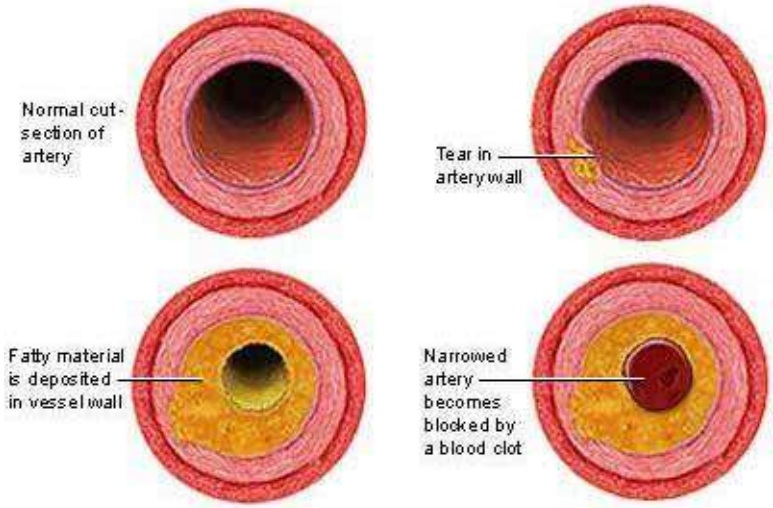


Diabetes Complications Treatment and Prevention

Patana Teng-umnuay MD PhD

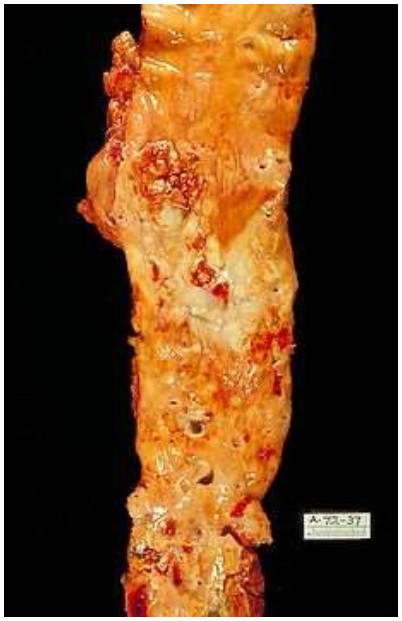
Diabetes Complications

- Atherosclerosis
  - Hypertension
  - Myocardial Infarction
  - Stroke
  - Peripheral Vascular Diseases
- Fatty liver and cirrhosis
- Diabetic Nephropathy

Injury and inflammation

(hypertension, smoking, high blood sugar, inflammation, infection)

