49th Annual Scientific Meeting The Heart Association of Thailand under the Royal Patronage of H.M. the King "Cardiology on the move" 24-25 March 2017 @Sheraton, HuaHin

Cardiovascular Pharmacotherapy in Special Population:

Cardio-Nephrology

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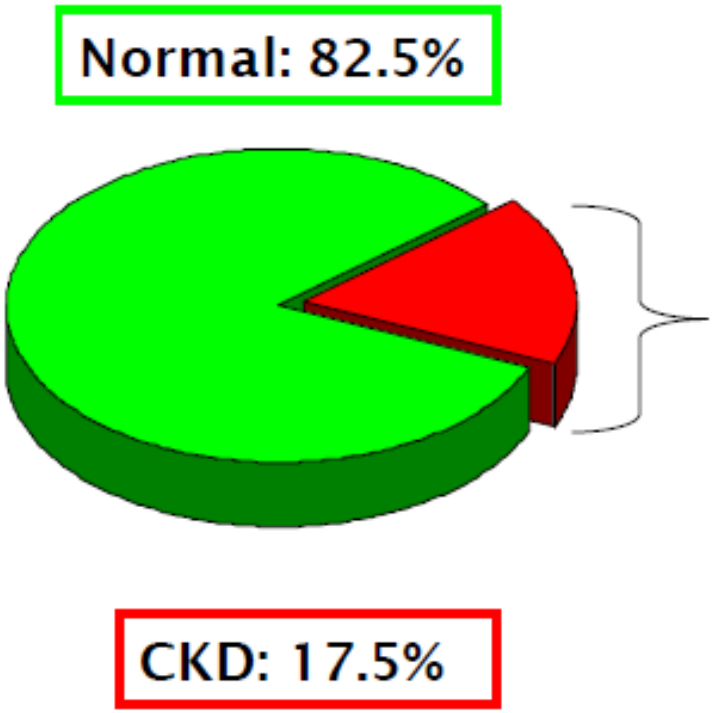
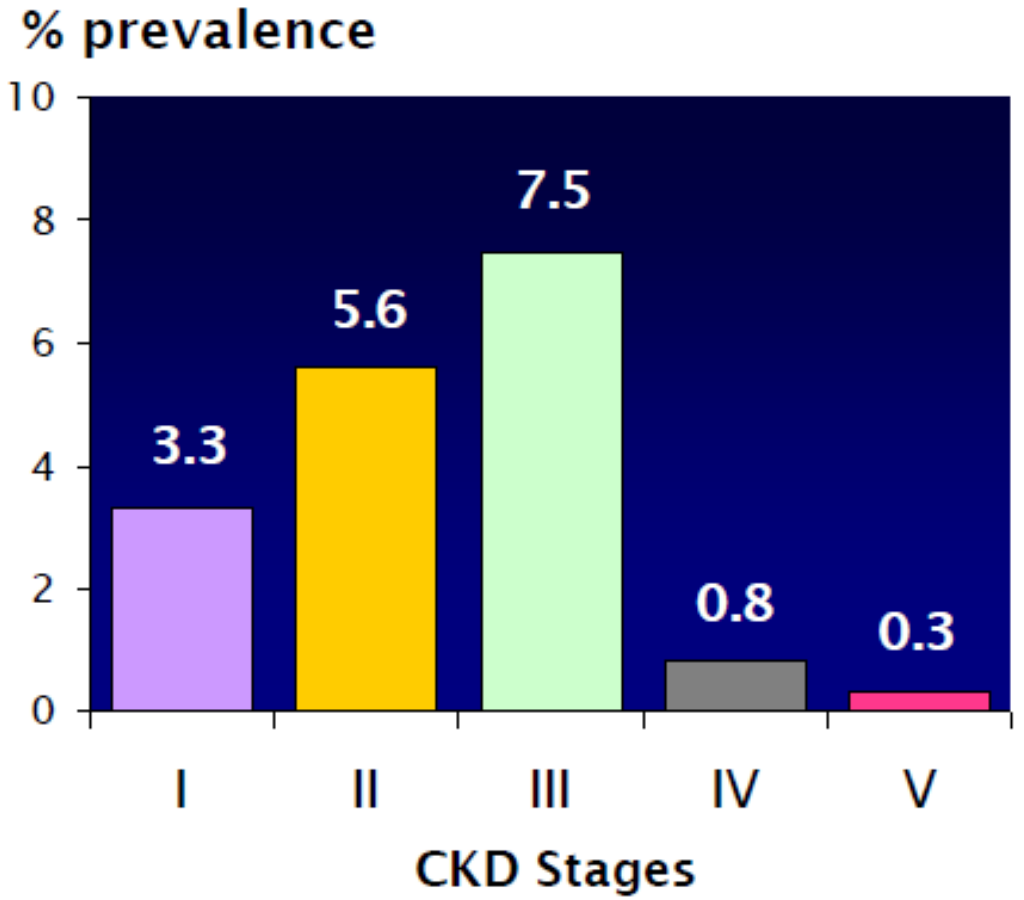
25 March 2017

