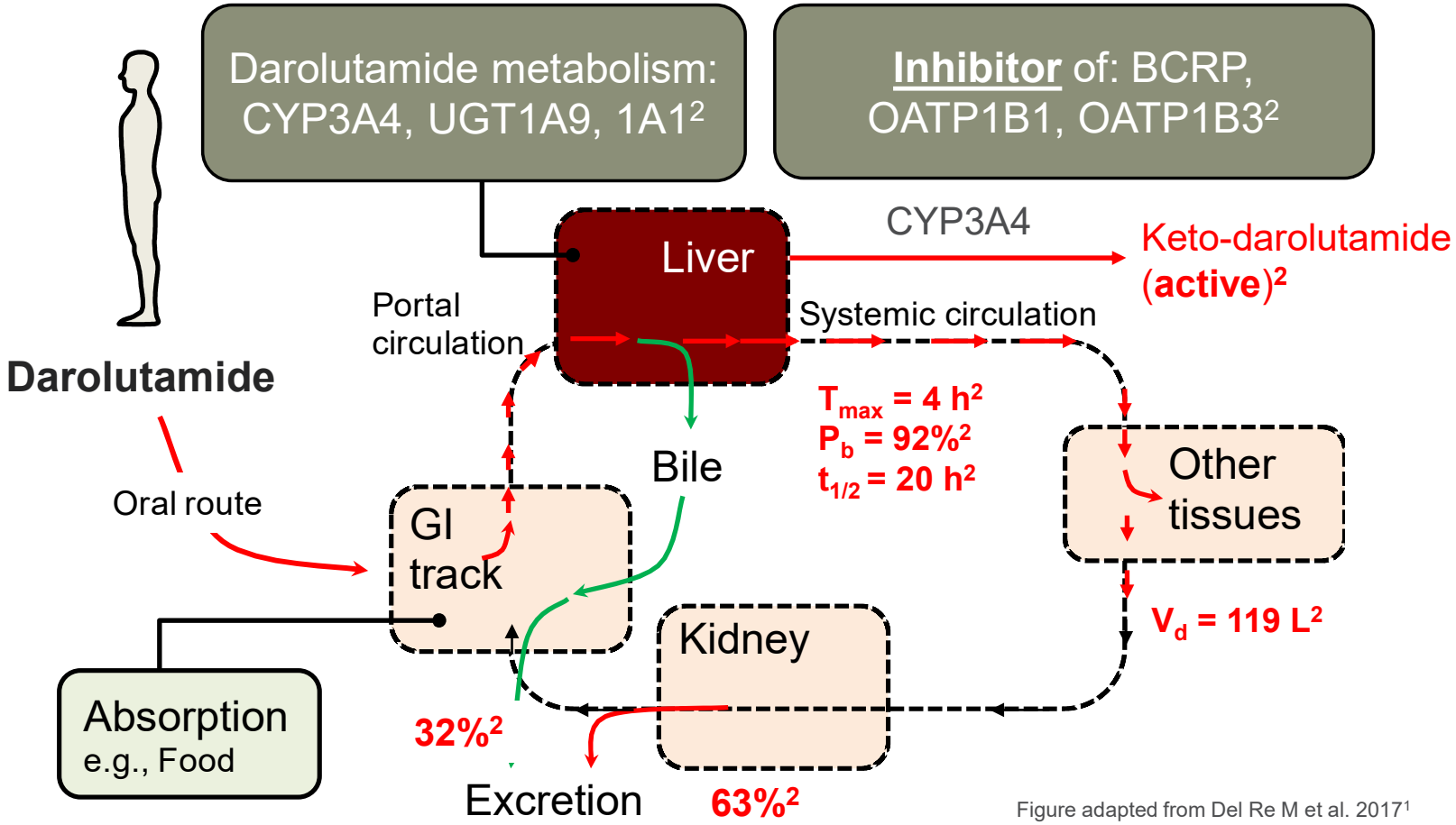


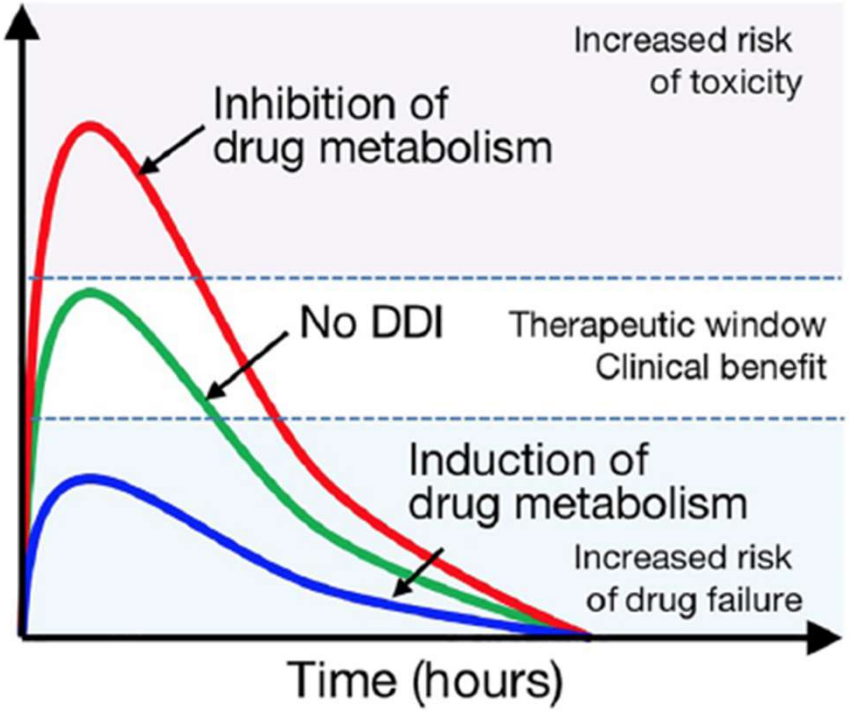
Figure adapted from Del Re M et al. 2017[1]

- GI, gastrointestinal; P_b, plasma protein binding; $t_{1/2}$, half life; T_{max}, time of maximum plasma concentration; V_d, mean apparent distribution volume.
- 1. Del Re M et al. *Cancer Treat Rev* 2017;55:71–82;
  2. Bayer plc. NUBEQA (darolutamide) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/11324. Accessed September 2021.

Drugs & CYPs

Drug	Substrate	Inducer/inhibitor
Abiraterone	CYP3A4	Inhibitor of 1A2, 2C8, 2D6, 2C9, 2C19
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3

PK overview of DDIs effect



Drug-drug interactions may further reduce the safety drugs with **narrow therapeutic index** (e.g., anticancer and immunosuppressants, opioid analgesics, selected cardiovascular medications, anticoagulants - warfarin).

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Drug-drug interactions - Cardiovascular

ADT	Substrate - metabolism	Induction/ inhibition	DDI effect	Concomitant drug	Substrate - metabolism	DDI effect
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓	Dabigatran	CES1, CES2, UGT1A9, 2B7, 2B15, PgP	✓
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✓
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	Perpetrator	Apixaban	CYP3A4/5, 1A2, 2C8, 2C9, 2C19, 2J2, PgP, BCRP	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	Perpetrator			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	Perpetrator			✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	Perpetrator	Rivaroxaban	CYP3A4, 3A5, CYP2J2, PgP, BCRP	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	Perpetrator			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	Perpetrator			✗ Victim

https://go.drugbank.com/drugs/

Drug-drug interactions - Diabetes

ADT	Substrate - metabolism	Induction/ inhibition	DDI effect	Concomitant drug	Substrate/ metabolism	DDI effect
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✗ Victim			Perpetrator
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim	**Metformin**	CYP3A4 down-regulation	Perpetrator
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✓
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓			✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✓	**Phenformin**	CYP2D6	✓
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓			✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✓	**Gliben-clamide**	CYP3A4, 2C9, 2C8	✓
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✗ Victim

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Drug-drug interactions - Hypertension

