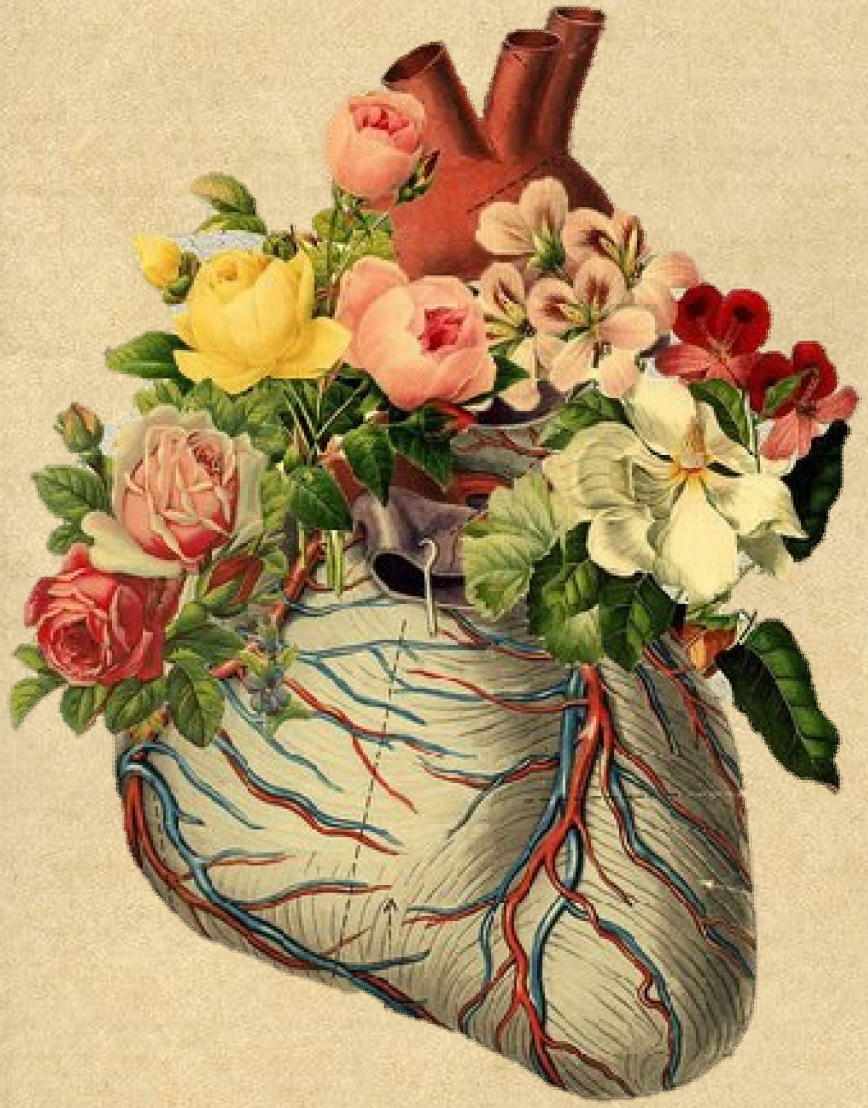


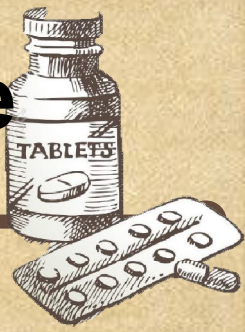
Update &Review Interaction on Cardiovascular drugs

ภญ.ปัทมวรรณ โกสุมา

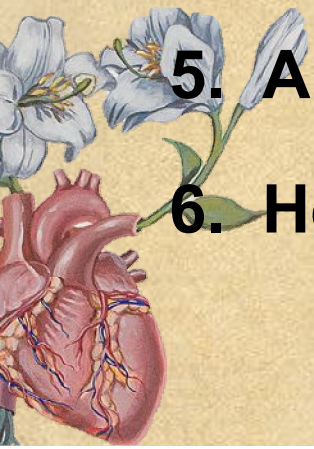
ภาควิชาเภสัชกรรมปฏิบัติ คณะเภสัชศาสตร์

มหาวิทยาลัยนเรศวร

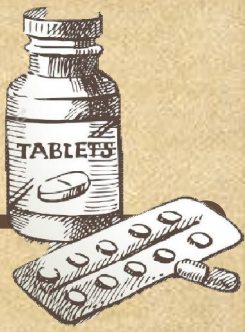
Drugs commonly used in cardiology practice



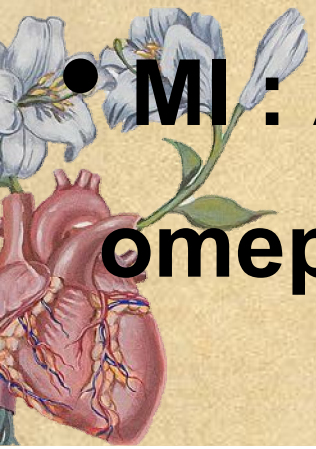
1. Antihypertensive: ARB, CCB, ACEIs, diuretics
2. Anti-dyslipidemia: Statin, fenofibrate, nicotinic acid
3. Anti-platelet drug: Aspirin, GP IIb/IIIa antagonist
4. Anti-coagulants: Warfarin, heparin, NOAC
5. Anti-arrhythmic: Amiodarone
6. Heart failure: Beta blocker, ACEIs, digoxin



