Training course:
Pharmacotherapy in Older People

Drug metabolism in older people

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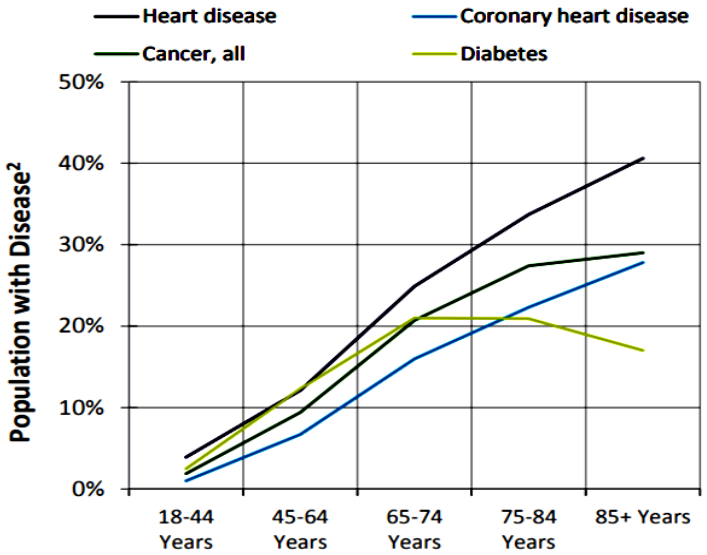
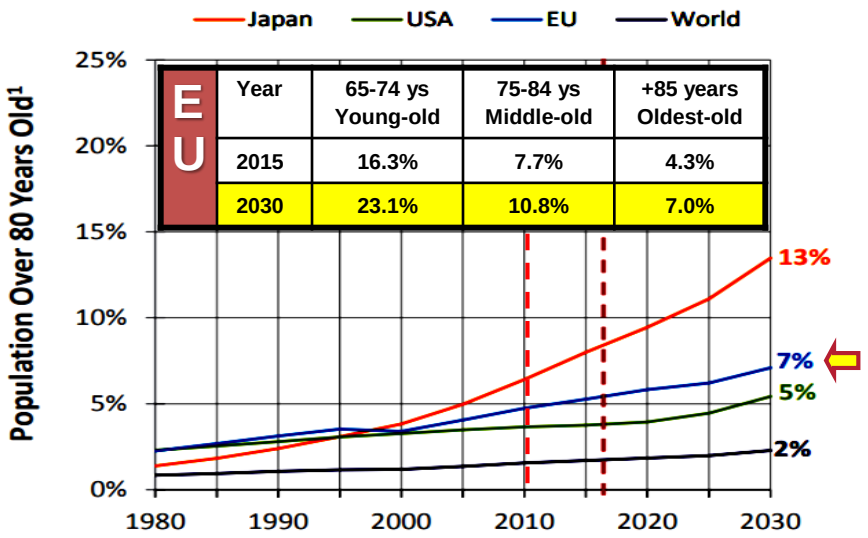
Aging populations worldwide are leading to more chronic diseases and greater demand of care





EU

Year	65-74 ys Young-old	75-84 ys Middle-old	+85 years Oldest-old
2015	16.3%	7.7%	4.3%
2030	23.1%	10.8%	7.0%

- Today, someone 65 years of age can anticipate living another 18-20 years
- Increasing life expectancy has resulted in a progressive increase in elderly adults with chronic diseases and comorbidities (pluripathology) leading to an increased number of medications (polypharmacy)
- Individuals aged >80 years are the fastest growing group

Health Advances analysis; OECD Health Statistics Database and CDD Health Interactive Data from NHIS , UK

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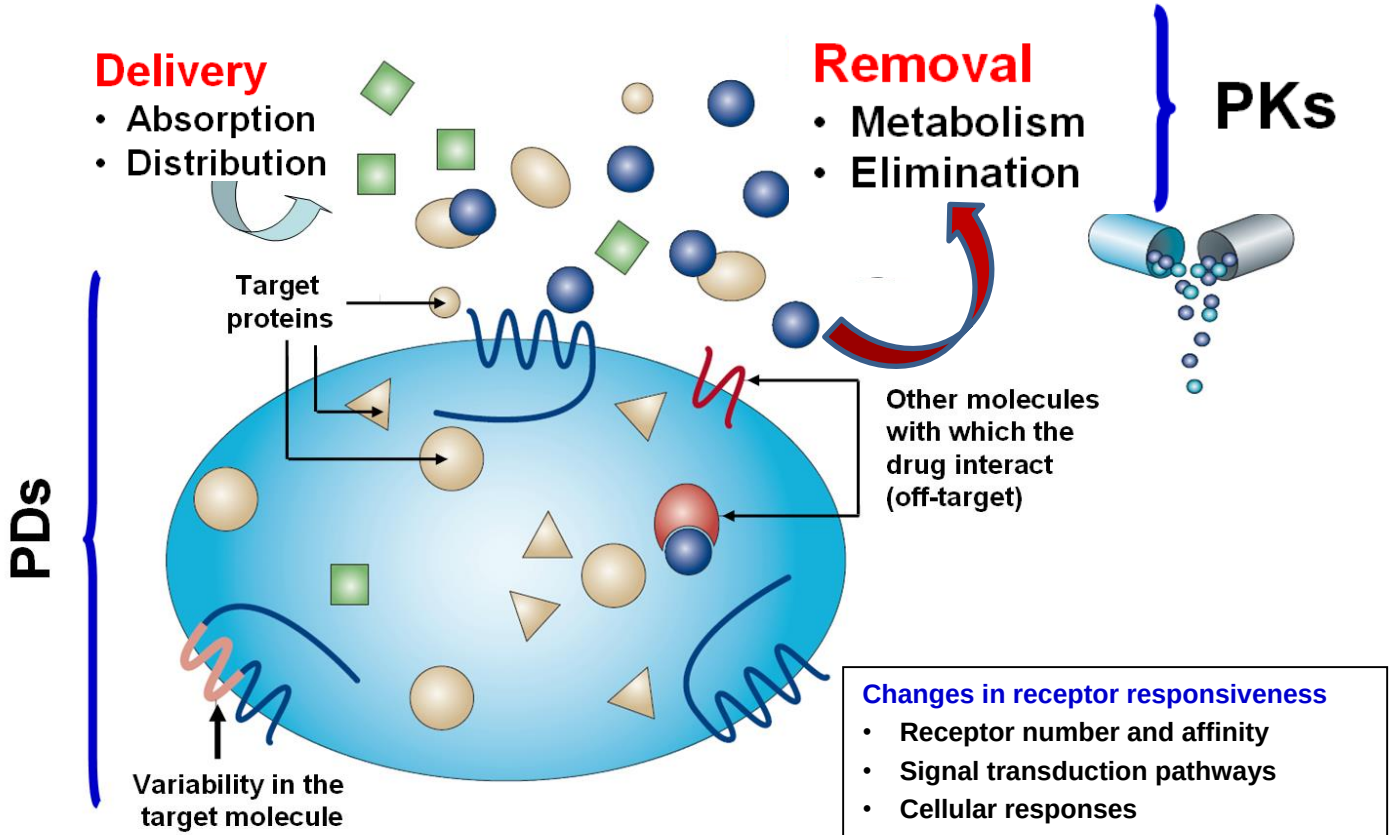
PK/PD determinants of drug action in the elderly



Changes in receptor responsiveness

- Receptor number and affinity
- Signal transduction pathways
- Cellular responses