ADT	Substrate - metabolism	Induction/ inhibition	DDI effect	Concomitant drug	Substrate/ metabolism	DDI effect
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✗ Victim	**Losartan**	CYP2C9, 3A4,2C8, UGT1A1	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim		Inhibitor of CYP2C8 and 3A4	✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✗ Victim			✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✗ Victim	**Amlodipine**	CYP3A4, 1A1, 2B6, 2C8, 2D6, UGT, PgP	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✗ Victim		Inhibitor of CYP1A1, 3A4, 2B6, 2C9, 2C8	✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓	**Hydrochloro thiazide**	No metabolism	✓
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✓			✓
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✓

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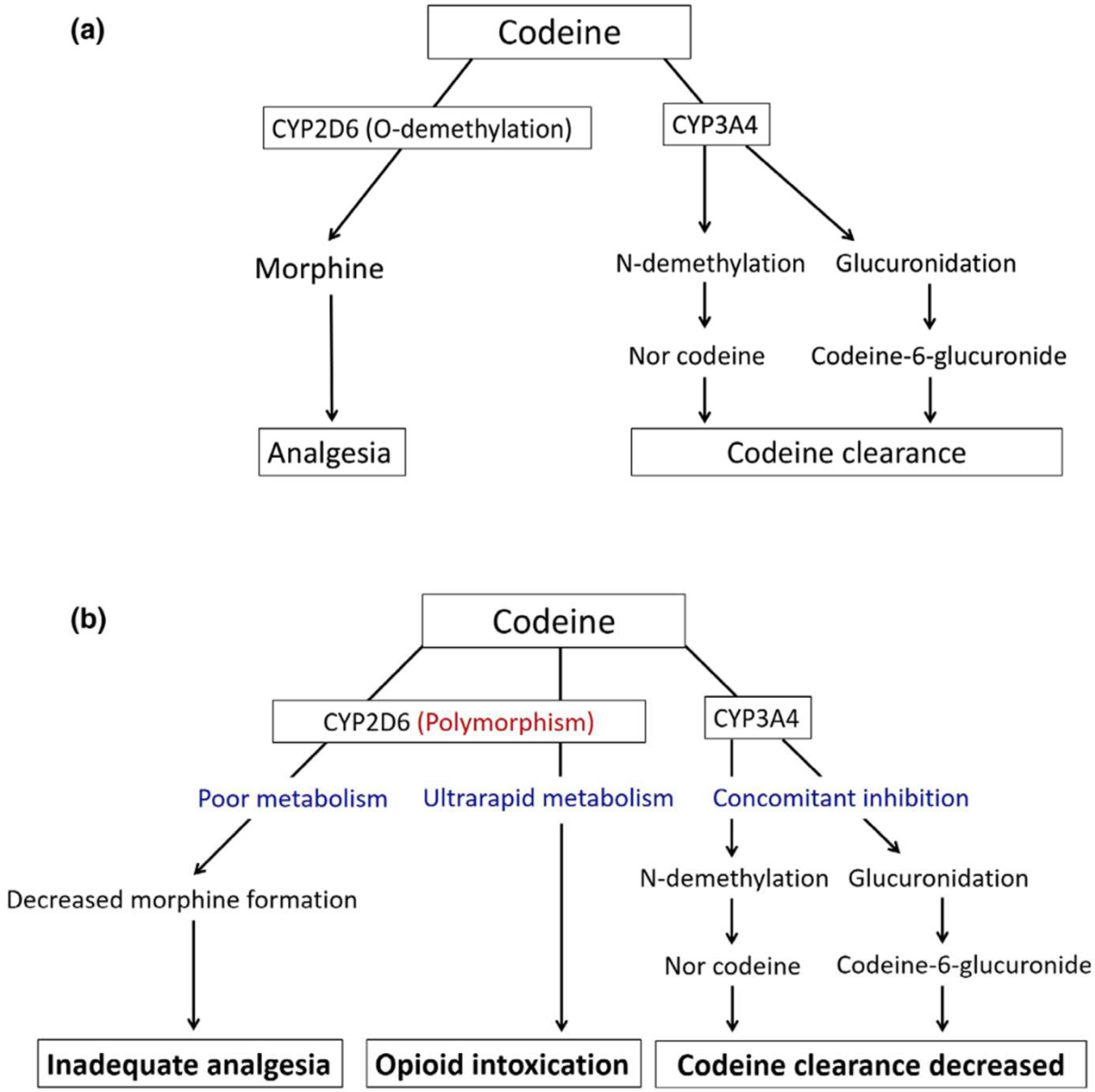
Sartani