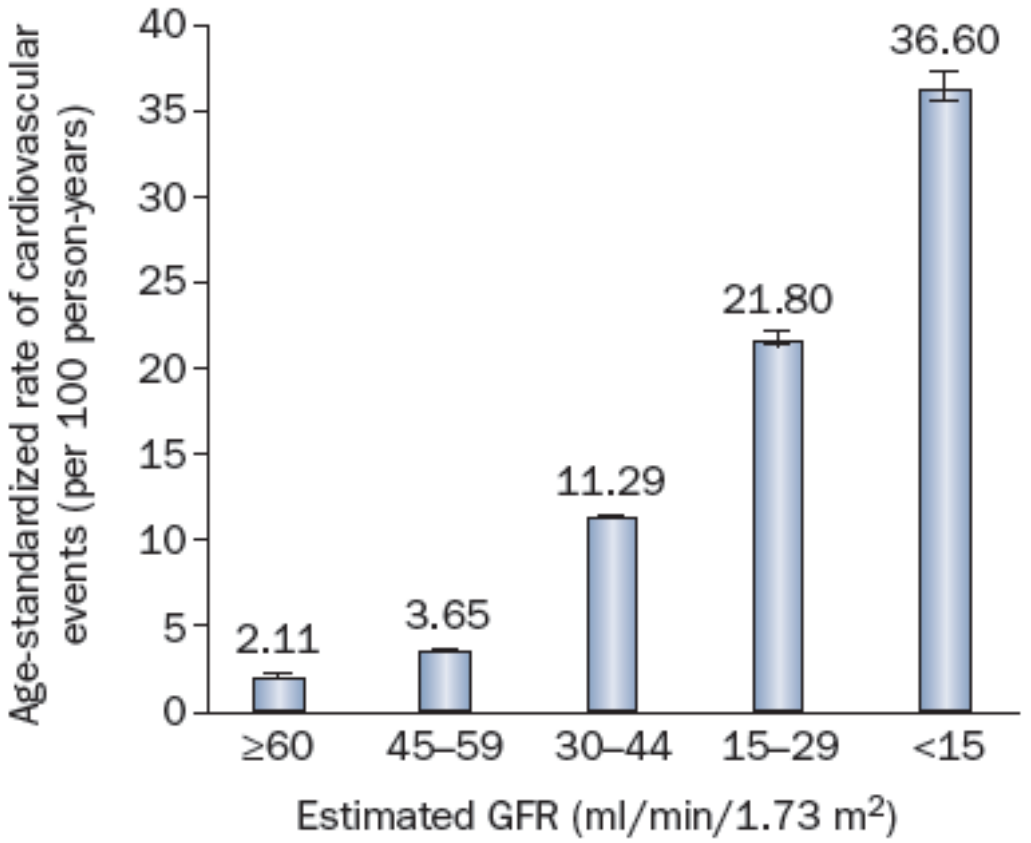
Prevalence of CKD in Thailand: THAI-SEEK study





Nephrol Dial Transplant. 2010 May;25(5):1567-75.

Rates of death from CV events according to eGFR



Number of events	73,108	34,690	18,580	8,809	3,824

N Engl J Med. 2004 Sep 23;351(13):1296-305.

Pathogenesis of CVD in CKD patients

Traditional risk factors

- Age
- Male gender
- Diabetes mellitus
- Smoking
- Hypertension
- Dyslipidemia
- Hyperhomocysteinemia
- Inflammation
- Oxidative stress

Uremia-associated risk factors

- Anemia
- Sympathetic nervous system activation
- Enhanced oxidative stress and inflammation
- Protein glycation and carbamylation
- Endothelial dysfunction
- Coagulation disorders
- Disturbances of mineral metabolism
- Uremic toxins
- Protein-energy wasting

Nat Rev Nephrol. 2012 Feb 21;8(4):214-23.

Case study

- A 65-year old woman
- Underlying disease
  - T2DM, Dyslipidemia 20 y PTA
  - Hypertension 25 y PTA
  - Dx. CKD 6 y PTA
- Physical examination
  - Vital sign: BT 36.7 °C HR 80/min, RR 20/min
  - BP 160/90 mmHg
  - GA: moderate pale, mild dyspnea
  - Others : WNL

Labs and medication history

Parameter	6/9/59	15/11/59	10/1/59	7/3/60
Serum creatinine (mg/dL)	2.8	2.3	2.5	2.1
eGFR (ml/min/1.73 m^2)	17	22	20	24
UACR (mg/g)	600	400	-	900

- **Furosemide (40 mg) 2 x 1 pc AM**
- **Hydralazine (50 mg) 1 x 4 pc**
- **Diltiazem SR 1 x 2 pc**
- Simvastatin (20 mg) 1 x HS
- Calcium carbonate (600 mg) 1 x 3 with meal
- Alfacalcidol (1 mcg) 1 tablet three times a week at bedtime
- Sodium bicarbonate (300 mg) 1 x 3 pc
- Erythropoietin 4000 u 2 times/week
- Ferrous sulfate (300 mg) 1 x 3 pc
- Folic acid (5 mg) 1 x 1 pc

Staging of CKD

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range			Persistent albuminuria categories Description and range		
			A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
			<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
G1	Normal or high	≥90			
G2	Mildly decreased	60-89			
G3a	Mildly to moderately decreased	45-59			
G3b	Moderately to severely decreased	30-44			
G4	Severely decreased	15-29			
G5	Kidney failure	<15			