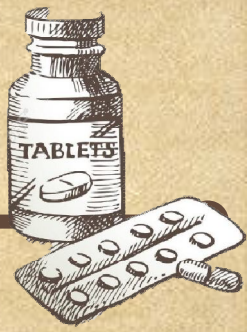
Drug in cardiovascular disease



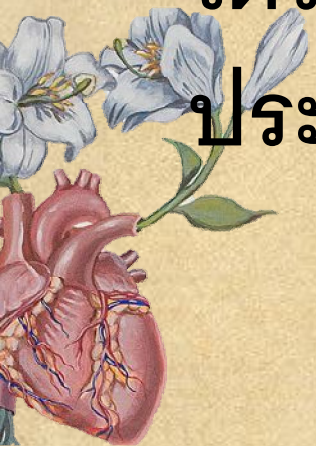
- Atrial fibrillation : warfarin/NOAC, amiodarone
- CHF : beta-blocker, ACEIs, diuretic, digoxin, spironolactone
- MI : Aspirin, clopidogrel/ticagrelor/prasugrel, omeprazole, statin, beta-blocker, ACEIs



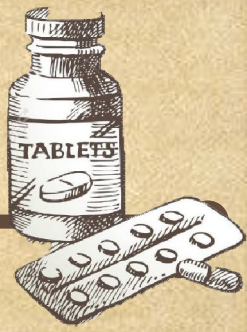
Drug interaction : คำจำกัดความ



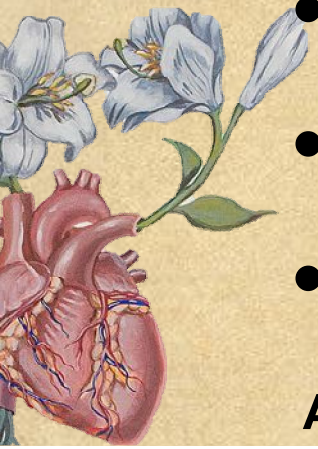
- ปฏิกิริยาต่อกันของยา ที่ทำให้ระดับยาหรือพารามิเตอร์ทางจลนศาสตร์ หรือ ฤทธิ์ทางเภสัชวิทยาของยาตัวหนึ่งในร่างกายเปลี่ยนแปลงไป เมื่อได้รับยาตัวอื่นร่วมด้วย ซึ่งอาจส่งผลให้เพิ่มหรือลดประสิทธิภาพของยาก็ได้



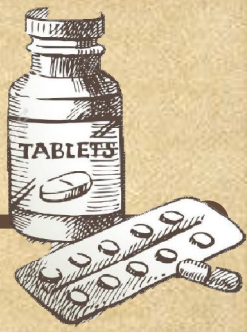
Drug interaction – risk factor



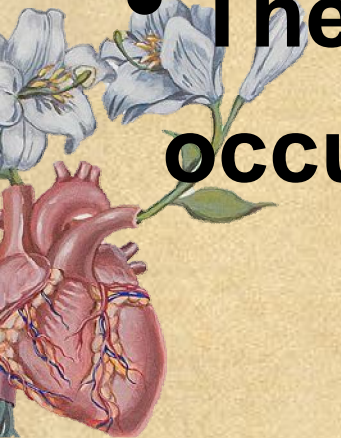
- Poly pharmacy
- Multiple prescribers
- Multiple pharmacies
- Genetic make up
- Specific population like . elderly, obese, criticaly ill patient
- Specific illness E.g. Hepatic disease, Renal dysfunction,
- Narrow therapeutic index drugs : Digoxin, Insulin, Lithium , Antidepressant, Warfarin



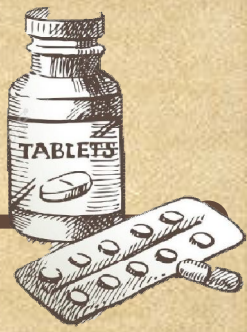
Clinical significance



- Significant rating
- The time of ONSET of the effect of interaction
- The potential SEVERITY of interaction
- The DOCUMENTATION that the interaction occurs clinically

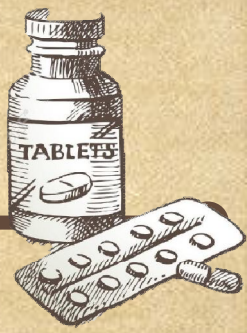


SIGNIFICANCE RATING



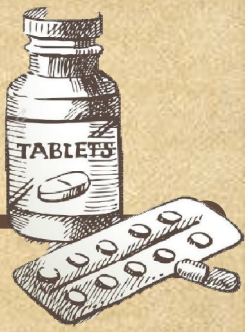
- Significant : 1,2,3,4,5
- Onset : rapid, delay
- Severity : major, moderate, minor
- Documentation : established, probable, suspected, possible, unlikely

Drug interaction effects

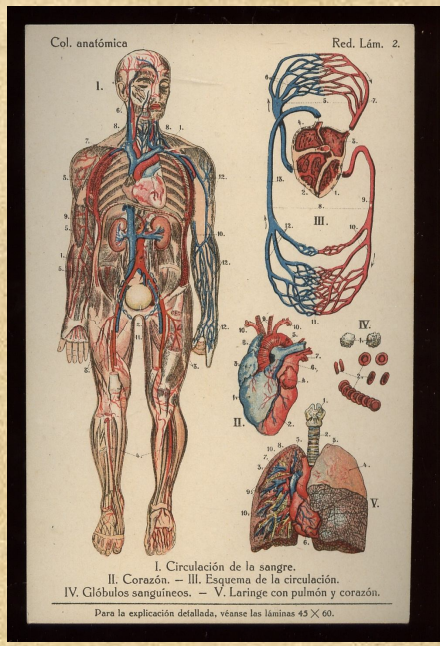


- Additive effect : 1 + 1 = 2
- Synergistic effect : 1 +1 > 2
- Potentiation effect : 1 + 0 = 2
- Antagonism : 1-1 = 0

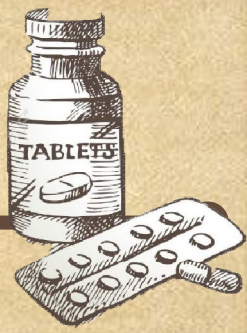
Mechanism of Drug Interaction



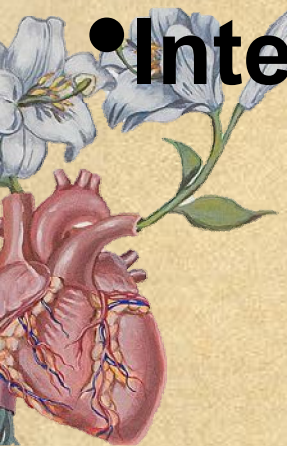
1. Pharmacodynamics
2. Pharmacokinetics
3. Direct chemical or physical mechanism