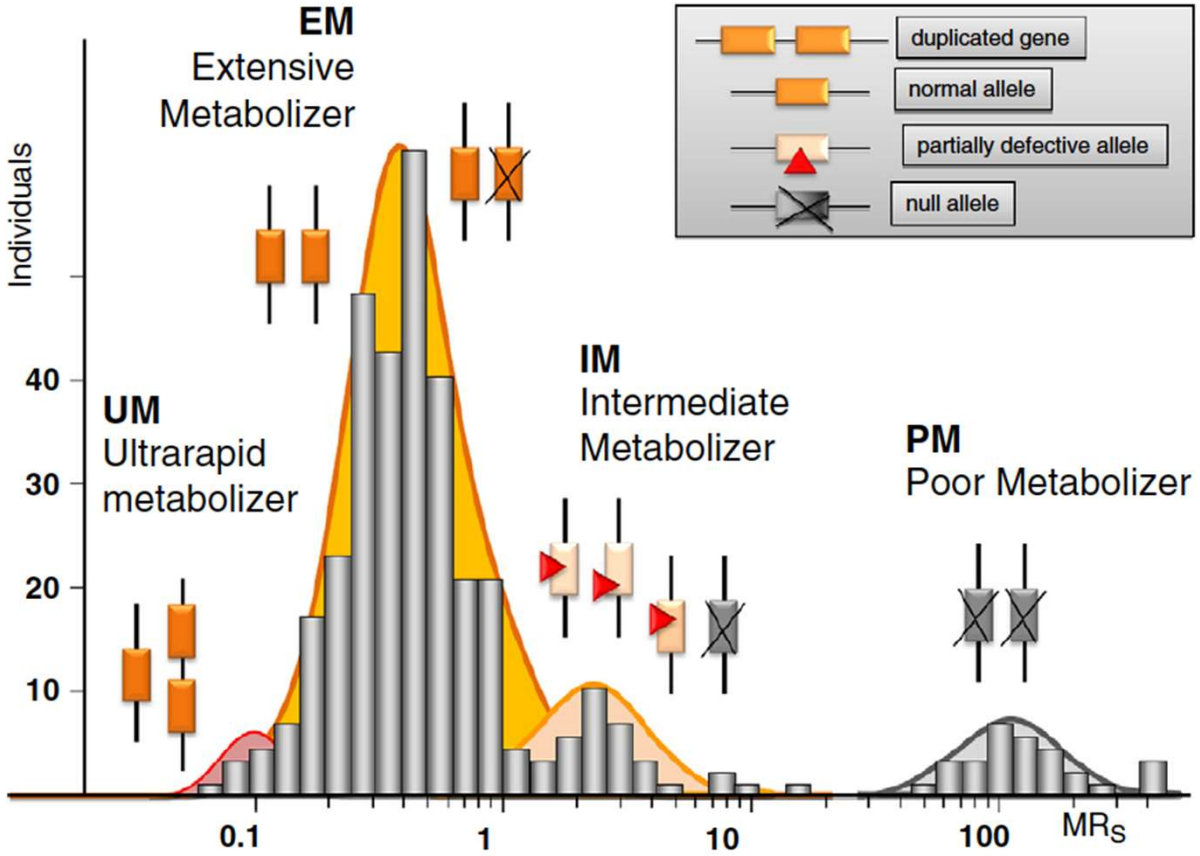
VALUTAZIONE COMPARATA DELLA FARMACOCINETICA					
Losartan	**Eprosartan**	**Valsartan**	**Irbesartan**	**Candesartan**	**Telmisartan**
Biodisponibilità: circa 33%	**Biodisponibilità**: circa 13%	**Biodisponibilità**: circa 23%	**Biodisponibilità**: circa 60 - 80%	**Biodisponibilità**: circa 14 %	**Biodisponibilità**: circa 42 - 58%
Cibo: nessun effetto su AUC / Cmax	**Cibo**: riduzione di circa il 25% della Cmax e dell'AUC	**Cibo:** riduzione della Cmax di circa il 50% e dell'AUC del 40%	**Cibo**: non influenza la biodisponibilità	**Cibo:** non influenza la biodisponibilità	**Cibo**: riduzione della AUC dal 6% al 20% in base al dosaggio
Metabolismo: epatico di 1° passaggio con formazione di un metabolita attivo (14% della quota di farmaco) e altri inattivi, tramite il citocromo P450 2C9 e gli isoenzimi 3A4	**Metabolismo:** epatico per una ridotta quota di farmaco, mediante coniugazione a glucuronide	**Metabolismo:** epatico per circa il 20% della quota di farmaco (con probabile coinvolgimento di isoenzimi del citocromo P450)	**Metabolismo**: epatico per una quota di farmaco < 20%, mediante ossidazione con isoenzimi del citocromo P450 (in particolare 2C9)	**Metabolismo**: epatico per una ridotta quota di farmaco con formazione di un metabolita inattivo	**Metabolismo**: epatico mediante coniugazione a glucuronide, metabolita inattivo (circa 11% della quota di farmaco)
Emivita: circa 2 h (6-9 h per il metabolita attivo)	**Emivita**: circa 5-9 h	**Emivita**: circa 6 h	**Emivita**: circa 11-15 h	**Emivita**: circa 9 h	**Emivita**: circa 24 h
Legame proteico: ≥ 99%	**Legame proteico:** 98%	**Legame proteico:** 94-97 %	**Legame proteico:** 96%	**Legame proteico:** > 99%	**Legame proteico:** > 99,5%
Eliminazione: per via biliare (60%) e per via urinaria (35%). Né losartan né il suo metabolita attivo vengono rimossi con emodialisi.	**Eliminazione**: principalmente per via biliare (90%); il 7% per via urinaria.	**Eliminazione:** principalmente per via biliare (83%); il 13% per via urinaria.	**Eliminazione:** principalmente per via biliare (80%); il 20% per via urinaria.	**Eliminazione:** per via biliare (67%) e per via urinaria (33%).	**Eliminazione:** quasi completamente per via biliare (97%).