Mononuclear cells and macrophage accumulation



Oxidised LDL cholesterol deposit

Smooth muscle cell proliferation,
fibrin and plaque formation

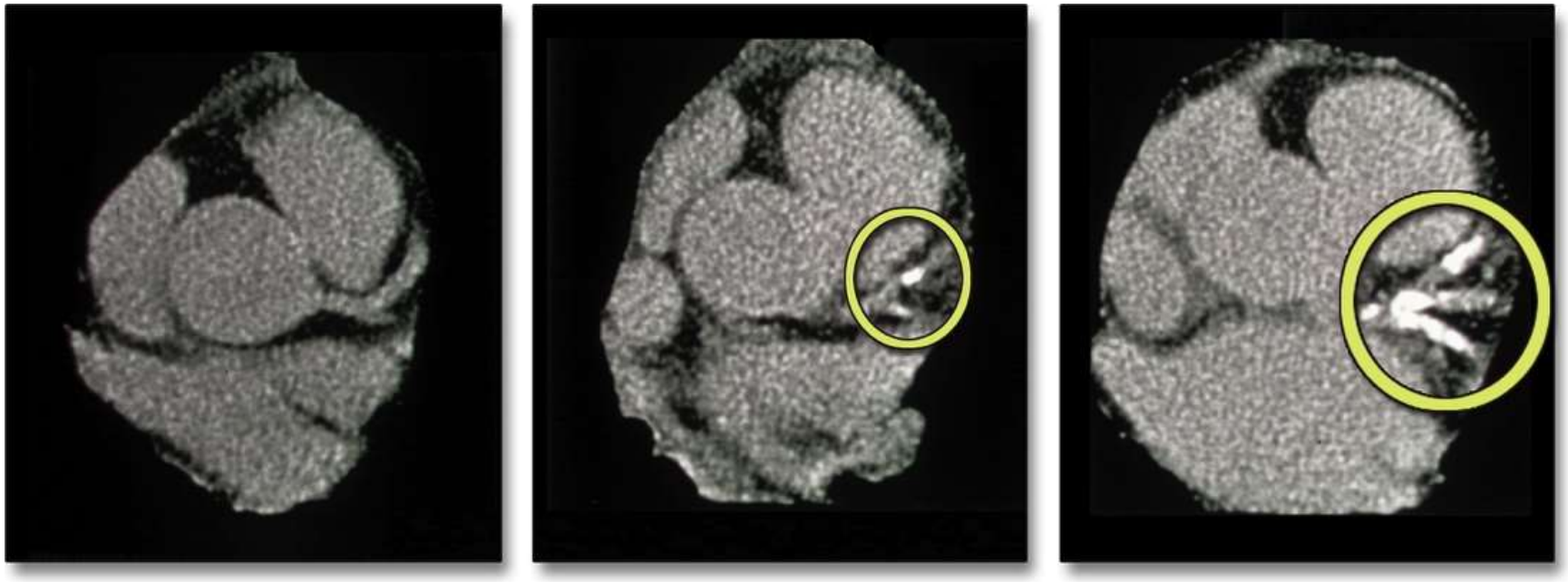
Vascular Calcification and thrombosis

Coronary Artery Calcium Scoring

- Calcification is part of the inflammation and repair processes that are ubiquitous in atherosclerotic lesions.
- Calcification occurs early in atherosclerosis, but we are not able to detect it with imaging until it increases in quantity, typically after the age of 40 in men and women.
- The coronary artery calcium score is a measurement of the amount of calcium in the walls of the arteries that supply your heart muscle, using a special computed tomography (CT) scan of your heart.