Pharmacokinetic interactions



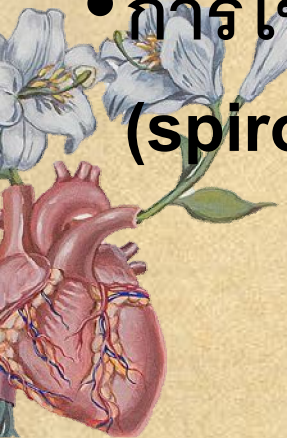
- Drug absorption interactions
- Drug displacement (protein-binding)
- Drug metabolism interactions
- Interaction due to changes in excretion



ADME

Common pharmacodynamics drug interaction

- การใช้ยา **anticoagulant** ร่วมกับยา **antiplatelet**
- การใช้ยากลุ่ม **Non-hydropyridine CCB (Verapamil)** ร่วมกับยากลุ่ม **beta-blocker**
- การใช้ยา **sildenafil** ร่วมกับยากลุ่ม **nitrate (vasodilator)**
- การใช้ยากลุ่ม **ACEIs** ร่วมกับยา **potassium-sparing diuretics (spironolactone)**

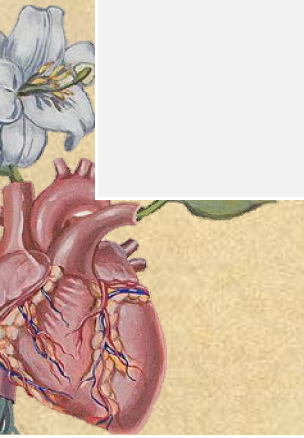


CYP3A4 inhibitor drug

Potency	Groups	Drugs
High	Antibiotics	Clarithromycin, Telithromyocin, Chloramphenicol
	Antifungal	Azole
Moderate	CCB	Verapamil, diltiazem

Drugs that induce cytochrome P450 izoenzyme

CYP	Inducing drugs
CYP3A4	Rifampicin Barbiturates Carbamazepine Dexamethasone St. John's wort



Drugs that induce cytochrome P450 isoenzyme

CYP P450 isoenzyme	Inducing drugs
CYP1A2	Barbiturate Omeprazole Phenytoin Tobacco smoke
CYP2C9	Barbiturate Rifampicin
CYP3A4	Barbiturates

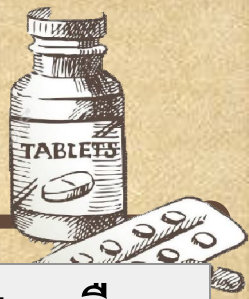
Drugs that inhibit cytochrome P450 isoenzymes

CYP P450 isoenzyme	Inhibit drugs
CYP1A2	Cimetidine, Fluvoxamine, Grapefruit
CYP2D6	Fluoxetine, Quinidine, Ritonavir

Medications that act as substrates, inhibitor or inducers of P-gp

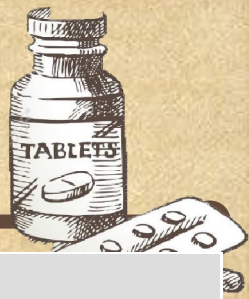
Substate	Inhibitors	Inducers
Cyclosporine	Amiloride Amiodarone Atorvastatin	Aspirin
Dipyridamole	Carvedilol Cyclosporine Digoxin	Cyclosporine
Digoxin	Diltiazem Dipyridamole	Paclitaxel
Diltiazem	Doxazosin Felodipine	Reserpine
Losartan	Lidocaine Lovastatin	
Quinidine	Nifedipine Propafenone	
Tacrolimus	Propafenone Propranolol	
	Quinidine Simvastatin	
	Spironolactone Verapramil	

Drug Interaction of beta blocker



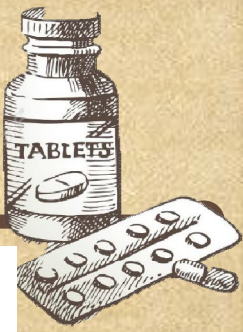
Pharmacodynamics	**Non-hydropyridine CCB (Verapamil or diltiazem)**	**อาจทำให้เกิด sinus bradycardia หรือ heart block**
Pharmacokinetic	**Propranolol and metoprolol**	**Metabolized ที่ตับ liver และผ่าน first pass clearance**