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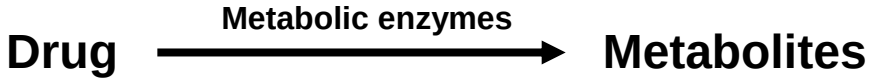
Agenda

- The concept of drug metabolism (biotransformation)
- Phases I and II of drug metabolism
  - Enzymes and sites of metabolism
- Enzyme induction and inhibition
- Factors affecting drug metabolism
  - Role of genetics in drug metabolism

Drug metabolism

- Many drugs are lipophilic compounds and do not pass ready into the aqueous enviroment of the urine
- They must first undergo a variety of enzymatic changes (i.e., biotransformed) in different tissues leading to metabolites that are readely eliminated in urine or bile
- Also applicable to endogenous compounds (steroid hormones, cholesterol, fatty acids)
- We need to understand these changes because they explain:
  - Changes in drug efficacy and safety
  - Drug interactions derived from the induction/inhibition of metabolic enzymes



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Hepatic function/metabolism progressively declines with advancing age

Paramater	Change	Consequence
Metabolism 	• ↓ liver size and mass (20-30%) • ↓ hepatic blood flow (20-40%) • ↓ liver´s capacity (≥30%) for phase I metabolism (CYPs)	• ↓ bioavailability of predrugs (ACEIs) • ↓ drug metabolism • ↑ exposure and $t_{½}$ of highly metabolized drugs

Analgesics	• NSAIDs: ibuprofen, naproxen, paracetamol • Meperidine
Cardiovascular	• Antiarrhythmics: amiodarone, lidocaine, propafenone, quinidine • β-blockers: labetalol, metoprolol, propranolol • CCBs • Theophylline • Warfarin

Psychoactive	• Benzodiazepines: alprazolam, chlordiazepoxide, diazepam, flurazepam, triazolam • Phenytoin • TCAs: Amitriptyline*, desipramine, imipramine, nortryptiline • Trazodone
Other	• Diphenhydramine • Levodopa • Tolbutamide

CCBs. Calcium channel blockers

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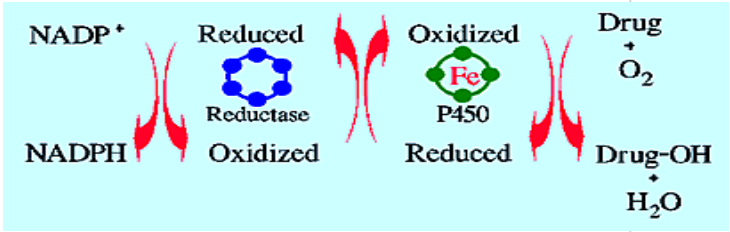
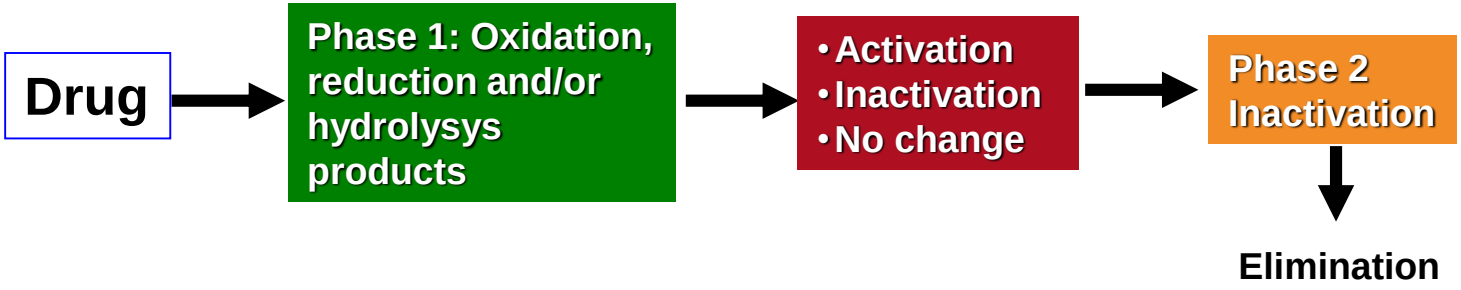
Drug metabolism (1)

Phase I reactions: oxidation, reduction and hydrolysys

- Cytochromes P450: a family of enzymes containing heme-iron as a cofactor that function as monooxygenases
- Lipophilic drugs are converted to water-soluble metabolites of lesser, equal, or greater effect
- Location: hepatocyte (smooth endoplasmic reticulum) and intestinal mucosa
  - Other organs: lungs, kidneys – they are substrate specific
- Phase I reactions DECLINE in the elderly





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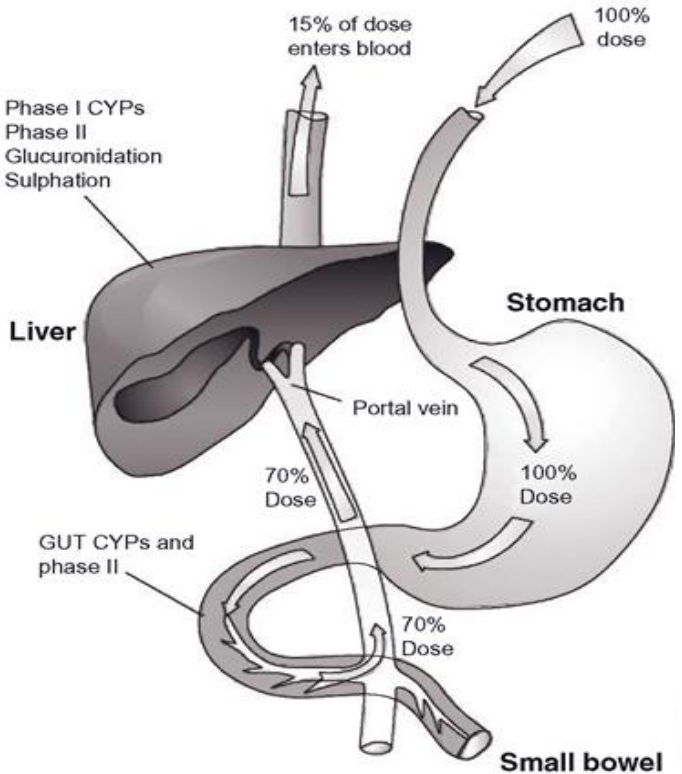
First-pass metabolism

- Following the oral administration of a drug, a percentage of the dose can be metabolized either the gut or the liver before it reaches the systemic circulation

- ↓ oral availability and activity of:
- Dabigatran, L-dopa, lidocaine, nitroglycerin, opioids, propranolol, simvastatin, theophylline, verapamil
- Some only I.V.