Opioids



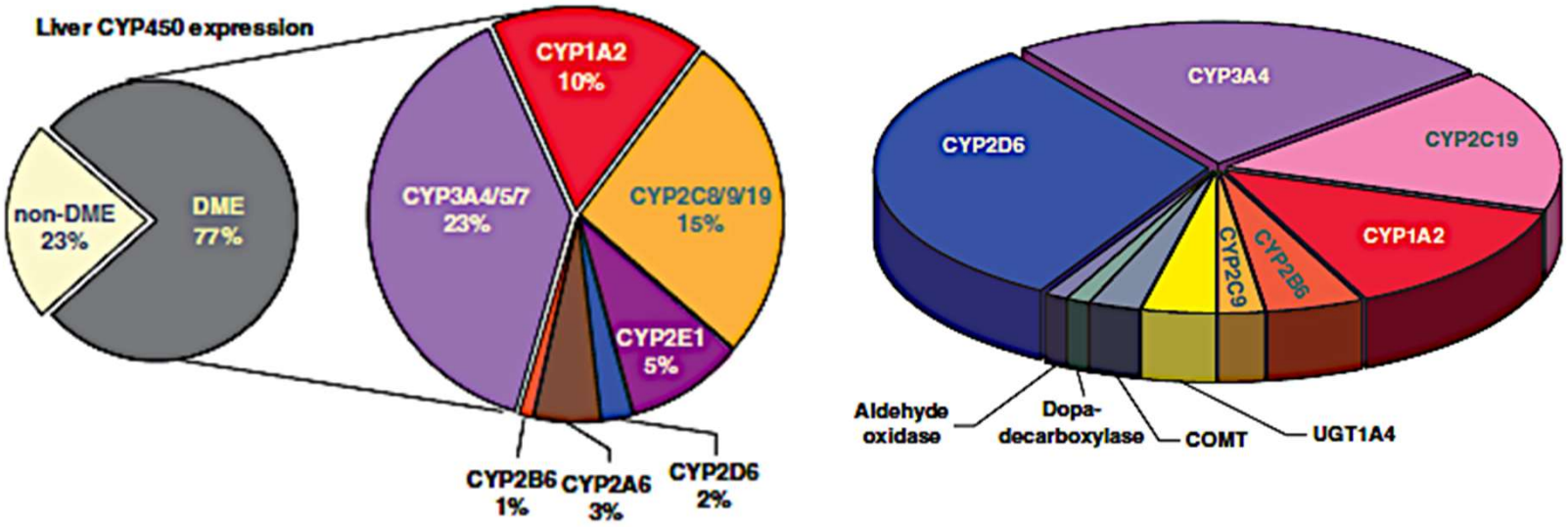
Anaesthesia 2019, 74, 1456-1470

Phenotype and genotype distribution and nomenclature