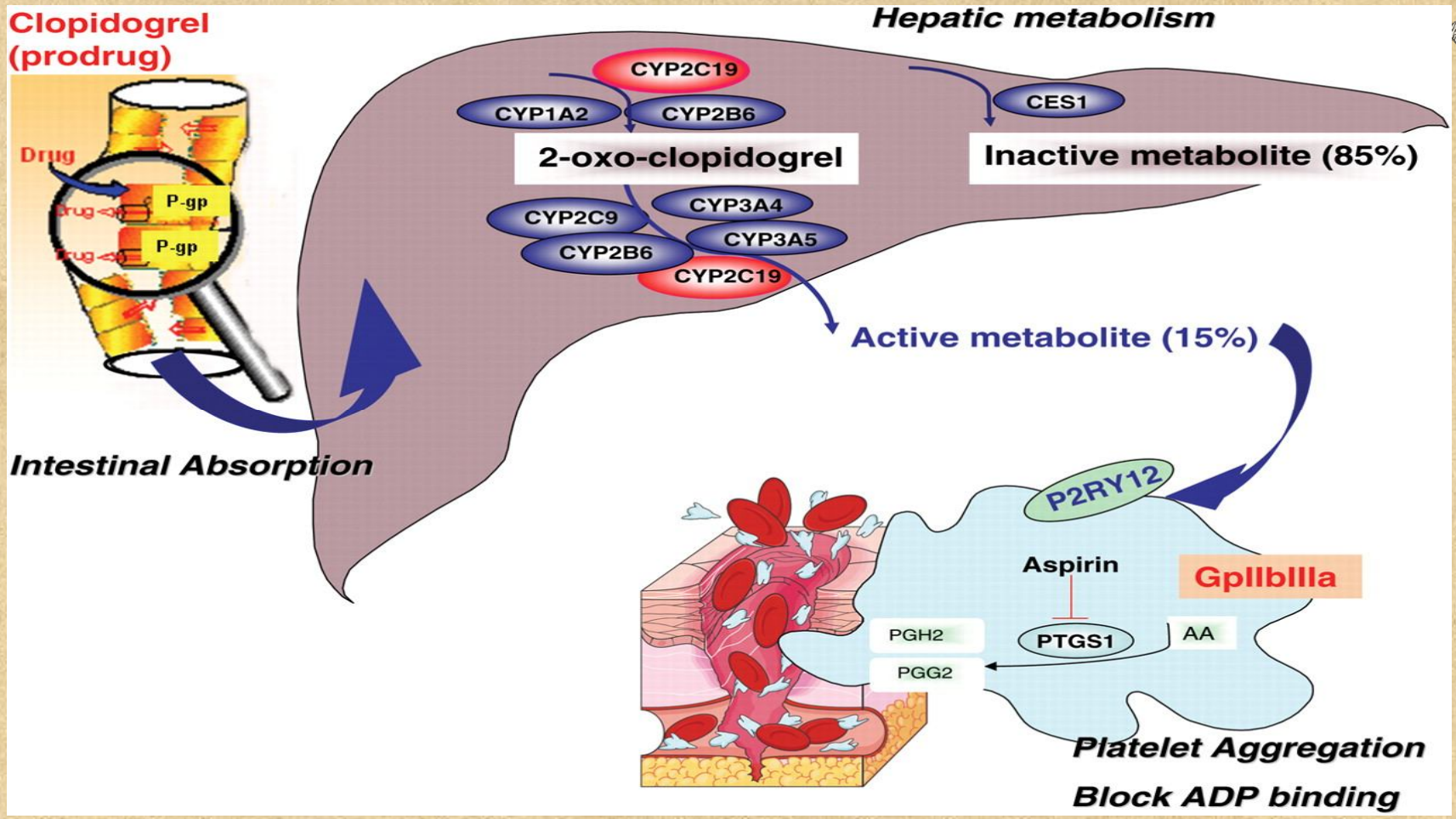
Drug interaction of Antiplatelet

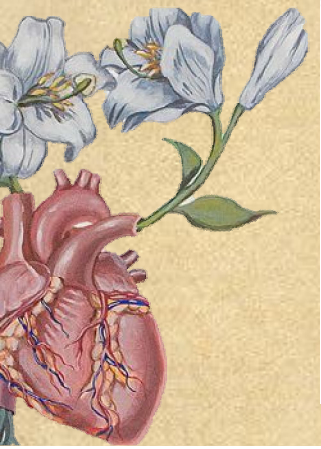


Antiplatelet	Interaction
Aspirin	Risk bleeding เพิ่มขึ้นเมื่อให้ร่วมกับยาantiplatelet หรือ anticoagulant ตัวอื่น

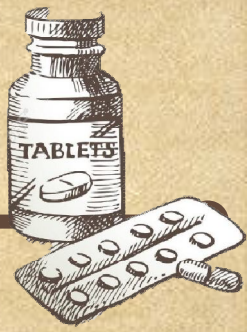
Drug interaction of Clopidogrel







Clopidogrel with or without Omeprazole in coronary artery disease: COGENT study



Cogent Criticisms

- Lower risk population – only 42% were taking clopidogrel for ACS
- Fixed dose formulation used quite distinct from individual dosing
- Study stopped early as sponsor lost funding – only 77% of planned subjects were enrolled

"There was no apparent cardiovascular interaction between clopidogrel and omeprazole, but our results do not rule out a clinically meaningful difference in cardiovascular events due to use of a PPI. "

Bhatt DL et al. NEJM 2010; 363: 1909-17

U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Home > Drugs > Drug Safety and Availability

Drugs

FDA reminder to avoid concomitant use of Plavix (clopidogrel) and omeprazole

Please note this is not a Drug Safety Communication, rather just a reminder of our recommendations from the previous DSC. It is posted on the Plavix Information[1] page.

The U.S. Food and Drug Administration (FDA) is reminding the public that it **continues to warn against the concomitant use of Plavix (clopidogrel) and omeprazole** because the co-administration can result in significant reductions in clopidogrel's active metabolite levels and antiplatelet activity. This information was added to the drug label of Plavix in November 2009, and has been the source of continued discussion in the medical literature.[1]

Patients at risk of heart attacks or strokes, who are given Plavix to prevent blood clots, will not get the full anti-clotting effect if they also take omeprazole. Omeprazole is found in prescription products (Prilosec, Zegerid, and generic products) and over-the-counter products (Prilosec OTC, Zegerid OTC, and generic products).

FDA wishes to emphasize additional facts that may be a source of confusion among healthcare professionals:

- With regard to the proton pump inhibitor (PPI) drug class, this recommendation **applies only to omeprazole** and not to all PPIs. Not all PPIs have the same inhibitory effect on the enzyme (CYP 2C19) that is crucial for conversion of Plavix into its active form.
- Pantoprazole (Protonix) may be an alternative PPI for consideration. It is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of Plavix than omeprazole.

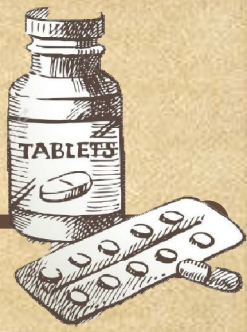
For more information, see FDA's previous Drug Safety Communication on the Plavix-omeprazole interaction[2].