- Elderly: ↓ the first-pass effect and ↑ the oral bioavailability and Pc of some of these drugs
- ↓ the bioavailability of prodrugs (ACEIs)



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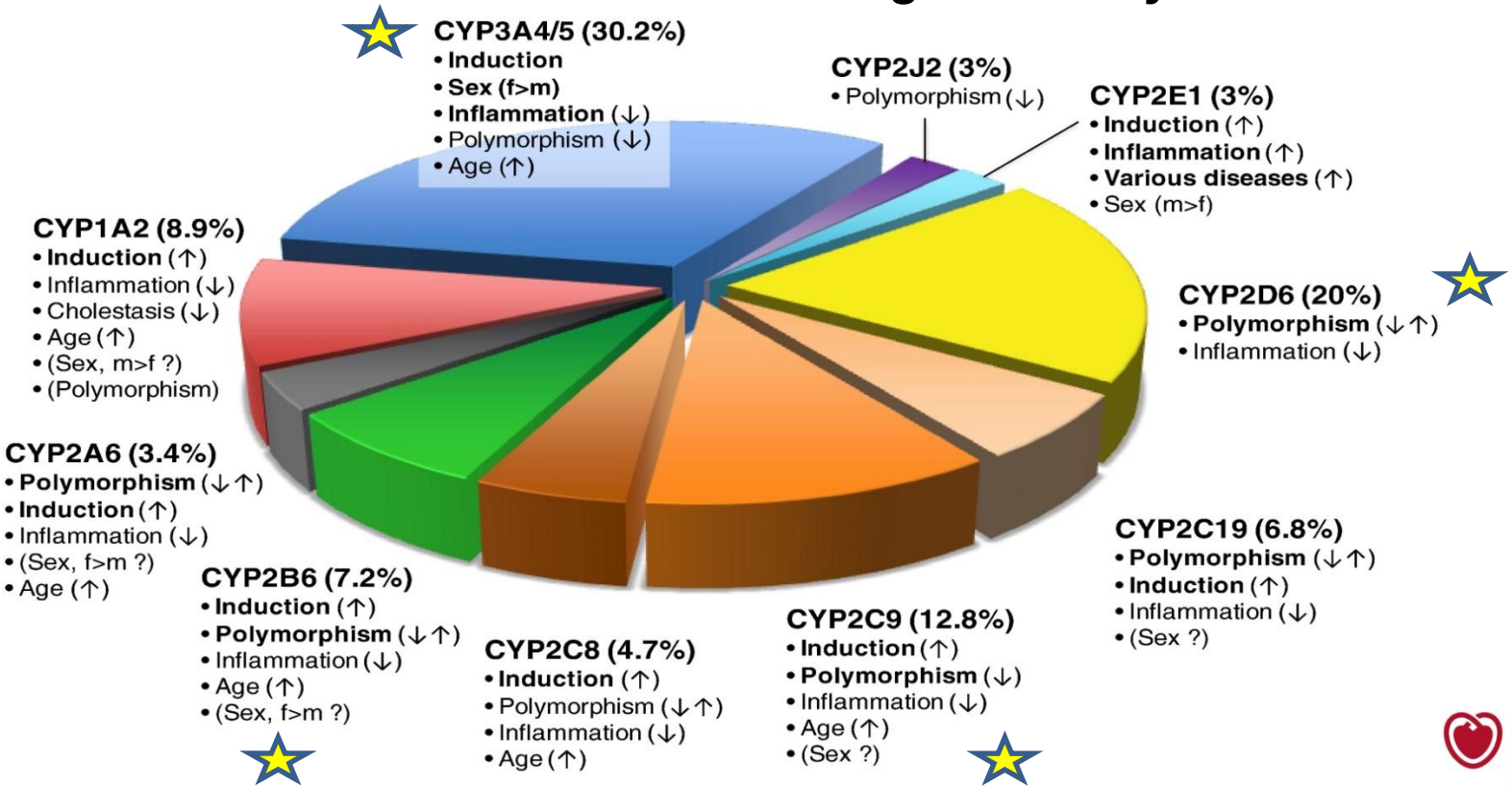
Fraction of clinically used drugs metabolized by P450 isoforms and factors influencing variability



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Phase II (conjugation) reactions

- Attach small, polar and water-soluble endogenous compounds to the drug or its phase I metabolites to form hydrophilic inactive metabolites
  - Easily excreted in urine and/or bile
- Glucuronidation, glutathione conjugation, N-acetylation, methylation, sulfation
- Non-microsomal enzymes located in the cytoplasm, hepatpcyte mitochondria, plasma
- Phase II metabolism generally preserved in the elderly

Medications undergoing Phase II metabolism are generally preferred in the elderly due to inactive metabolites (no accumulation)

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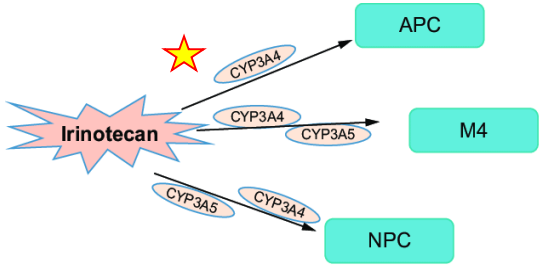
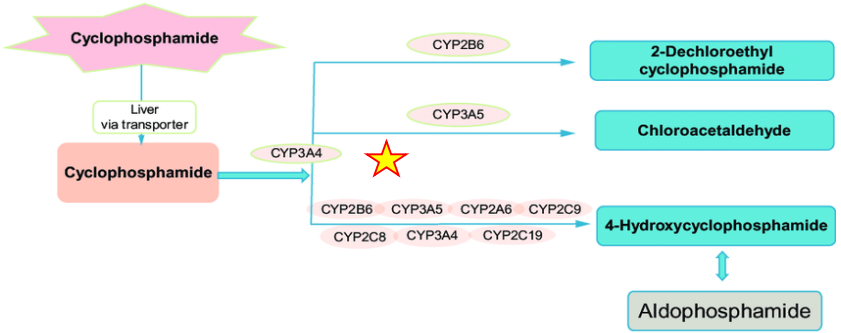
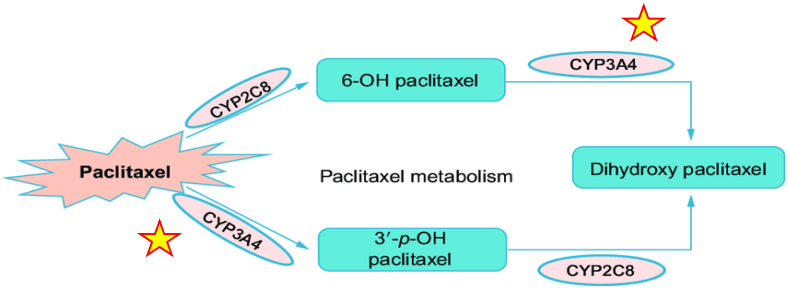
Consequences of drug biotransformation

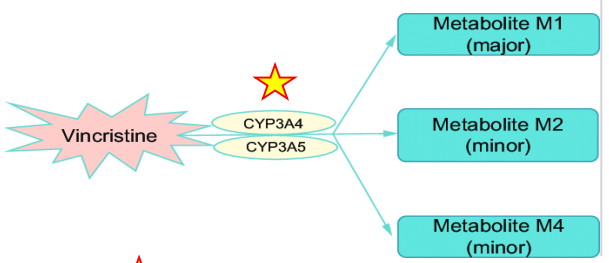
- **Active drug → inactive metabolites: the most common fate for most drugs**
- **Active drug → active metabolites:**
  - **Diazepam → Oxazepam**
  - **Imipramine → Desipramine, Amitryptiline → Nortriptyline**
  - **Chemotherapy drugs**
- **Inactive drug (prodrug) → biologically active metabolites:**
  - **Prodrugs → hydrolysis of ester or amide bond**
    - **Some ACEIs, dabigatran, clopidogrel**
  - **Many chemotherapy drugs**
  - **L-dopa → Dopamine**
- **A metabolite with a new action:**
  - **Procainamide (Class IA) → NAPA (class III)**
- **Toxic metabolites:**
  - **Acetaminophen metabolites - liver failure; lidocaine/meperidine metabolites - seizures**