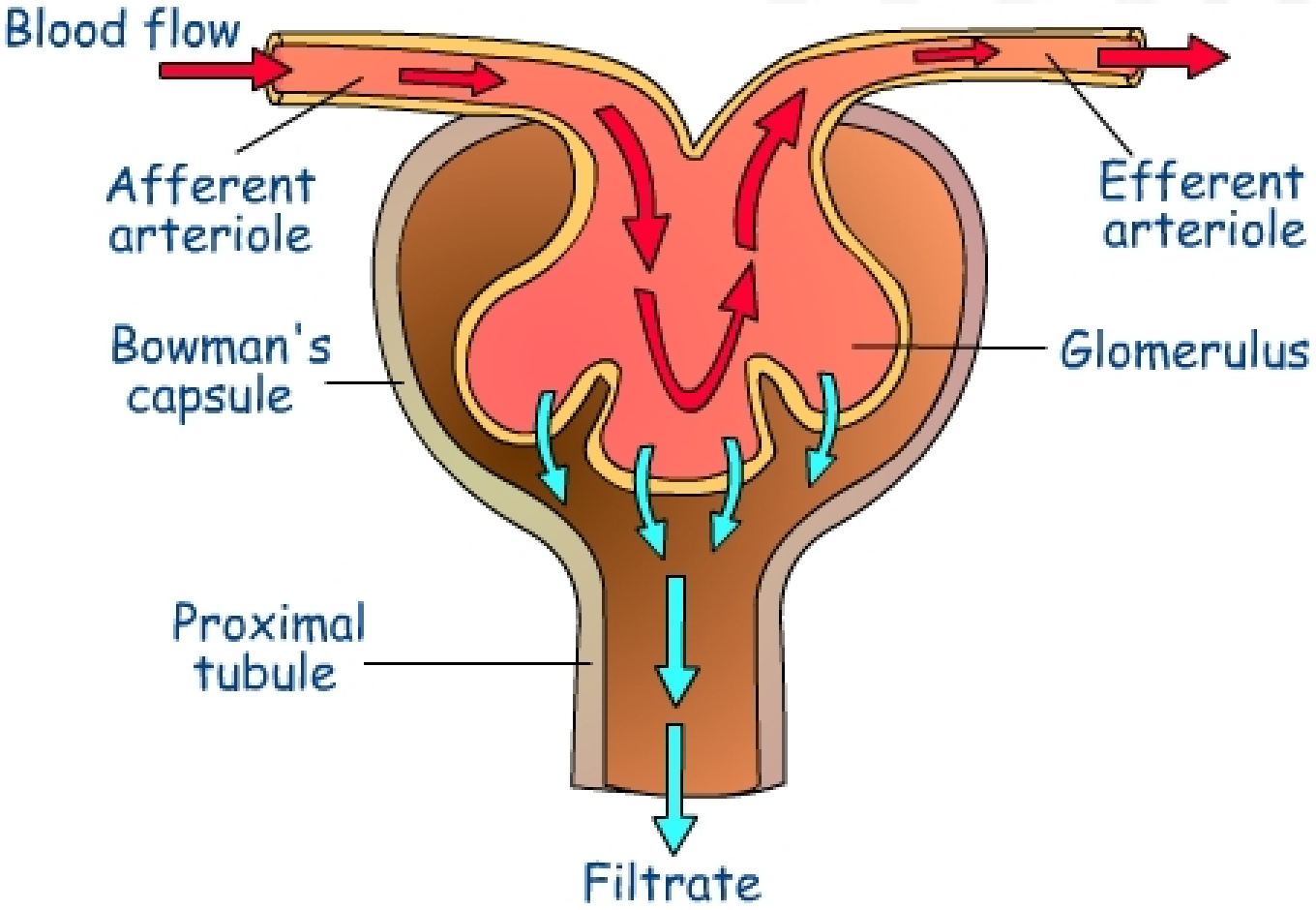
Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

- **Stage G4 CKD** (severely decreased GFR)
- **A3 albuminuria** (severely increased albuminuria