[1]Bhatt, DL, Cryer, BL, Contant, CF, et al. Clopidogrel with or without Omeprazole in Coronary Artery Disease; NEJM, 2010; epub ahead of print.

Related Information

…to warn against the concomitant use of Plavix and omeprazole because the co-adinistration can result in significant reductions in clopidogrel's active metabolite…

Package insert : Plavix

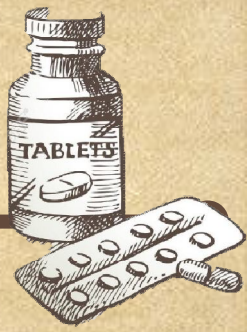


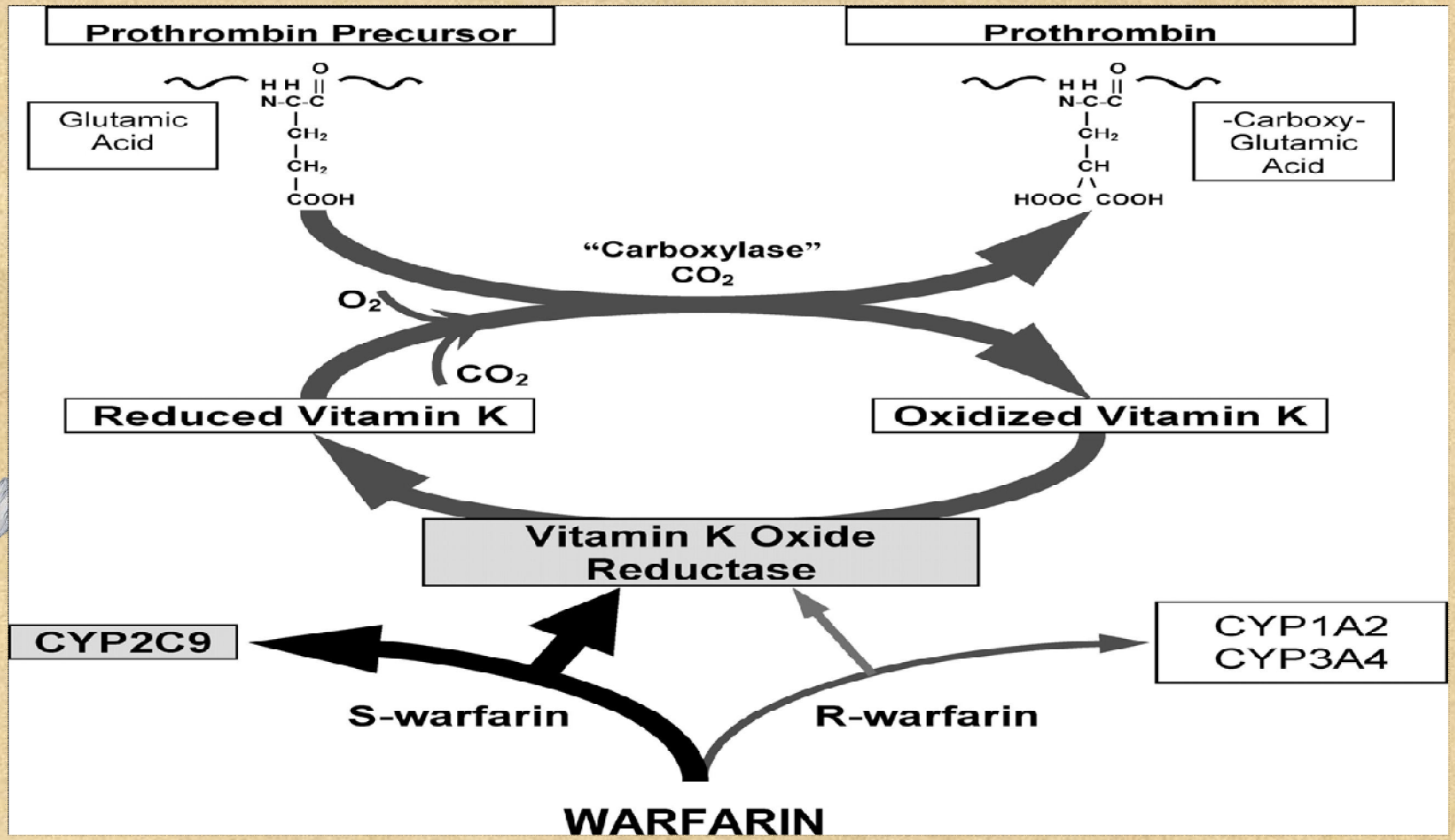
Use with Proton Pump Inhibitors (PPI):

Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of PLAVIX. Avoid use of strong or moderate CYP2C19 inhibitors with PLAVIX. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity, or alternative treatment strategies.

Pantoprazole, a weak CYP2C19 inhibitor, had less effect on the pharmacological activity of PLAVIX than omeprazole