Coronary Calcium Score:Agatston Method

JACC 1990;15:827-832



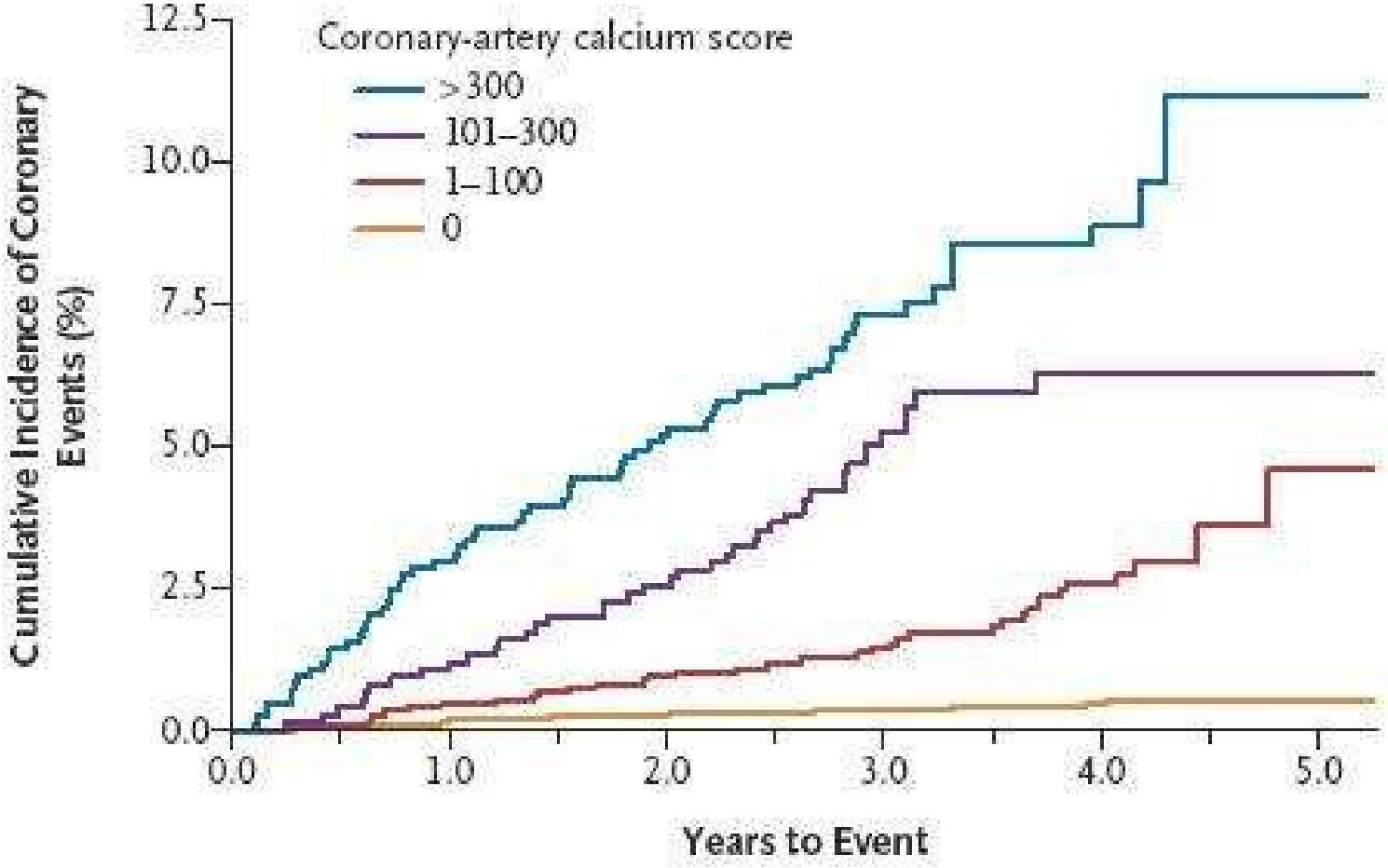
Normal

Moderate Calcification

Severe Calcification

Coronary Calcium and Coronary Events (MESA Study)

New Engl J Med 2008; 358: 1336 -1345.



Mesa Score

www.mesa-nhlbi.org

MESA 10-Year CHD Risk with Coronary Artery Calcification Back to CAC Tools

Gender	Male ◉	Female ○	
Age (45-85 years)	55	Years	
Coronary Artery Calcification	0	Agatston	

Race/Ethnicity	**Choose One**
Caucasian	○
Chinese	◉
African American	○
Hispanic	○

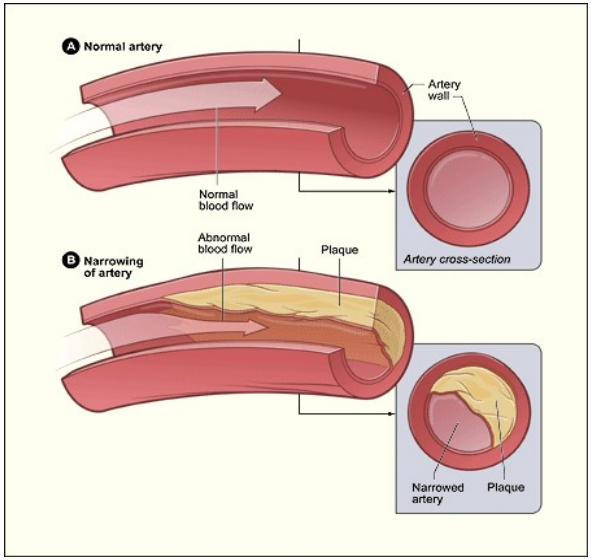
Diabetes	Yes ○	No ◉	
Currently Smoke	Yes ○	No ◉	
Family History of Heart Attack	Yes ○	No ◉	History in parents, siblings, or children
Total Cholesterol	230	mg/dL	
HDL Cholesterol	40	mg/dL	
Systolic Blood Pressure	120	mmHg	
Lipid Lowering Medication	Yes ○	No ◉	
Hypertension Medication	Yes ○	No ◉	