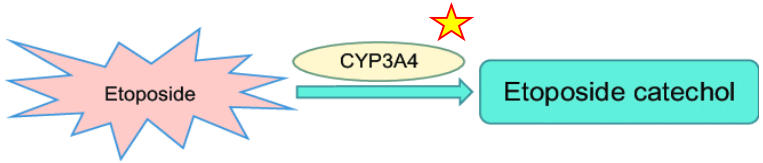
The role of active metabolites

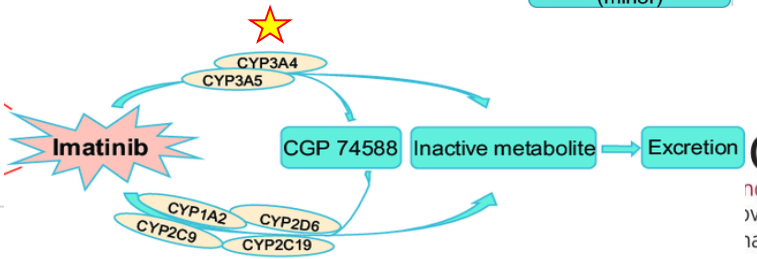












Hepatic clearance decreases with age

- **It quantifies the loss of drug during its passage through the liver. It is a function of:**
  - **Hepatic blood flow**
  - **Plasma protein binding (e.g. hypoalbuminemia, displacement by other drugs)**
  - **Activity of liver enzymes and transporters (e.g. liver failure, specific inhibition or induction by drugs, genetic polymorphisms)**
- **Other factors: Nutritional state, comorbidities, other drugs**
  - **Hepatic diseases (cirrhosis, alcohol liver disease, jaundice, carcinoma) are more common in elderly**
  - **↓ liver´s ability to recover from injury**
- **Drugs with high intrinsic clearance are rapidly metabolized and rate of drug loss is determined by the hepatic blood flow**
  - **Diltiazem, lidocaine, imipramine, metoprolol, nifedipine, propranolol, verapamil**
  - **Congestive HF, shock, hepatic diseases: reduce the dose up to 40%**
- **Drugs with low intrinsic clearance are slowly metabolized and the rate of elimination is mainly dependent on the enzyme activity in the liver**
  - **Carbamazepine, diazepam, phenytoin, theophylline, and warfarin**

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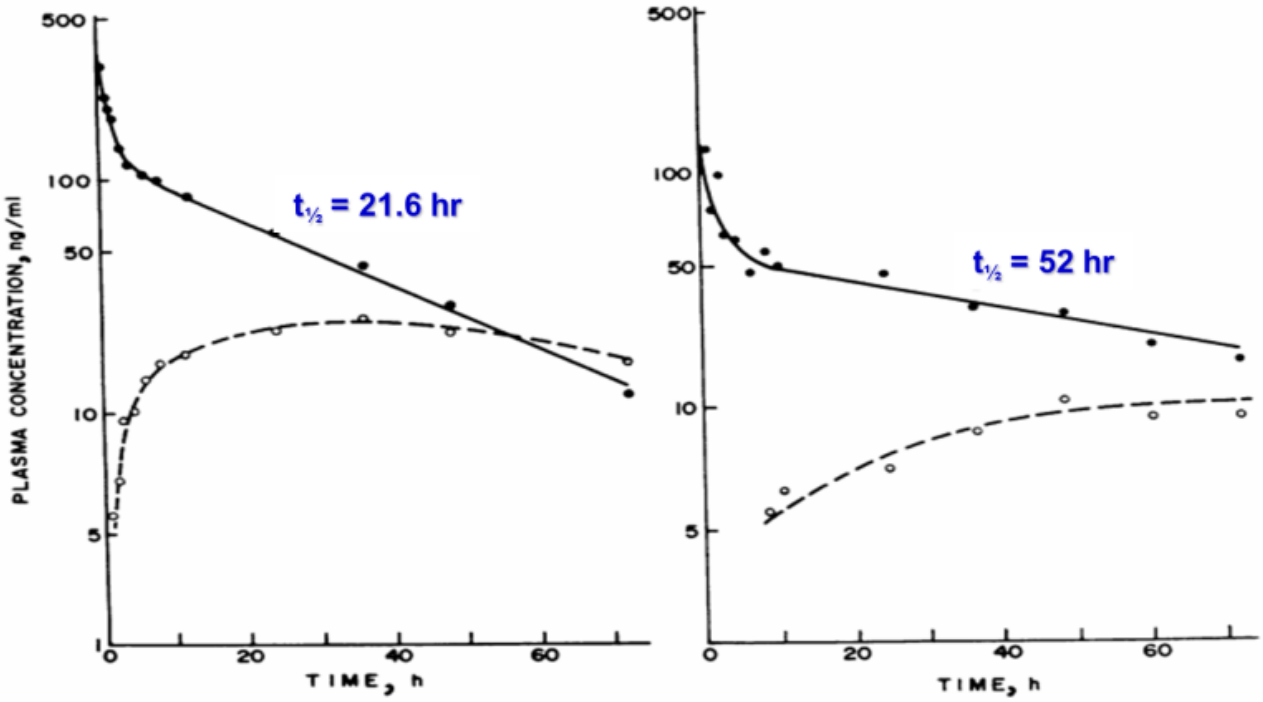
The effects of age and liver disease on the disposition and elimination of diazepam and desmethyldiazepam in adult man



Patients with cirrhosis: t½ 105.6±15.2 vs. 46.6±14.2 h, P<0.001. With acute viral hepatitis 74.5±27.5 h, with chronic active hepatitis of 59.7+23.0 h vs 32.7±8.9 h (P < 0.01)

There is an increase in diazepam half-life with increasing age

Klotz U et al. J Clin Invest 1975;55:347-59

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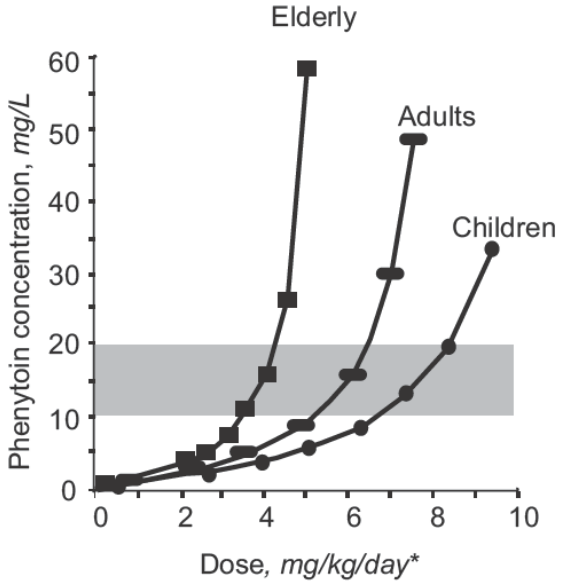
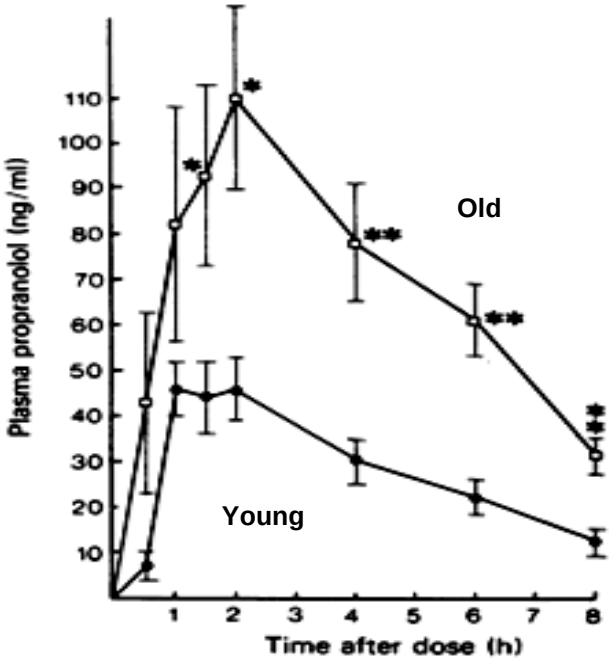
PD/PK values for verapamil in hypertensive patients