Drug interaction of warfarin





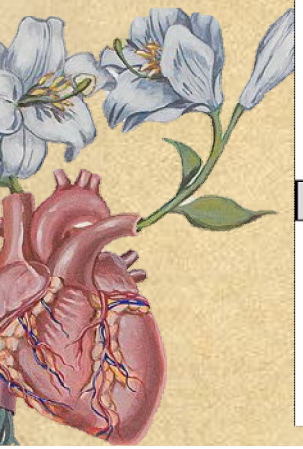


Table 1: The 8 A's — drugs that interact with warfarin*

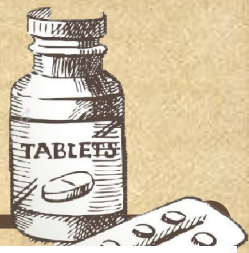
Drug or drug class	Risk of hemorrhage	Mechanism
Antibiotics		
Most agents, but especially co-trimoxazole, metronidazole, macrolides and fluoroquinolones	↑	Inhibition of vitamin K synthesis by intestinal flora, inhibition of hepatic warfarin metabolism, or both
Rifampin	↓	Induction of cytochrome P450 (CYP) isoenzyme 2C9
Antifungals		
Fluconazole, miconazole	↑	Inhibition of CYP 2C9
Antidepressants		
Serotonergic agents (selective serotonin reuptake inhibitors)	↑	Interference with primary hemostasis; some (e.g., fluoxetine) also inhibit CYP 2C9
Antiplatelet agents		
Acetylsalicylic acid, clopidogrel, ticlopidine	↑	Interference with primary hemostasis
Amiodarone	↑	Inhibition of CYP 2C9
Anti-inflammatory agents		
All, including selective cyclooxygenase-2 inhibitors	↑	Direct mucosal injury; interference with primary hemostasis may also play a role
Acetaminophen	↑	Direct interference with vitamin K cycle
Alternative remedies		
Gingko biloba, dong quai, fenugreek, chamomile	↑	Multiple and often incompletely characterized
St. John's wort	↓	Multiple and often incompletely characterized

*This is only a partial list of drugs that can alter the response to warfarin. A more detailed discussion is given in references 4 and 5. Of note, some patients exposed to specific drug combinations will exhibit no interaction, in part because pharmacogenetics and other factors govern the expression of many interactions.

Drug interaction of warfarin

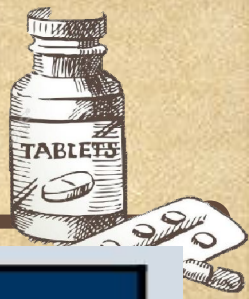
เพิ่ม INR	ลด INR
Chondroitin/ glucosamine supplements กระเทียม, ขิง Fish oil, vitamin E มะม่วง มะละกอ น้ำgrape friut น้ำทับทิม น้ำแคนเบอรรี่	อาหารที่มีวิตามิน K ได้แก่ ตับ, บรอคเคอรี่, ผักใบเขียวต่างๆ, ถั่ว, นมถั่วเหลือง ยาสมุนไพร (Herbal) เช่น แปะก๊วย (Gingko biloba), โสม (Ginseng) อาหารเสริม ผักสกัดอัดเม็ด คลอโรฟิลด์อัดเม็ด อัลฟาฟ่า ชาเขียว ตำ  ะถิน, กระเฉด, คะน้า, ผักบุ้ง, ชะอม,สะตอ **Vitamin K 100 mcg→ INR ↓ 0.3**

Drug interaction with NOACs



Dabigatran[1–3]	Apixaban[4–6] and Rivaroxaban[7–9]
Contraindicated Note: Effect may last for several weeks after discontinuation of inducers of P-glycoprotein and/or CYP3A4	
Anticoagulants • anti-thrombin agents (e.g., bivalirudin) • Factor-Xa inhibitors (e.g., apixaban and rivaroxaban) • heparin (unless used to maintain a patent central venous or arterial catheter) • heparin derivatives (e.g., fondaparinux) • low molecular weight heparins (e.g., dalteparin and enoxaparin) • warfarin (unless switching to or from a NOAC)	**Contraindicated with potent CYP3A4 and/or P-glycoprotein inhibitors**
Strong inhibitors of P-glycoprotein • azole-antimycotics (e.g., itraconazole, ketoconazole, posaconazole, and voriconazole) • HIV protease inhibitors (e.g., darunavir fosamprenavir, indinavir, lopinavir nelfinavir, ritonavir, and saquinavir) Contraindicated with potent P-glycoprotein inhibitors	**Strong inhibitors of both P-glycoprotein and CYP3A4** • azole-antimycotics (e.g., itraconazole, ketoconazole, posaconazole, and voriconazole) • boceprevir • cobicistat • HIV protease inhibitors (e.g., darunavir fosamprenavir, indinavir, lopinavir nelfinavir, ritonavir, and saquinavir) • imatnib
Avoid use Note: Effect may last for several weeks after discontinuation of inducers of P-glycoprotein and/or CYP3A4	

Drug interaction with NOACs



	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp weak CYP3A4	+18%	no data	no effect	no effect
Digoxin	P-gp	no effect	no data	no effect	no effect
Verapamil	P-gp weak CYP3A4	+12-180% reduce dose take together	no data	+53% (SR) reduce dose	minor effect use with caution if CrCL: 15-50ml/min
Diltiazem	P-gp weak CYP3A4	no effect	+40%	no data	minor effect use with caution if CrCL: 15-50ml/min
Quinidine	P-gp	+50%	no data	+80% reduce dose	+50%
Amiodarone	P-gp	+12-60%	no data	no effect	minor effect use with caution if CrCL: 15-50ml/min
Dronedarone	P-gp weak CYP3A4	+70-100%	no data	+88% reduce dose	No data yet

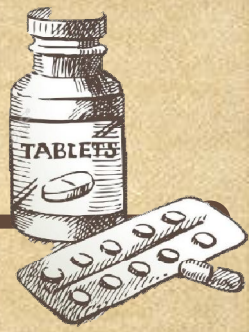
Heidbuchel H, et al. *Europace*. 2013;15:625-651.[31]

Not recommended/contraindicated
Reduce dose if 2 factors or more
Reduce dose
No data yet

Interaction of amiodarone with other drugs:

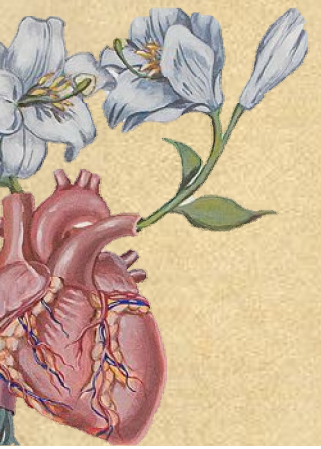
Drug	Result of interaction
Digoxin	Elevated digoxin plasma concentration
Warfarin	Elevated prothrombin time

Amiodarone : drug interaction



- **Inhibitor of CYP1A2, 2C9, 2D6 และ 3A4**
- **Inhibitor of P-glycoprotein system**