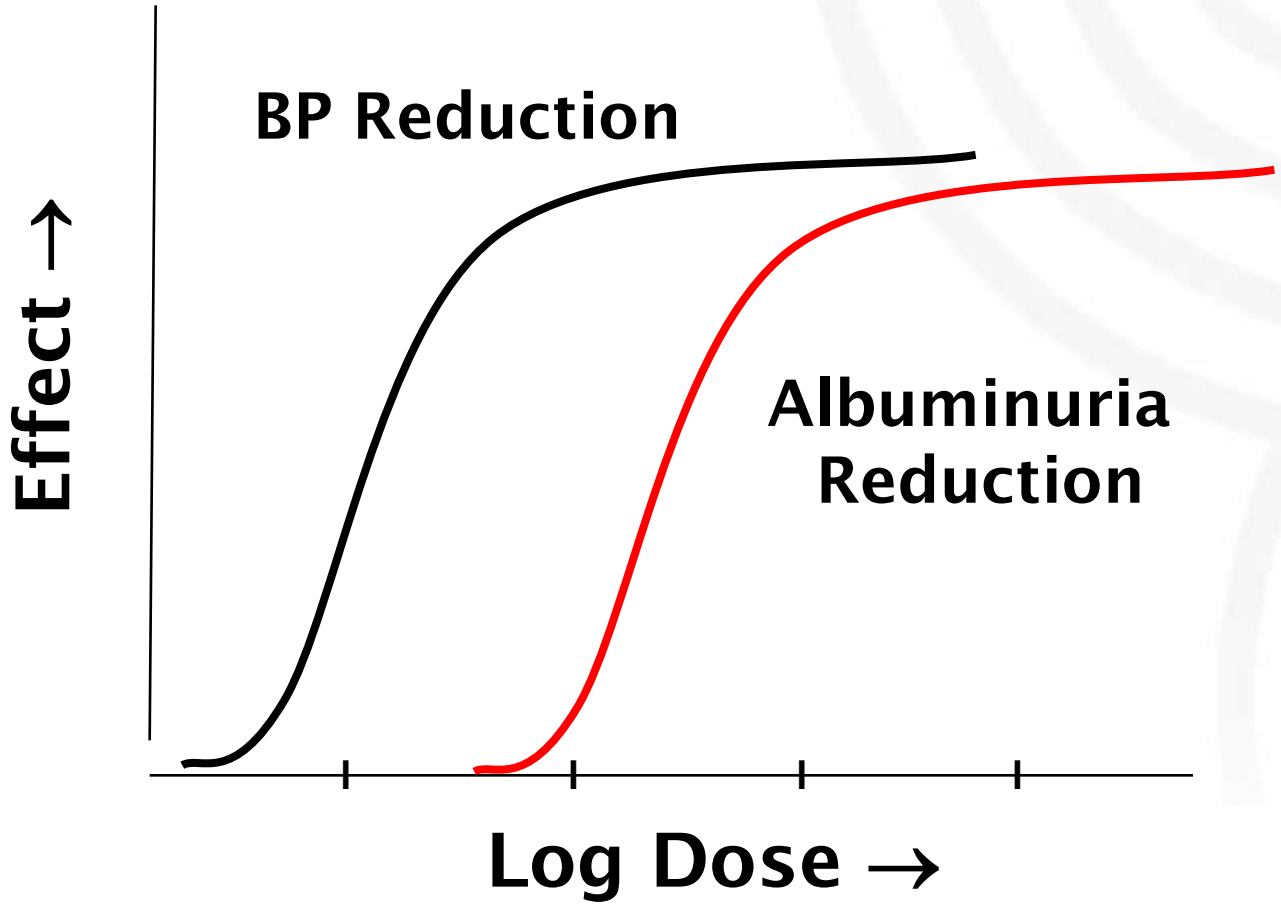
CKD ND with DM

- Urine albumin excretion (UAE)
  - < 30 mg/24 hours (or eqivalent*)---> ≤140/90 mmHg (1B)
  - ≥ 30 mg/24 hours (or eqivalent*)---> ≤130/80 mmHg (2D)
    - 30-300 mg/24 hours ---> ARBs or ACEIs (2D)
    - > 300 mg/24 hours ---> ARBs or ACEIs (1B)