	Young	Elderly	Very elderly
Change in mean SBP (mmHg)	-7.3 ± 4.2	-13.5 ± 5.9*	-15.9 ± 9.6*
Change in HR (bpm)	+8.0 ± 5.0	-1.0 ± 10.0	-6.0 ± 8.0*
Bioavailability (%)	34 ± 11	29 ± 16	---
AUC (ng/mL x h^{-1})	142 ± 3	180 ± 52	372 ± 177*
t½ (h)	4.8 ± 1.5	5.8 ± 1.9	10.7 ± 1.8*
Total clearance (mL/min x kg)	15.5 ± 4.5	10.5 ± 3.4	8.0 ± 4.1*

Abernethy DR et al. Ann Intern Md 1986;105:329-336.

Effect of age on plasma concentrations of phenytoin and propranolol





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Cloyd et al. Fam Med 1994;3: 589-98. Castleden CM, George CF. Br J Clin Pharmacol 1979;7:49-54

Genetic variation

1. Genetic diversity is the rule rather than the exception with drug metabolizing enzymes
   - There is a wide inter-individual variability in drug response (efficacy/safety)
2. Due to the presence of genetic polymorphisms and differences in gene regulation/expression

- Allelic variants with different catalytic activities from the WT form:
  - Lack of (PMs), intermediate (IMs) or anhanced catalytic ability (ultrarapid-UM, extensive-EM)
  - PM phenotype - higher risk of serious AEs due to drug accumulation in the body
  - Metabolic inhibiton can convert a normal metabolizer into a poor metabolizer
- Frequency of the polymorphisms varies with the ethnic ancestry

"If it were not for the great variability among individuals medicine might as well be a science and not an art". *Sir William Osler, 1892*

Pharmacogenetics in phase II and phase I metabolism

Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	7% in Caucasians 1% in China[17]	Fluoxetina Haloperidol Paroxetine Codeine	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England[29] (those homozygous for the *2 and *3 alleles)	Warfarin[29,30] Phenytoin[31,32]	Enhanced drug effect[29-32]
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans[33] 3.3% in Sweden 20-30% in Asians	Omeprazole[34,35]	Enhanced drug effect[36,37]
N-Acetyltransferase 2	52% among white Americans[10] 17% of Japanese[58]	Isoniazid[10] Hydralazine[11] Procainamide[12]	Enhanced drug effect[13]
Uridine diphosphate–glucuronosyltransferase 1A1 (TATA-box polymorphism)	10.9% among whites[59] 4% of Chinese[60] 1% of Japanese[60]	Irinotecan[61] Bilirubin[62]	Enhanced drug effect[63] Gilbert's syndrome[62]
Thiopurine *S*-methyltransferase	Approximately 1 in 300 whites[50,57] Approximately 1 in 2500 Asians[57]	Mercaptopurine[51] Azathioprine	Enhanced drug effect (toxicity)[51-53]
Catechol *O*-methyltransferase	Approximately 25% of whites[51,64]	Levodopa[51,65]	Enhanced drug effect[51,65]

Weinshilboum R. N Engl J Med 2003;348:529-537

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Consequences of Induction/inhibition

- **Enzyme induction**: ↑ the rate of hepatic metabolism
  - ↑ the first-pass effect and reduces oral bioavailability
  - ↓ the Pc, intensity/duration of drug effect
  - ↑ the effect of active metabolties
  - Dosing rates may need to be increased to maintain effective Pc
- **Enzyme inhibition**: ↓ the rate of hepatic metabolism
  - ↑ Pc of the parent drug and increases/prolongs drug effects
  - ↑ the risk of drug-induced toxicity
  - ↓ metabolite(s) levels: less effect if active metabolites (clopidogrel)

Pc: plasma concentrations

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CYP3A4 modulation

CYP3A4 SUBSTRATES

- Amiodarone, dronedarone
- Most benzodiazepines
- Calcium channel blockers
- Ciclosporin, sirolimus, tacrolimus
- Ivabradine
- Lidocaine
- Macrolides: clarithromycin, erythromycin, telithromycin
- Methadone
- NOACs: apixaban, edoxaban, rivaroxaban
- SSRIs: citalopram
- Statins: atorvastatin, lovastatin, simvastatin
- Ticagrelor
- VIH protease inhibitors: indinavir, nelfinavir, ritonavir, saquinavir
- Warfarin

CYP3A4 INHIBITORS

1. Weak: cimetidine
2. Moderate:

- Amiodarone
- Ciprofloxacin
- Fluconazole, miconazole
- Diltiazem, verapamil
- Delarvidine
- Grapefruit juice
- VIH protease inhibitors: amprenavir, fosamprenavir

3. Strong:

- Macrolides: clarithromycin, telithromycin, troleandomicin
- Azoles: itraconazole, ketoconazole
- Nefazodone
- VIH protease inhibitors**: atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir

CYP3A4 INDUCERS

1. Berbiturales
2. Carbamazepine
3. Dexamethasone
4. Phenytoin
5. Primidone
6. Rifamycins
7. St John´swort**

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CYP2D6 modulation

SUBSTRATES

- Antiarrhythmics: Flecainide, Lidocaine, Mexiletine
- Antidepressants: SSRIs, Trazodone, Tricyclics, Venlafaxine
- Beta blockers
- Dextromethorphan
- Haloperidol
- Omeprazole
- Phenothiazines
- Opioids: codeine****, morphine, tramadol
- Risperidone
- Tamoxifen***
- Testosterone

INHIBITORS

- Amiodarone
- Bupropion
- Celecoxib
- Cimetidine
- Metoclopramide
- Methadone
- Paroxetine
- Quinidine
- Ritonavir
- SSRIs***: fluoxetine, fluvoxamine, sertraline