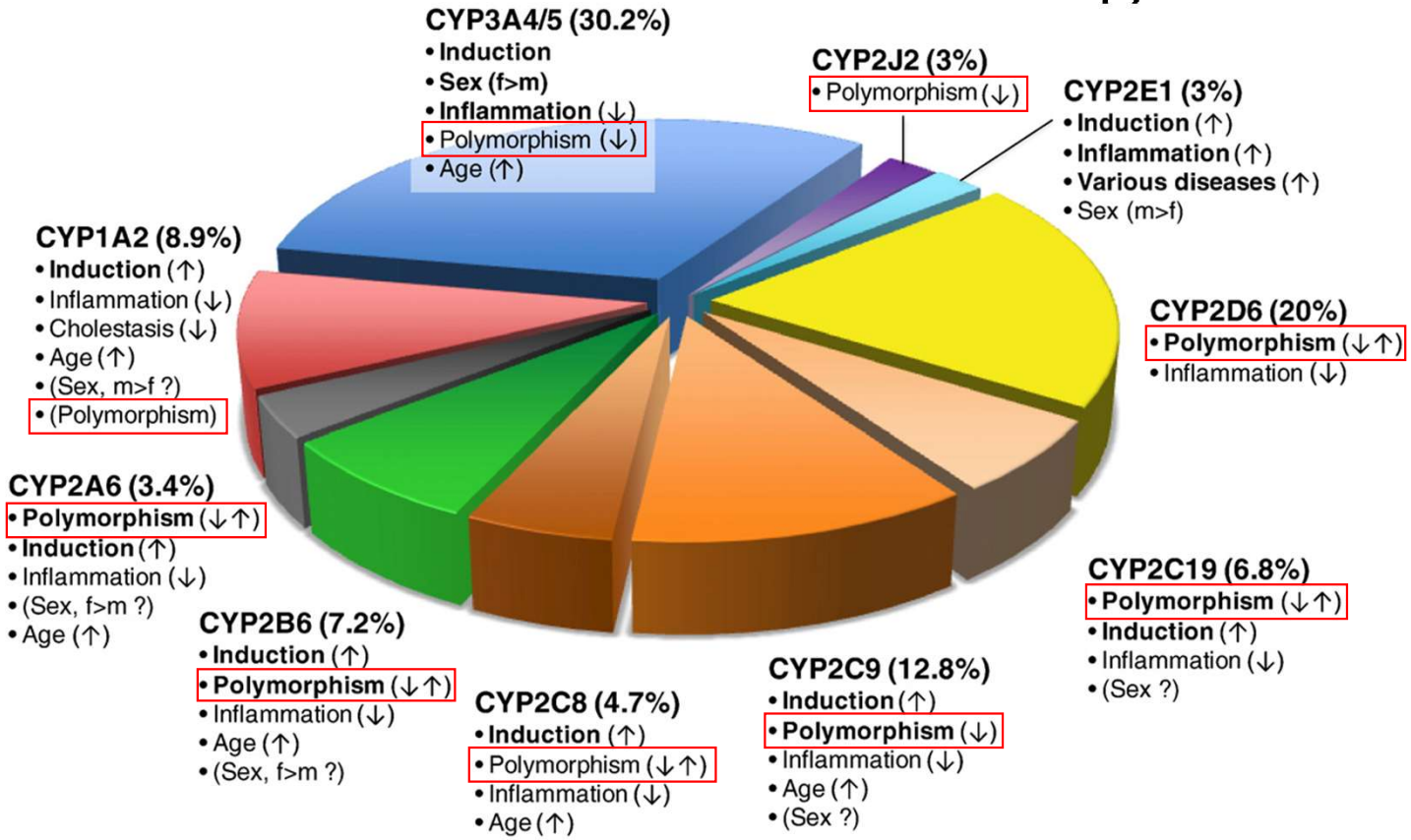
Zanger UM, Schwab M. Pharmacology & Therapeutics 138 (2013) 103–141