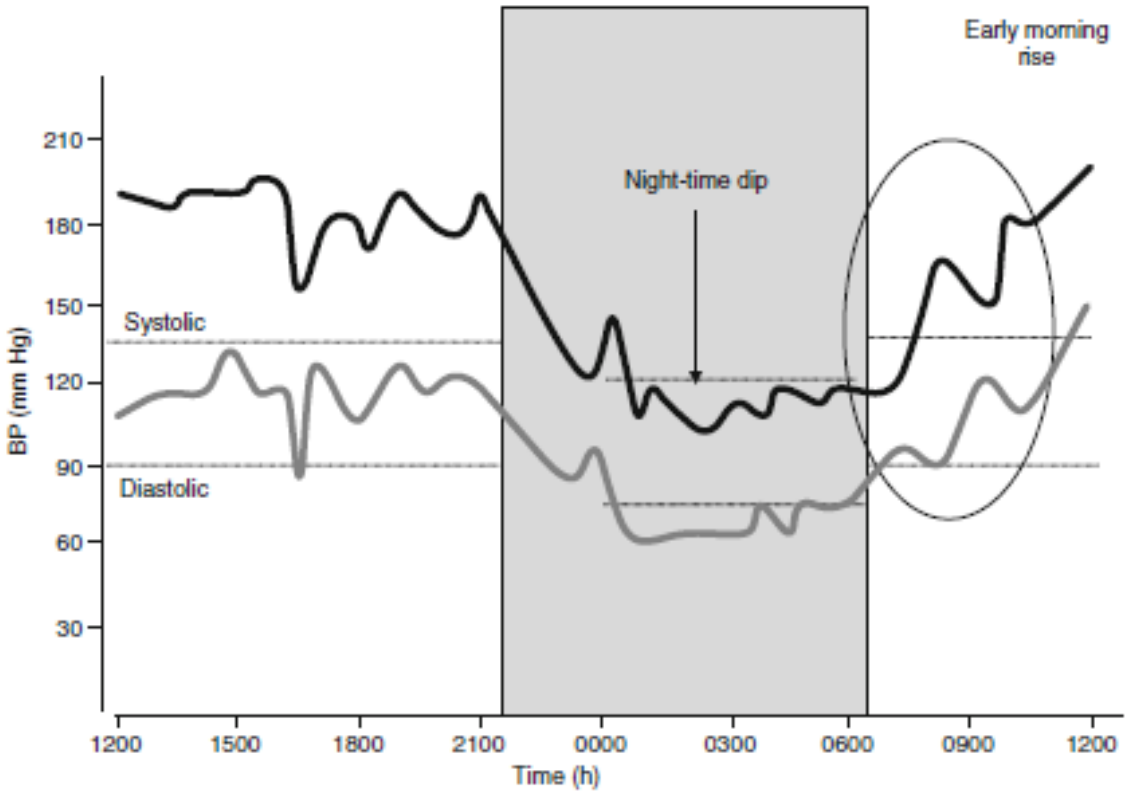
ACEIs/ARBs and proteinuria



Dose-Response Relationships for BP and albuminuria



BP pattern in CKD patients

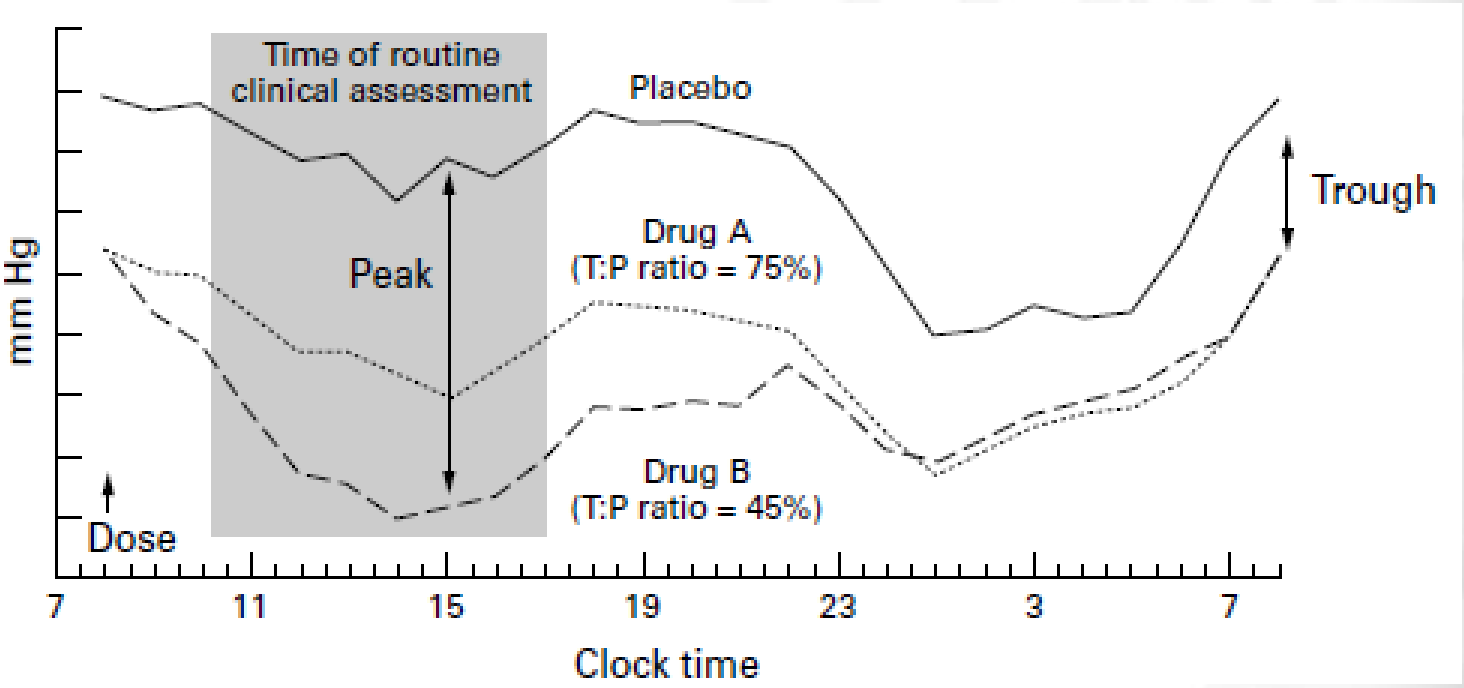


- Nocturnal hypertension (non-dippers) is not only frequent, but also highly predominant, in patients with CKD.

CKD pt who do not have the normal decrease in BP during sleep have worse cardiovascular and kidney outcomes when compared with dippers

J Am Soc Nephrol. 2011 Dec;22(12):2313-21., KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease 2012.

Interpretation of T:P ratio



- Small T:P ratio
  - The larger peak effect
    - Excessive BP reduction
  - The smaller trough effect
    - Insufficient duration coverage

Heart. 2000 Sep;84 Suppl 1:i39-41

TABLE 1. Pharmacology of ACE Inhibitors Approved in the United States

	Captopril	Enalapril	Lisinopril	Benazepril	Quinapril	Ramipril
Zinc ligand	Sulfhydryl	Carboxyl	Carboxyl	Carboxyl	Carboxyl	Carboxyl
Prodrug	No	Yes	No	Yes	Yes	Yes
t_{max} active drug, h	0.7–0.9	2–8	6–8	1–2	2	3
$t_{1/2}$ active drug, h	1.7	11	12	10–11	1.9–2.5, 25 terminal	Triphasic 4, 9–18, >50
Route of elimination	Kidney	Kidney	Kidney	Kidney	Kidney	Kidney
Dosage range, mg	6.25–300	2.5–40	5–40	5–80	5–80	1.25–20
F, %*	75–91	60	6–60	>37	>60	50–60

	Trandolapril	Moexipril	Fosinopril
Zinc ligand	Carboxyl	Carboxyl	Phosphinyl
Prodrug	Yes	Yes	Yes
t_{max} active drug, h	4–10	1.5	3
$t_{1/2}$ active drug, h	15–24 terminal	2–9	12
Route of elimination	Kidney, liver	Kidney	Liver, kidney
Dosage range, mg	1–8	7.5–30	10–80
F, %*	70	13	36

Comparative PK of ACEI

Circulation

Cardiovascular Drugs

Angiotensin-Converting Enzyme Inhibitors

ARBs: Pharmacokinetics

ARBs	T ½ (hrs)	F (%)	Met/Elim	T/P Ratio
Losartan	2 (6-9)	33	Liver (70%)	58-78
Valsartan	9	25	Liver (80%)	69-76
Irbesartan	11-15	70	Liver (75%)	> 60
Candesartan	9-12	42	Liver (67%)	80
Telmisartan	24	43	Liver (100%)	≥ 97
Olmesartan	10-15	25.6	Renal (50%)	60-80
Azilsartan	11	60	Liver (55%), Renal (15%)	95-97