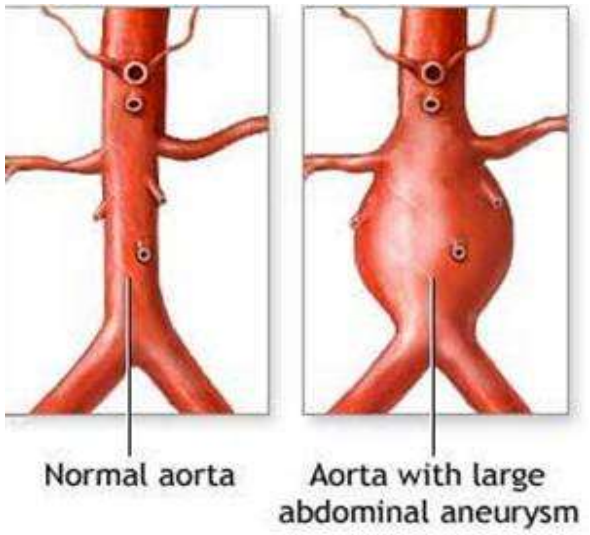
Calculate 10-year CHD risk

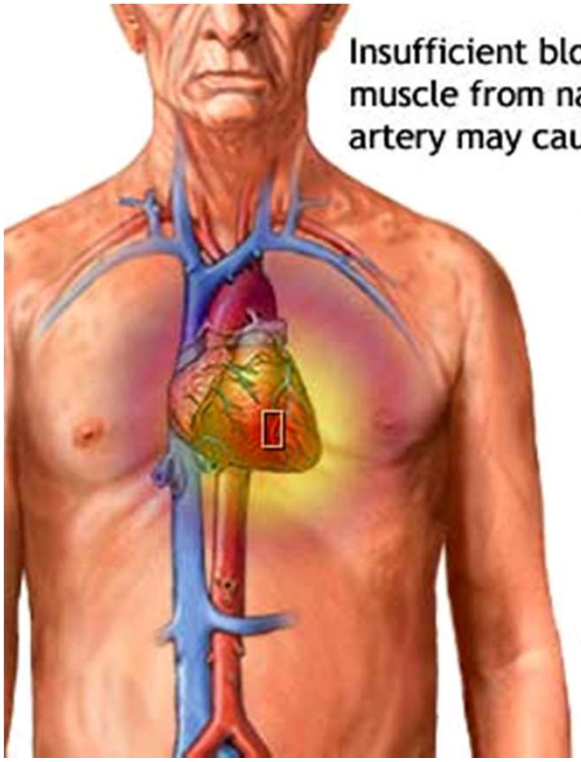
The estimated 10-year risk of a CHD event for a person with this risk factor profile including coronary calcium is 1.7%. The estimated 10-year risk of a CHD event for a person with this risk factor profile if we did not factor in their coronary calcium score would be 3.1%.

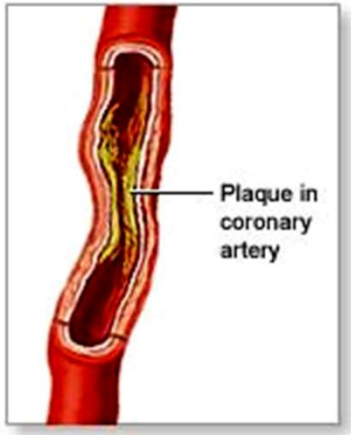
Consequences of atherosclerosis

- **Inadequate blood flow or ischemia (infarction)**
  - Ischemic heart disease
  - Stroke
  - Peripheral vascular disease
  - Renal vascular disease (must be bilateral)
  - Ischemic bowel disease
- **Aneurysm**