INDUCERS

- Carbamazepine
- Dexamethasone
- Phenobarbital
- Phenytoin
- Rifampin

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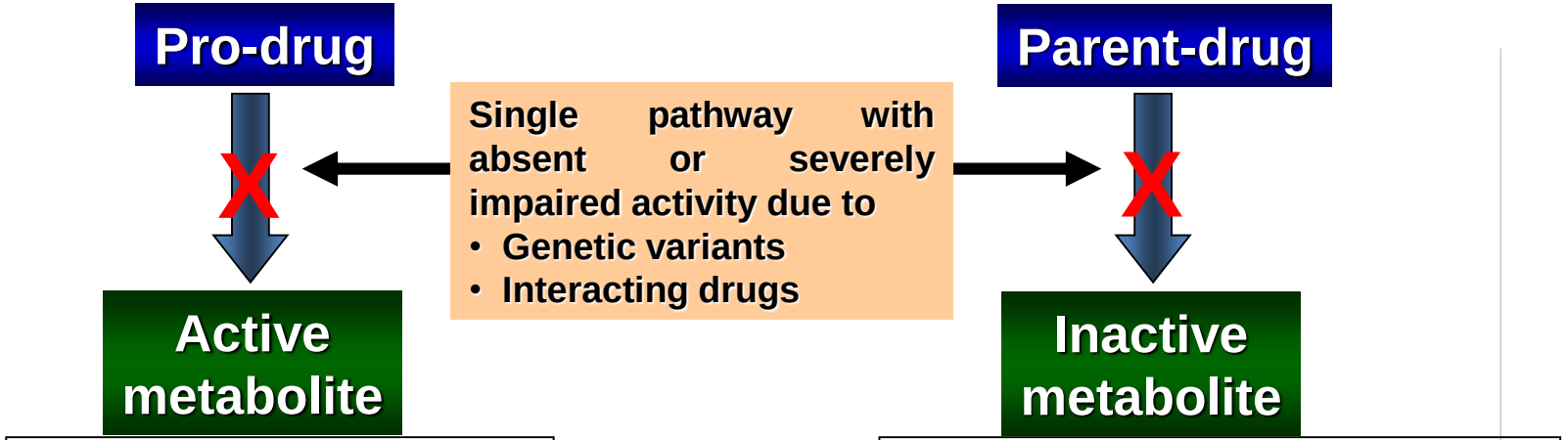
Clinical consequence of metabolized phenotypes on drug response



1) UM – good drug efficacy, rapid (and exaggerated) effects
2) UM – poor drug efficacy, requires higher dosage. AEs in PMs

Roden and Stein. Circulation. 2009;119:2127–2130

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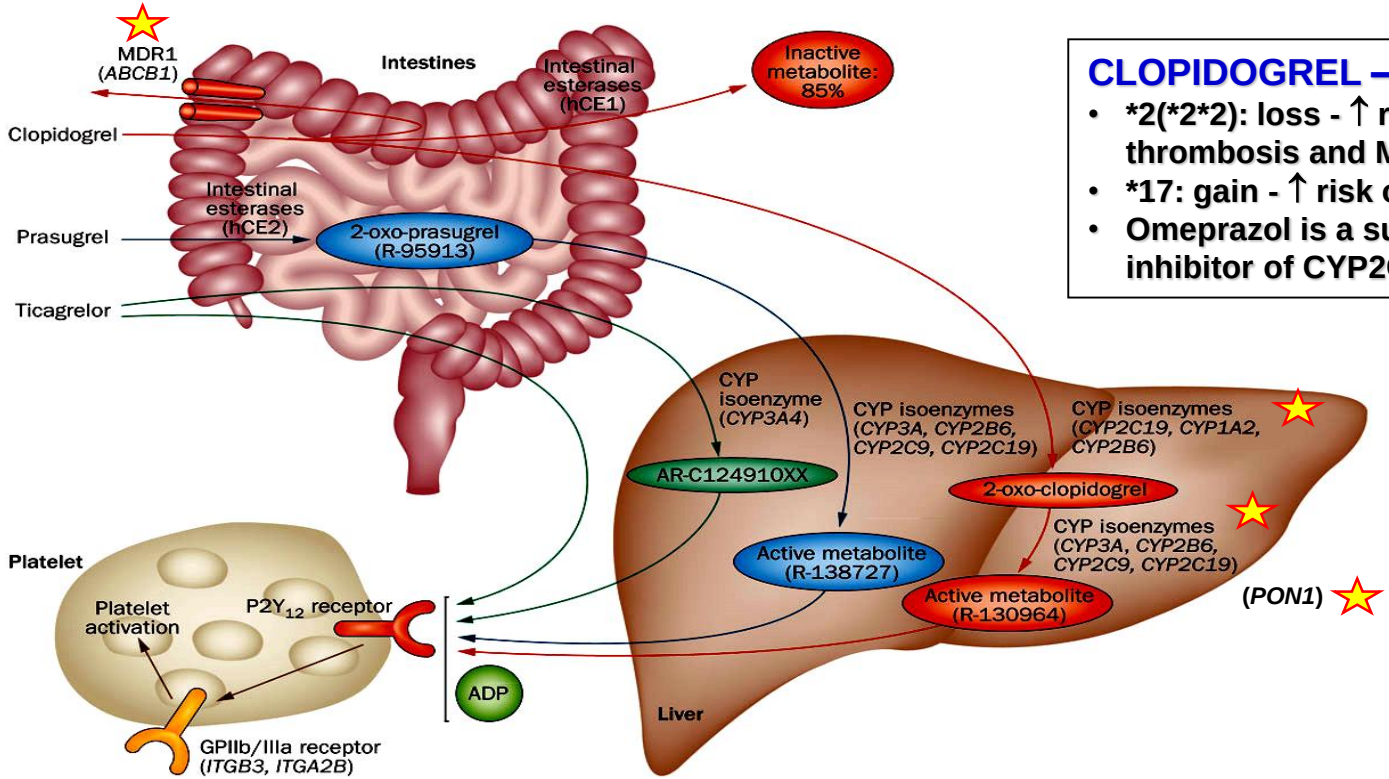
Metabolic pathway of $P2Y_{12}$-receptor inhibitors



CLOPIDOGREL – CYP2C19:

- *2(*2*2): loss - ↑ risk of stent thrombosis and MACE after PCI
- *17: gain - ↑ risk of bleeding
- Omeprazol is a substratei and inhibitor of CYP2C19

Levine GN et al. Nat Rev Cardiol 2011;8:560-571

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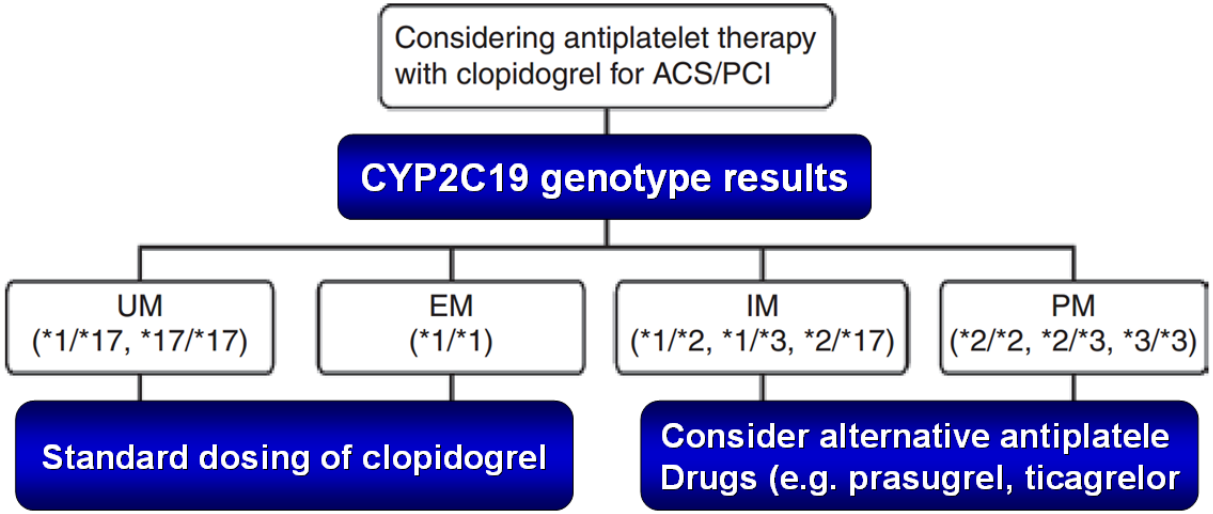
Algorithm for suggested clinical actions based on CYP2C19 genotype when considering treatment with clopidogrel for ACS patients undergoing PCI