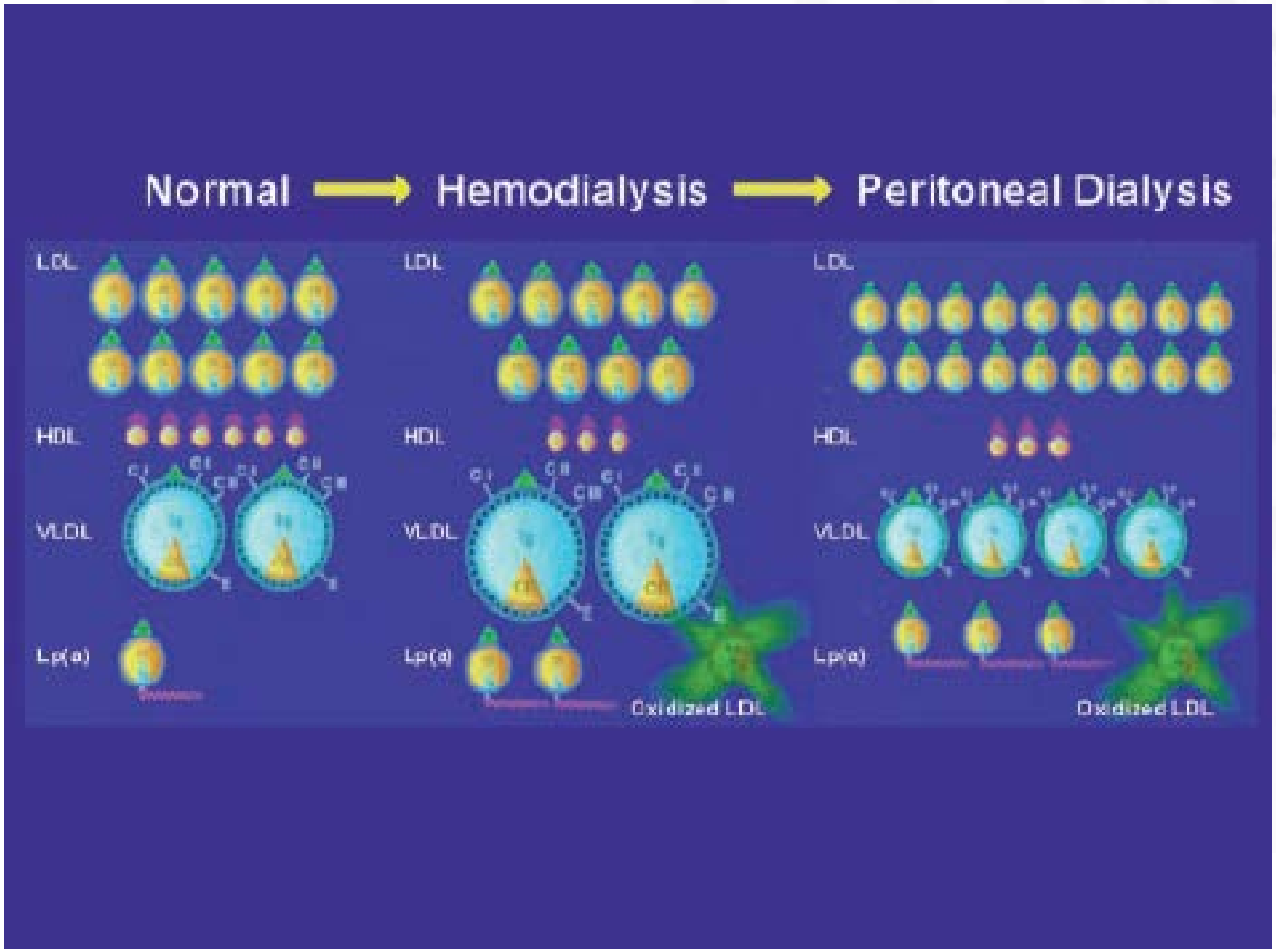
Metabolic Pathway of ARBs

ARBs	Met/Elim	CYP	Others
Losartan	Liver (70%)	2C9 (major) 1A2,3A4	-
Valsartan	Liver (80%)	-	OATP1B1, 1B3, MRP2
Irbesartan	Liver (75%)	2C9 (Major) 1A2,3A4	-
Candesartan	Liver (67%)	- (minor 2C)	-
Telmisartan	Liver (100%)	-	UGT + OATP1B1, 1B3
Olmesartan	Renal (50%)	-	OATP1B3
Azilsartan	Liver (55%), Renal (15%)	2C9	-

Anti-HTN vs Dialysis

Drugs	Dose	Peritoneal	Hemodialysis	Suppl Dose
Captopril	12.5 – 50 mg tid	-	50%	12.5 – 25 mg
Enalapril	2.5 – 10 mg bid	-	50%	2.5 – 5 mg
Lisinopril	2.5 – 10 mg OD	-	50%	2.5 – 5 mg
Ramipril	2.5 – 10 mg OD	-	20%	2.5 mg
Atenolol	25 – 100 mg OD	-	50-75%	25-50 mg
Methyldopa	250-500 mg tid	30-40%	60%	250-500 mg
Hydralazine	25-50 mg t/qid	25-40%	25-40%	25 mg

Lipid abnormalities in ESRD



J Am Soc Nephrol. 2003 Sep;14(9 Suppl 4):S315-20.

Lipid abnormalities in CKD

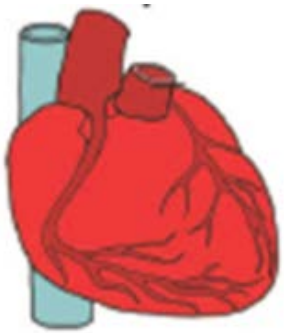
	Nephrotic syndrome	CKD 1-4	Hemodialysis	PD	KT
TC	↑↑	↔	↔	↑↑	↑
Triglyceride	↑↑	↔ or ↑	↑	↑↑↑	↔ or ↑↑
LDL-C	↑	↔ or ↑ (but ↑ small dense particles)	↔ or ↓ (but ↑ small dense particles)	↑	↔ or ↑
HDL-C	↓	↓ or ↔	↓	↓	↔

- **Lipid abnormailties in CKD**
  - **High TG, low HDL**
  - **Normal LDL (but increase small, dense LDL)**

Atherosclerosis. 2008 Feb;196(2):823-34.

Dyslipidemia in CKD patients

- What is the question?
  - How and When to prescribe statins treatment in the CKD population?
  - How should the dose of anti-dyslipidemic agents be determined in CKD patients?
  - How about adverse effects and drug interaction of statins in CKD patients?



Role of statins for CV events

- NKF-DOQI 2003 recommendation, CKD is CHD risk equivalent
  - Based on general population