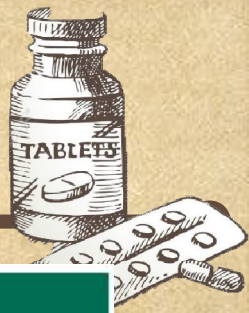
Warfarin	Statins	Other
CYP2C9 and 3A4 inhibition	CYP3A4	↑ Digoxin levels
Potentiates warfarin anticoagulant effects	Increased statin concentrations and increased risk of statin-induced myopathy	↓ lidocaine clearance
Increased INR Onset: 4—6 days Peak: 7 weeks	Lovastatin: Max 40 mg/day Simvastatin: Max 20 mg/day	Potentiate beta blocker and calcium channel blocker effects



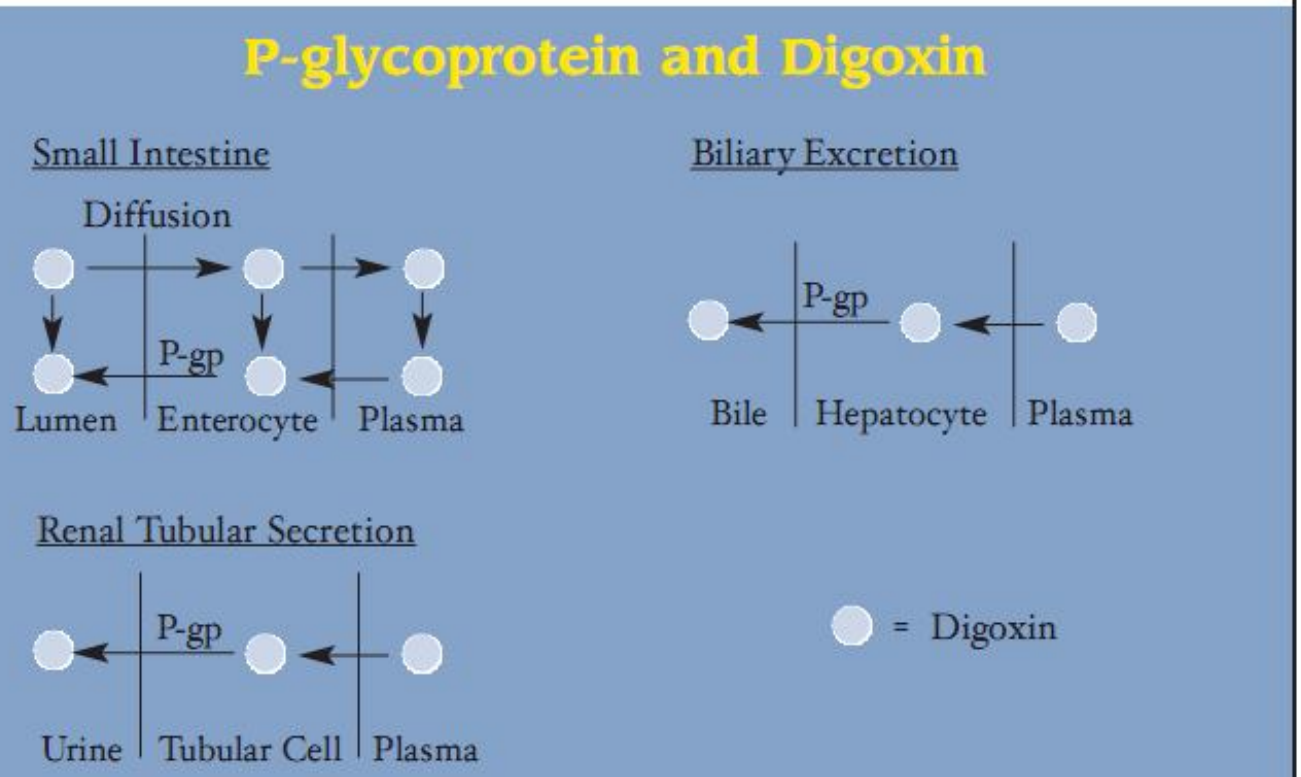
Important Amiodarone Drug Interaction

Drug	Result of interaction
Cyclosporine	Increased cyclosporine plasma concentration
Antiarrhythmic drugs	Additive effects: possible elevated plasma concentrations of quinidine, disopyramide,flecainide, propafenone and dofetilide

Drug Interactions with Digoxin



Figure



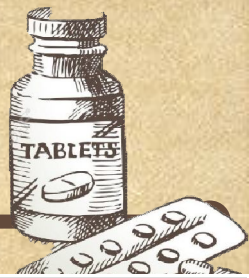
P-gp = P-glycoprotein. P-gp is found in the enterocytes, hepatocytes, and renal tubular cells. It acts by pumping digoxin out of cells, resulting in a reduction in digoxin absorption and an increase in its biliary and urinary excretion.

Selected Drugs That Affect P-glycoprotein

Inhibitors	Inducers
Amiodarone	Rifampin
Clarithromycin	St. John's wort
Cyclosporine	
Diltiazem	
Erythromycin	
Felodipine	
Indinavir	
Itraconazole	
Ketoconazole	
Nicardipine	
Quinidine	
Ritonavir	
Sirolimus	
Tacrolimus	
Verapamil	

Adapted from Hansten PD, Horn JR. *The Top 100 Drug Interactions: A Guide to Patient Management.* Edmonds, WA: H&H Publications; 2004:157-169.