Genotype	Platelet inhih.	Residual platelet aggreg.	CV risks
UM (32.9%)	↑	↓	↓ (↑ bleeding)
EM (38.5%)	Normal	Normal	Normal
IM (26.1%)	↓	↑	↑
PM (1.7%)	↓↓↓	↑↑	↑↑↑

Scott et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update. Clin Pharmacol Ther 201394:317-323

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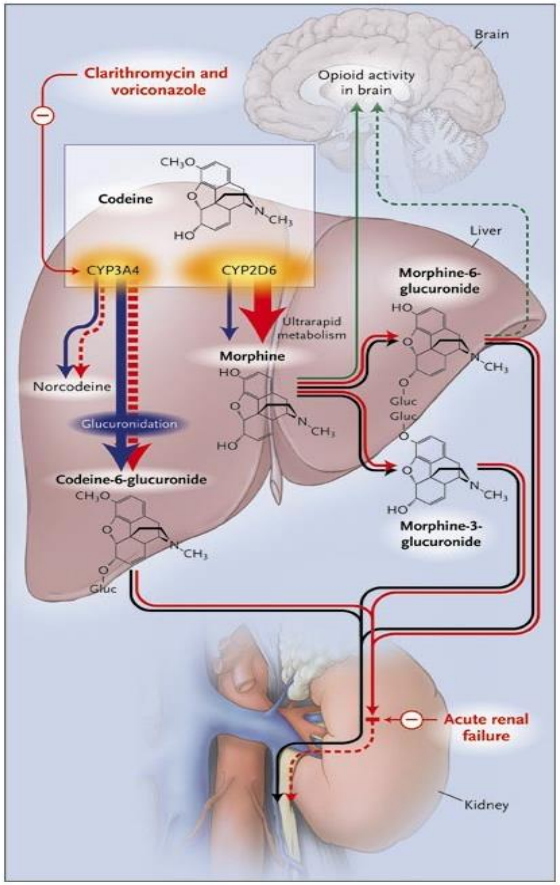
If the parent drug needs to be metabolized to the active compound and metabolism is inhibited, then a therapeutic failure could result



- 80% of codeine is converted via CYP3A4 to glucuronide, eliminated by kidney
- 5-10% is metabolized into morphine by CYP2D6
- Inhibition of CYP3A4 or rapid metabolic variants of CYP2D6 during renal failure would cause opioid intoxication
  - 7% of caucasians have a non-functional CYP2D6 variant
  - <2% are ultrarapid metabolizers

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Gasche et al. N Engl J Med 2004; 351:2827-2831

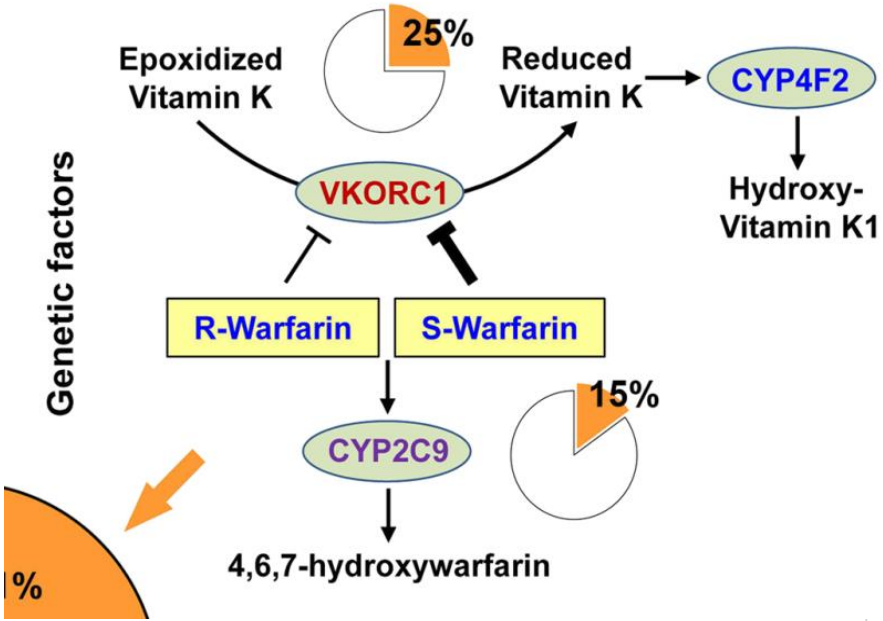
Enzyme inhibition

Increasing bleeding risk with warfarin in the elderly:

- **Age explains 40% of dosing variation**
- **Variants in VKORC1 can explain 25%**
- **Variants in CYP2C9 can explain 15%**

- **Deficiency in vitamin K-dependent clotting factors (hepatic diseases), decreased hepatic clearance (↓ hepatic blood flow and warfarin plasma protein binding)**

VKORC1: Vitamin K epOxide Reductase Complex subunit 1



	Mean Warfarin Daily Dose (mg)				
Patient Age	<50	50–59	60–69	70–79	>80
Gurwitz, et al, 1992 (n=530 patients total study)	6.4	5.1	4.2	3.6	ND
James, et al, 1992 (n=2,305 patients total study)	6.1	5.3	4.3	3.9	3.5

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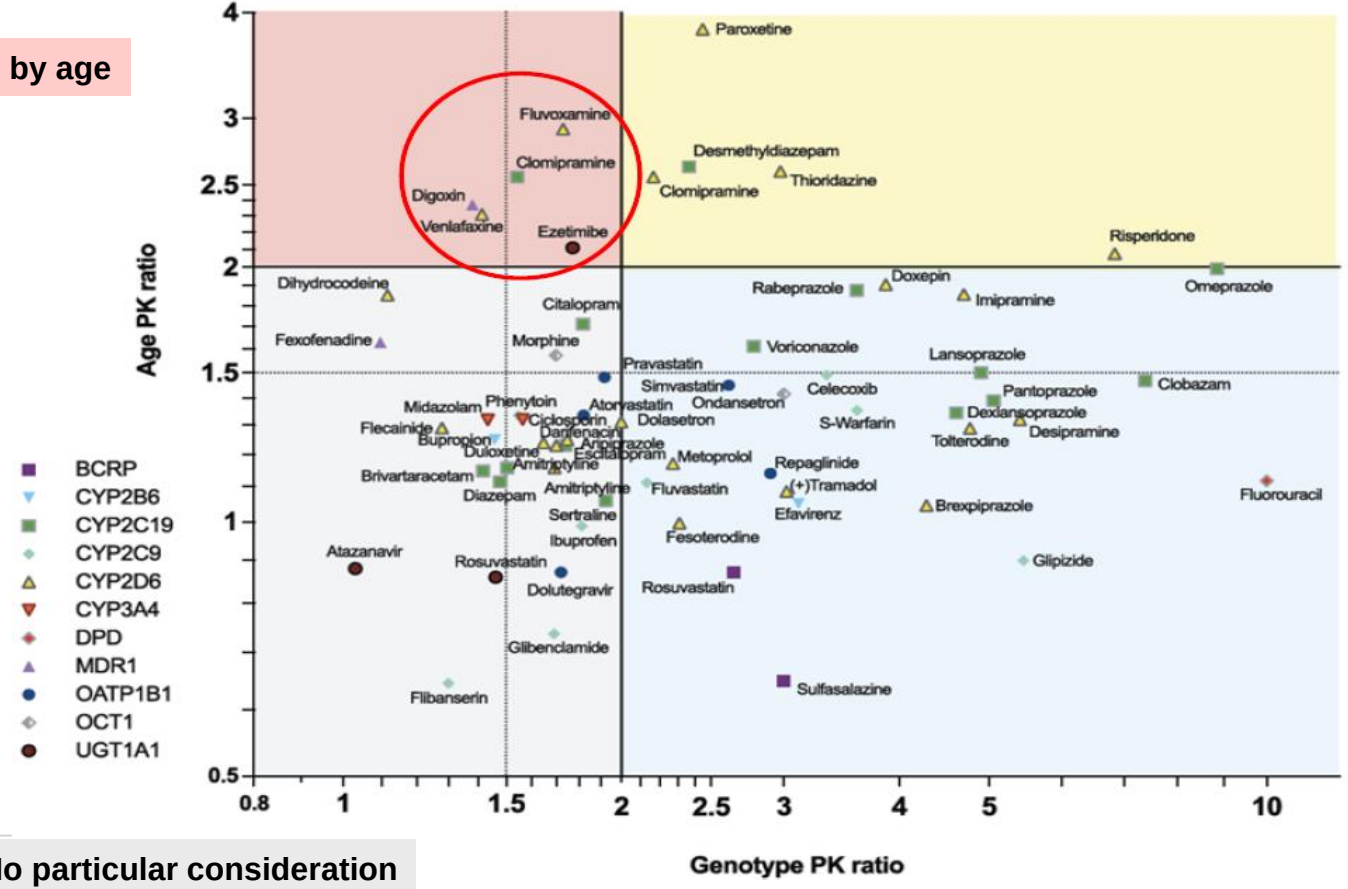
Drugs in which both genotype and age ratios may be of particular concern