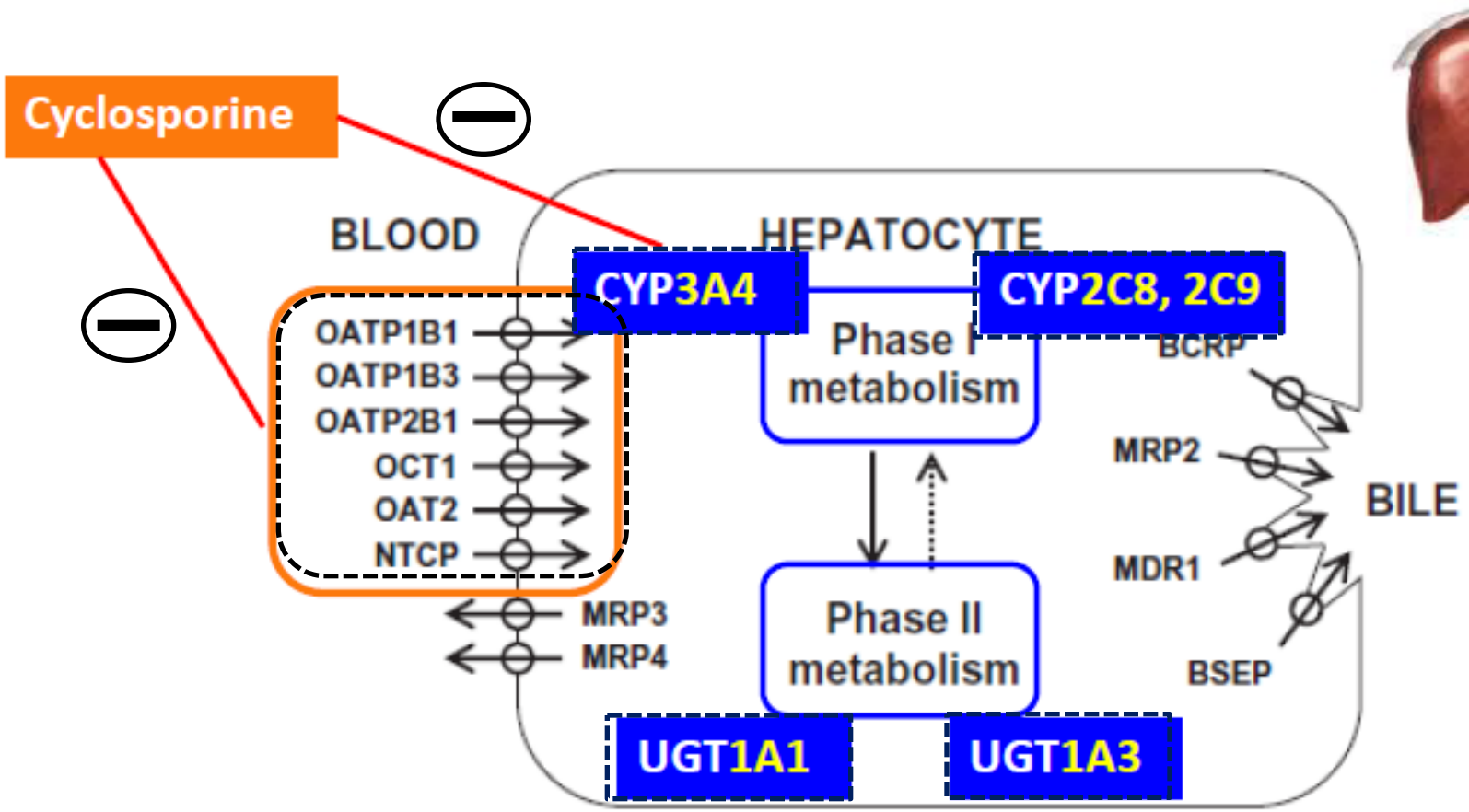
- Lowering LDL-C and pleiotropic effect of statins reduce risk for CHD in patient *without* CKD In large RCT
- Statins show CV benefit for patient with *CKD* in *subgroup analysis* from large trial of statins

Chapter 2: Pharmacological cholesterol-lowering treatment in adults

Kidney International Supplements (2013) **3**, 271–279; doi:10.1038/kisup.2013.34

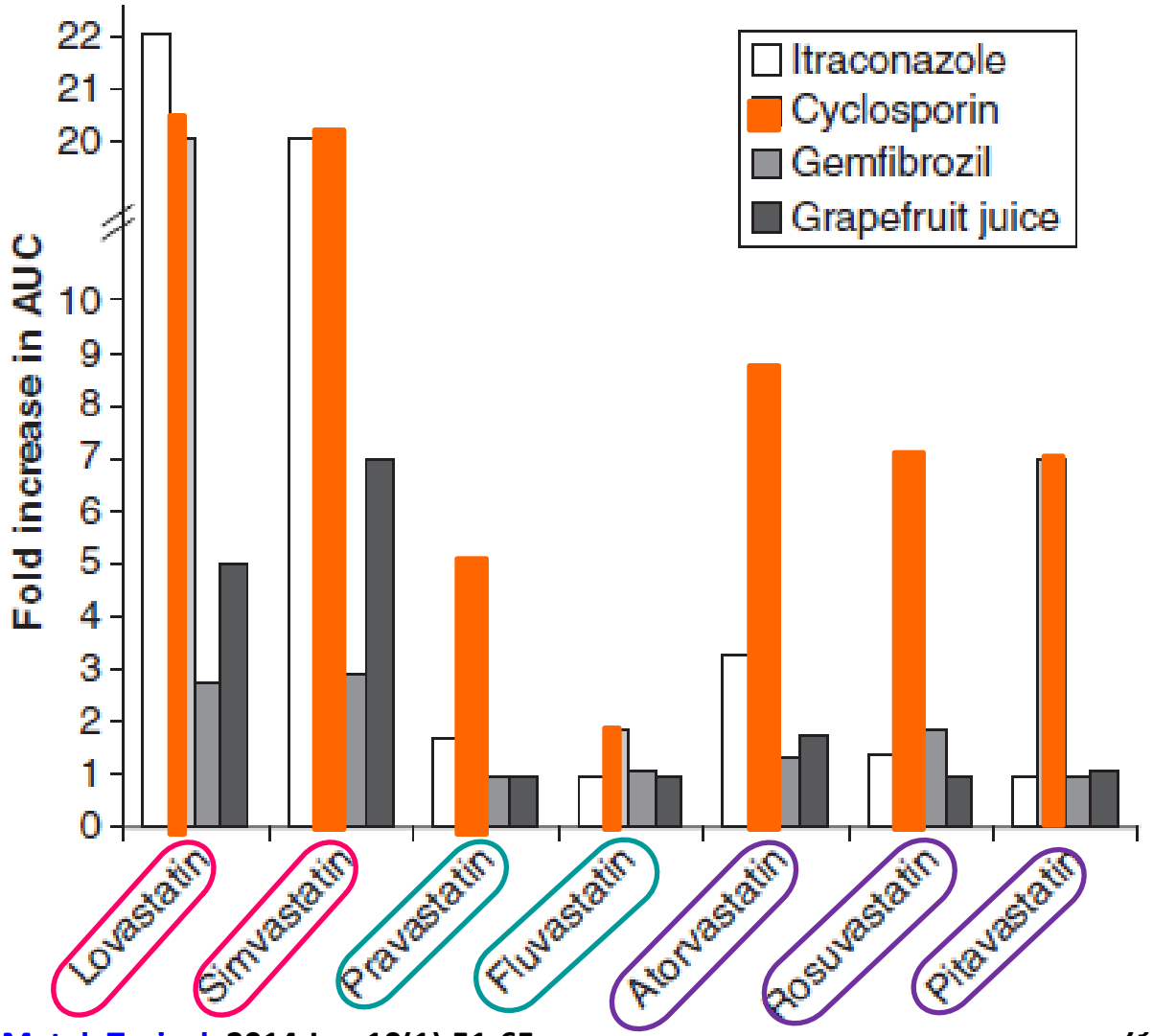
อายุ (ปี)	ระยะของโรคไตเรื้อรัง[a]			
	G1-G2	**G3a-G5**	**ผู้ป่วยที่ได้รับการฟอกเลือด**	**ผู้ป่วยที่ได้รับปลูกถ่ายไต**
≥50	Statins ***(1B)***	Statins or statin/ezetimibe ***(1A)***	ไม่ควรเริ่ม statins หรือ statin/ezetimibe combination ***(2A)*** -แต่ในกรณีที่ผู้ป่วยเคยได้รับ statins หรือ statin/ezetimibe มาก่อนเริ่มการฟอกเลือด แนะนำให้ยาต่อได้ ***(2C)***	แนะนำให้เริ่มยา statins ***(2B)***
18-49	Statin ในผู้ป่วยที่มีปัจจัย ≥1 ข้อต่อไปนี้ ***(2A)*** -known coronary disease (โรคหัวใจขาดเลือด; myocardial infarction หรือ coronary revascularization) -เบาหวาน -มีโรคหลอดเลือดสมองมาก่อน -ประเมิน 10-year incidence of coronary death หรือ non-fatal myocardial infarction > 10%			