Relative amount of the CYP450 enzymes in the liver and their role in drug metabolism



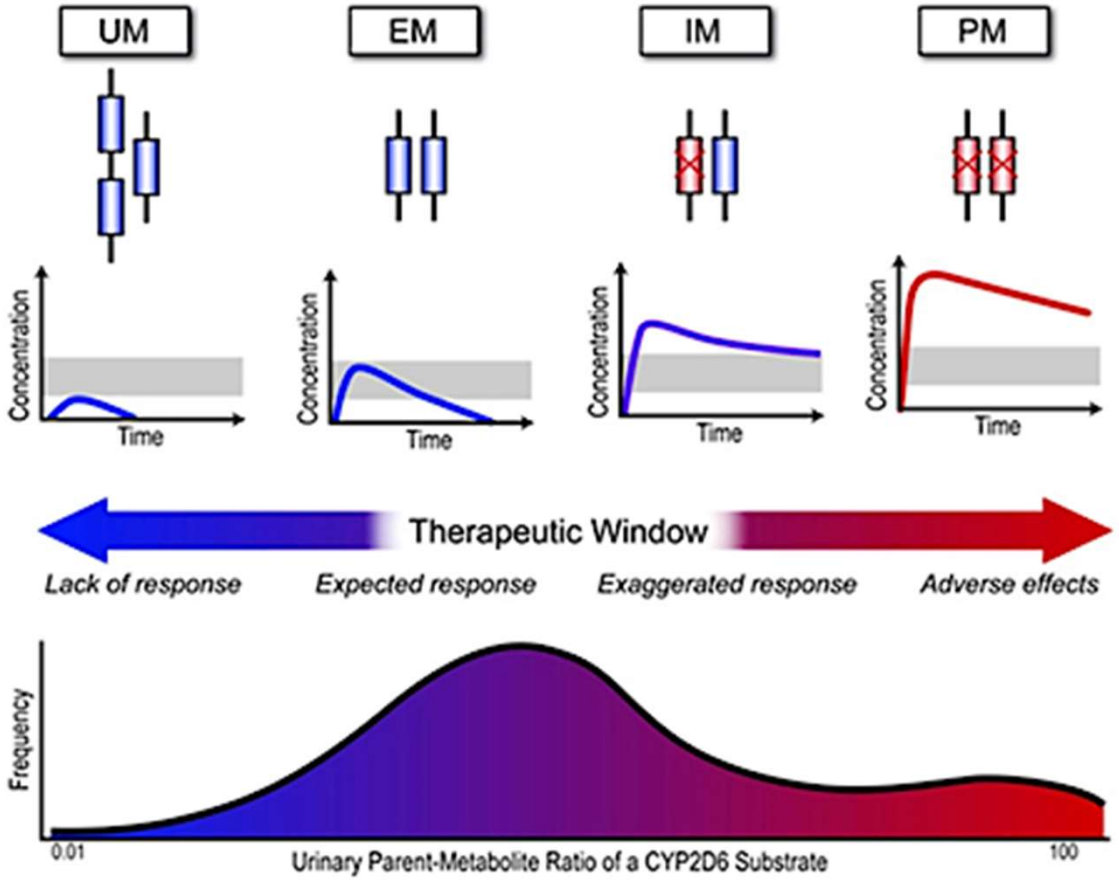
Stingl JC et al. Molecular Psychiatry (2013) 18, 273-287