Afected by age

Afected by age and genotype



Afected by genotype

No particular consideration

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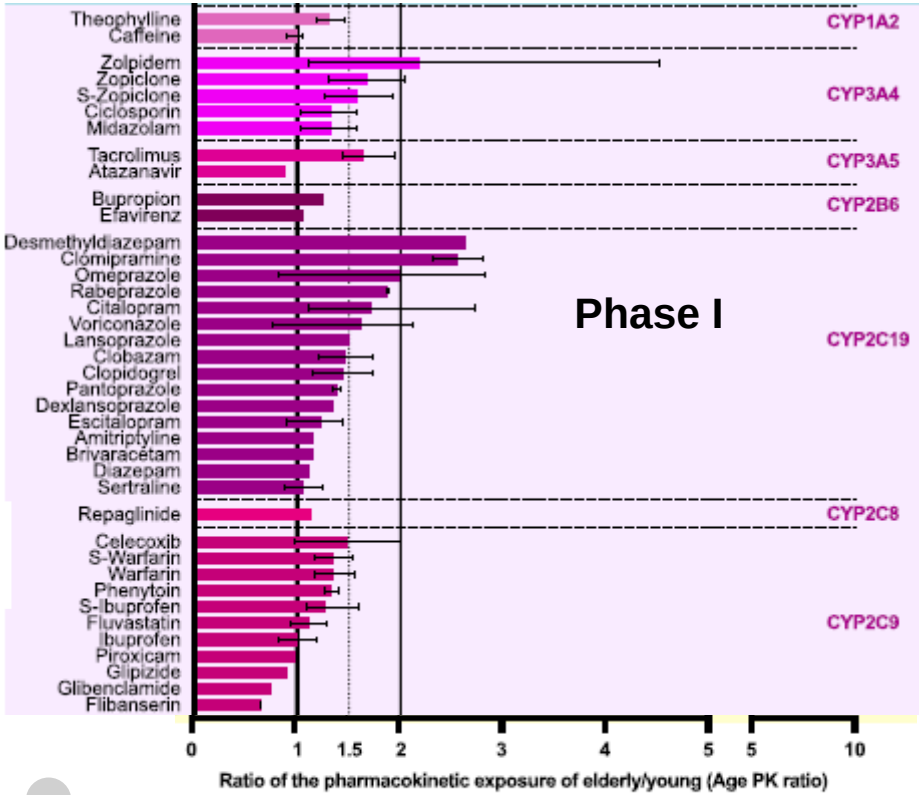
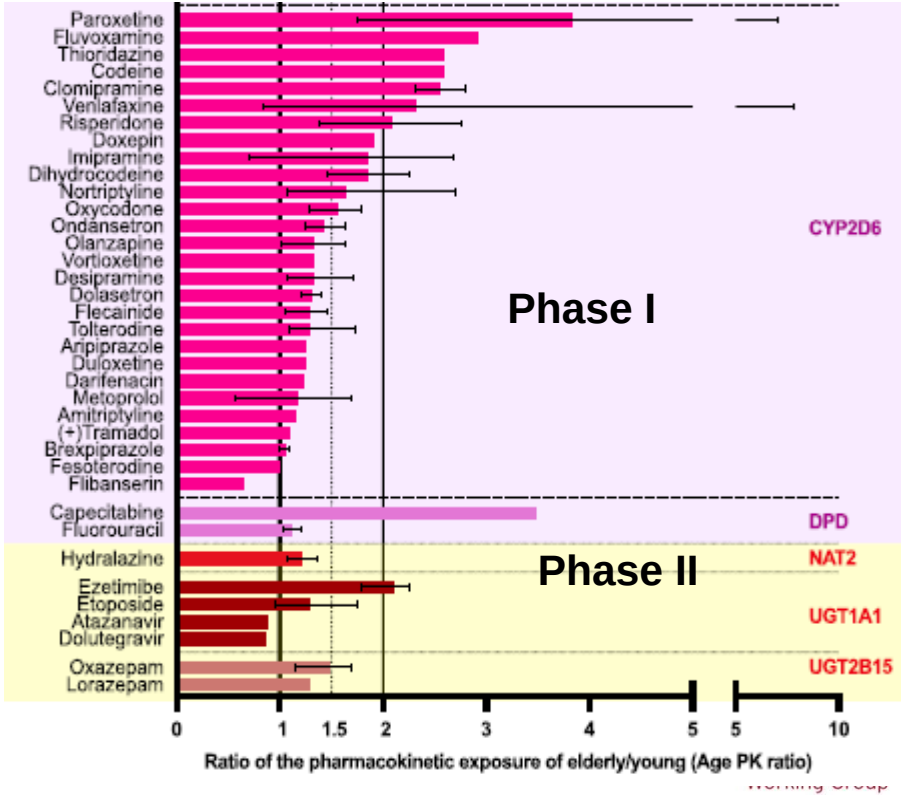
Age-related increase in the systemic exposure to drugs

A PK ratio of 1 indicates no difference between younger and older people having received the same drug dose





Cardiovascular Pharmacotherapy

Dücker et al. Clin Pharmacol Ther 2019;105:625-640

Take home messages

1. Aging is associated with pluripathology leading to polypharmacy
2. The PD/PK of CV drugs are modified due to age- and comobidities-related changes in organ function/body composition
   - Elderly people present a decrease in hepatic clearance
   - Differences in drug efficacy/safety
   - Monitor hepatic function and drug efficacy/safety
3. Genetic diversity is the rule rather than the exception with drug metabolizing enzymes
4. Evidence from RCTs in patients >75 years of age are sparse
   - Guidelines do not mention the elderly population
5. We need to better understand the pharmacology in the elderly (BEERS, STOP/START)
6. Physicians, pharmacists, nurses…… must work together to improve drug therapy in the elderly

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