Mechanism of CsA & statins



Br J Pharmacol. 2009 Oct;158(3):693-705.

PK drug interaction of statins



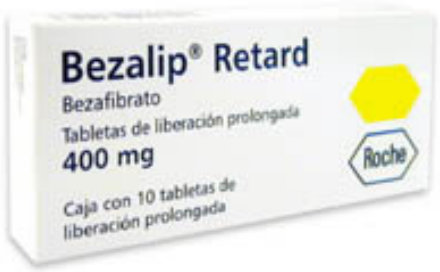
Expert Opin Drug Metab Toxicol. 2014 Jan;10(1):51-65

Dose modifications for statins in CKD

Statins	eGFR G1-G2	eGFR G3a-G5 และ ผู้ป่วยที่ได้รับการฟอกเลือด และผู้ป่วยที่ได้รับการเปลี่ยนถ่ายไต (ขนาดยาสูงสุดต่อวัน)
Lovastatin	ขนาดยาเท่ากับผู้ป่วยปกติ	ไม่มีการศึกษา
Fluvastatin	ขนาดยาเท่ากับผู้ป่วยปกติ	80 มิลลิกรัม
Atorvastatin	ขนาดยาเท่ากับผู้ป่วยปกติ	20 มิลลิกรัม
Rosuvastatin	ขนาดยาเท่ากับผู้ป่วยปกติ	10 มิลลิกรัม
Simvastatin/ezetimibe	ขนาดยาเท่ากับผู้ป่วยปกติ	20/10 มิลลิกรัม
Pravastatin	ขนาดยาเท่ากับผู้ป่วยปกติ	40 มิลลิกรัม
Simvastatin	ขนาดยาเท่ากับผู้ป่วยปกติ	40 มิลลิกรัม
Pitavastatin	ขนาดยาเท่ากับผู้ป่วยปกติ	2 มิลลิกรัม

KDIGO 2013 clinical practice guideline for lipid management of chronic kidney disease. Kidney Int Suppl 2013; (3):259-305.

Fibrates

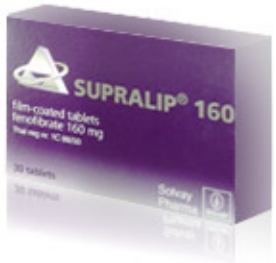


- T ½ : 2.4 hr

Contribution of kidney for metabolism / elimination: 95%

- T ½ : 1.5 hr

Contribution of kidney for metabolism / elimination: 72%



- T ½ : 16-23 hr

Contribution of kidney for metabolism / elimination: 60%

Non-statins	GFR (ml/min/1.73 m^2)			Notes
	60-90	15-59	<15	
Bezafibrate	No	40-60 ml/min→ 400 mg/day 15-40 ml/min→200 mg/day[1]	200 mg every third day[1]	
Gemfibrozil	No	No	No	NLA recommends a dose 600 mg/d for GFR 15-59 ml/min/1.73m^2 and avoiding use for GFR <15 ml/min/1.73m^2
Fenofibrate	Reduced to 50%	Reduced to 25%	Avoid	May increase Scr
Nicotinic acid	No	No	Reduced to 50%	34% kidney excretion
Ezetimibe	No	No	No	
Omega-3 FA	No	No	No	

J Am Coll Cardiol. 2008 Jun 24;51(25):2375-84., Micromedex 2.0.[1]

Take Home Messages

- Optimal CV risk reduction should be determined as gold standard in all CKD patients
- PK alteration, dialysis procedure or evidenced-studies in CKD are concerning factors to help optimize both kidney and heart function as well as patient outcomes


อ้วนกลม
ระทม
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