Fraction of clinically used drugs metabolized by P450 isoforms and factors influencing variability



Zanger UM, Schwab M. Pharmacology & Therapeutics 138 (2013) 103–141

Relative contribution of individual DMEs in the metabolism



Selected genetic polymorphisms of human CYP3A4/5

CYP allele designation[a]	Key mutation(s)[b] rs number	Location, protein effect	Allele frequencies[c]	Functional effect
*CYP3A4*22*	15389 C>T (rs35599367)	Intron 6	gMAF 0.021 0.043 AA 0.043 As 0.025–0.08 Ca	↓ Expression & activity
*CYP3A5*3*	6986A>G (rs776746)	Intron 3, splicing defect	gMAF 0.312 0.37 AA 0.12–0.35 Af 0.66–0.75 As, Hs 0.88–0.97 Ca	↓↓ Expression & activity
*CYP3A5*6*	14690A>G (rs10264272)	Exon 6, K208, splicing defect	gMAF 0.045 0.15–0.25 Af 0.12 AA 0.00 As, Ca, His	↓↓ Expression & activity

gMAF, global allele frequency of the minor allele as reported in the 1000Genome phase 1 genotype data. Selected frequencies of individual ethnicities (AA, African American; Af African; As Asian; Ar, Arab; Ca Caucasian; Hs, Hispanic; In, Indian; Pc, Pacific; SA, South American) were compiled from dbSNP.

Zanger UM, Schwab M. Pharmacology & Therapeutics 138 (2013) 103–141

Selected genetic polymorphisms of human CYP2D6

CYP allele designation[a]	Key mutation(s)[b] rs number	Location, protein effect	Allele frequencies[c]	Functional effect
*CYP2D6*3*	2549delA (rs35742686)	Frameshift	gMAF 0.009 ~0.01 all ethnicities	*Null* allele
*CYP2D6*4*	1846G>A (rs3892097)	Splicing defect	gMAF 0.106 0.01–0.10 AA, Af, As, Hs 0.15–0.25 Ca	*Null* allele
*CYP2D6*5*	Recombination	Deletion	0.03–0.06 all ethnicities	*Null* allele
*CYP2D6*6*	1707delT (rs5030655)	Frameshift	gMAF 0.01 ~0.01 all ethnicities	*Null* allele

gMAF, global allele frequency of the minor allele as reported in the 1000Genome phase 1 genotype data. Selected frequencies of individual ethnicities (AA, African American; Af African; As Asian; Ar, Arab; Ca Caucasian; Hs, Hispanic; In, Indian; Pc, Pacific; SA, South American) were compiled from dbSNP.

Zanger UM, Schwab M. Pharmacology & Therapeutics 138 (2013) 103–141

Take home messages

- Due to the different induction and inhibition of CYPs and transporters a different DDI profile is expected.
- Drug-drug interactions may further reduce the safety of drugs with narrow therapeutic index (e.g., anticancer and immunosuppressants, opioid analgesics, selected cardiovascular medications, anticoagulants - warfarin).
- Interaction between drugs with narrow therapeutic index should be carefully evaluated and, whenever a drug substitution is not possible, therapeutic drug monitoring should be performed.

With your genes? Take one of these, three times a day

Truly 'personalized' medicine remains a distant goal. But researchers are now thinking about how to use genomic data to avoid prescribing drugs that may kill, or won't work. Alison Abbott reports.

Abbott A. Nature, 2003

My **pharmacogenetic** ID