Drug Interactions with Digoxin



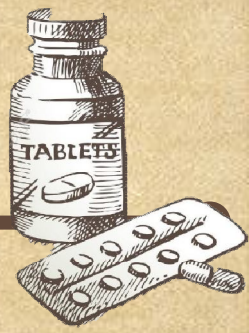
Serum levels	Medications
Increase digoxin level	Amiodarone, benzodiazepine, cyclosporine, indomethacin, Itraconazole, macrolides, spironolactone, verapamil

Drug Interactions with simvastatin

Interacting agents	Prescribing Recommendations
Itraconazole, Ketoconazole, Posaconazole (New)	Contraindicated with simvastatin
Erythromycin, Clarithromycin, Telithromycin	
HIV protease inhibitors, Nefazodone, Gemfibrozil	
Cyclosporine, Danazol	

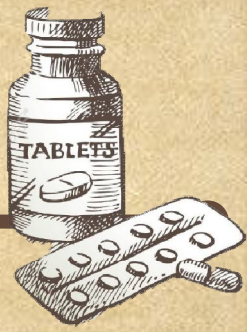
Avoid large quantities of grapefruit juice (>1 quart daily)

Drug interaction : Statins vs ARV



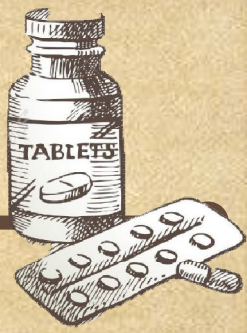
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV, ATV/c, ATV/r, DRV/c	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
	DRV/r	DRV/r plus atorvastatin 10 mg similar to atorvastatin 40 mg administered alone	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily.
	FPV, FPV/r,	FPV +/– RTV ↑ atorvastatin AUC 130% to 153%	
	SQV/r	SQV/r ↑ atorvastatin AUC 79%	
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary.
	TPV/r	↑ atorvastatin AUC 836%	**Do not coadminister.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31%, C_{max} ↑ 60% ATV: no significant effect DRV/r: no significant effect LPV/r ↓ pitavastatin AUC 20% LPV: no significant effect	No dose adjustment necessary.
Pravastatin	ATV/c, ATV/r	No data	Use lowest starting dose of pravastatin and monitor for efficacy and adverse effects.
	DRV/c, DRV/r	With DRV/r, pravastatin AUC • ↑ 81% following single dose of pravastatin • ↑ 23% at steady state	Use lowest possible starting dose of pravastatin with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary.
	SQV/r	pravastatin AUC ↓ 47% to 50%	No dose adjustment necessary.

Cardiac drug interaction with alternate medicine or herb

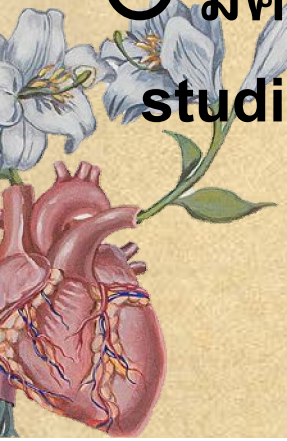


Herb	Result of interaction
Ginkgo biloba extract	Reduces the therapeutic potency of the Calcium channel blocker, nicardipine

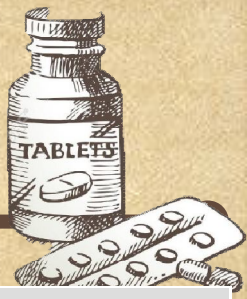
การกำหนดคู่ยาที่เป็นFatal Drug Interaction



- มีรายงานการเสียชีวิตอันเป็นผลจากอันตรกิริยาระหว่างยา
- ระดับความมีนัยสำคัญทางคลินิกระดับ1
- ความรุนแรงอยู่ในระดับMajor หมายความว่า “ผลที่เกิดขึ้นจะก่อให้เกิดอันตรายถึงชีวิตและเป็นสาเหตุของความเสียหายอย่างถาวร”
- มีความน่าเชื่อถือของข้อมูลอยู่ในระดับน่าเชื่อถือโดยมีWell controlled-studies (Established) และน่าจะใช่ (Probable)

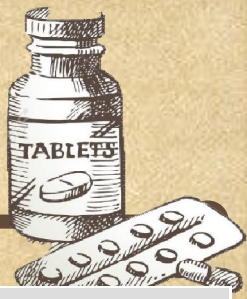


การเฝ้าระวังอาการของผู้ป่วย



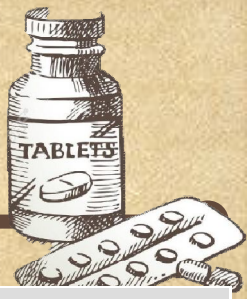
ชื่อยาที่มีปฏิกิริยาต่อกัน		Onset	Effect	Management
Drug 1	**Drug 2**			
Diuretic	**Digoxin**	Delayed	เพิ่มการขับ K ทางปัสสาวะ และมีผลต่อการทำงานของกล้ามเนื้อหัวใจ อาจเกิด arrhythmia อาจเกิด digoxin toxicity ได้ง่าย	- วัดระดับ K และควรเสริมให้ผู้ที่มีระดับK ต่ำ - หรือให้ใช้ยาในกลุ่ม potassium-sparing diuretic

การเฝ้าระวังอาการของผู้ป่วย



ชื่อยาที่มีปฏิกิริยาต่อกัน		Onset	Effect	Management
Drug 1	**Drug 2**			
Amiodarone	**Digoxin**	Delayed	เพิ่ม digoxin level ประมาณ 70% กลไกจาก amiodarone ไป inhibit p-glycoprotein	- หากใช้ร่วมกันอาจพิจารณาลด dose digoxin ประมาณ 50% - ติดตามอาการไม่พึงประสงค์ของ digoxin toxicity

การเฝ้าระวังอาการของผู้ป่วย



ชื่อยาที่มีปฏิกิริยาต่อกัน		Onset	Effect	Management
Drug 1	**Drug 2**			
Simvastatin	**clarithromycin**	Not Specified	Contraindication เพิ่มฤทธิ์ในการเกิด rhabdomyolysis	- ไม่ควรใช้ร่วมกัน มีรายงานการเกิด rhabdomyolysis ภายใน 14 วันหลังได้ยา clarithromycin - อาจหลีกเลี่ยงไปใช้ ATB ชนิดอื่น


Thank you
for your attention