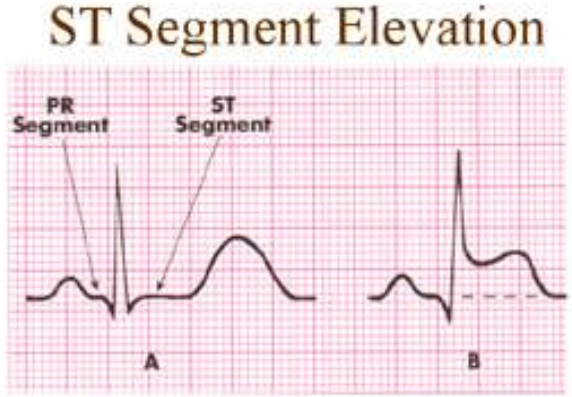






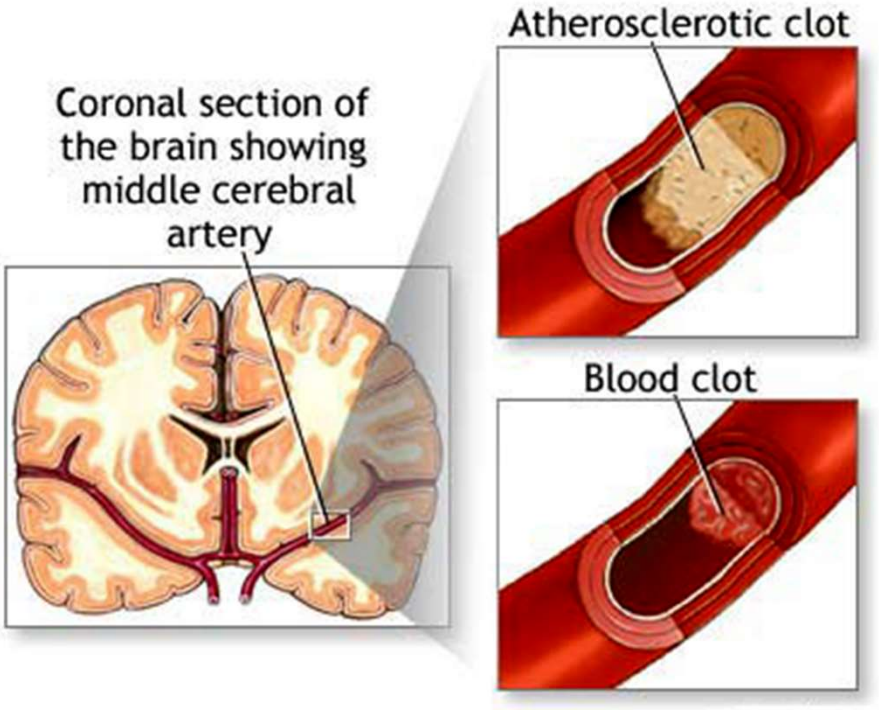


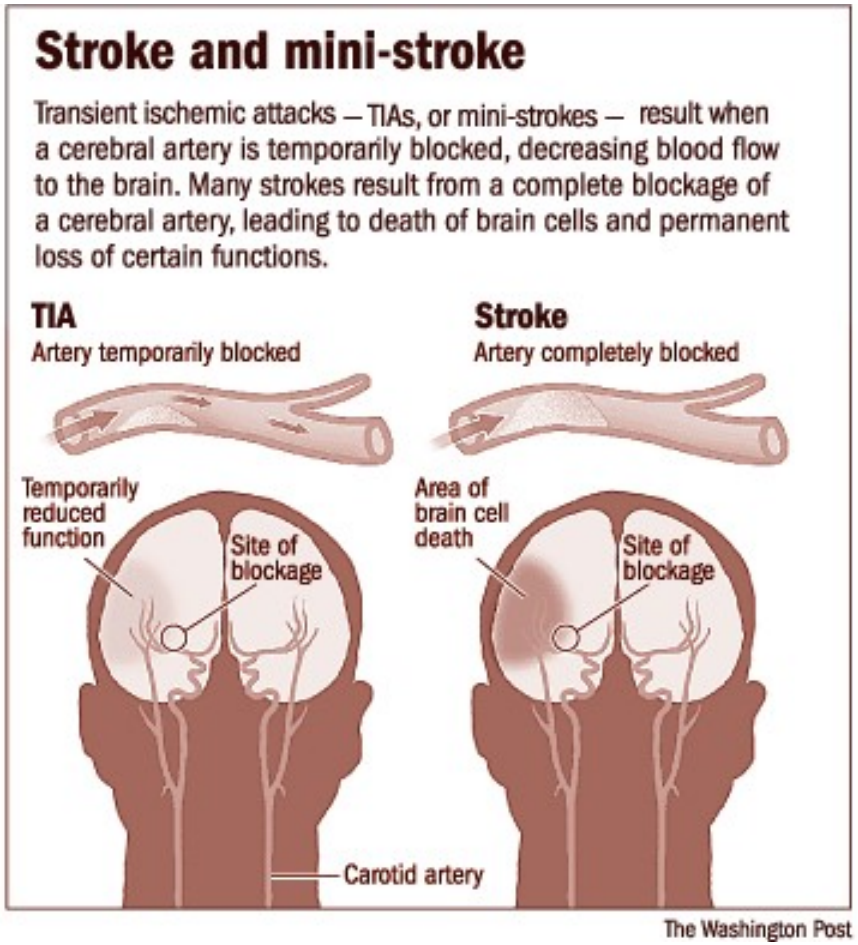
Angina Pectoris and myocardial infarction



↑ 1 mm above baseline (limb)
↑ 2 mm above baseline (chest)
.08 sec to right of J point
Look for in two or more leads facing same area

Stroke


Coronal section of the brain showing middle cerebral artery
Atherosclerotic clot
Blood clot


Stroke and mini-stroke
Transient ischemic attacks — TIAs, or mini-strokes — result when a cerebral artery is temporarily blocked, decreasing blood flow to the brain. Many strokes result from a complete blockage of a cerebral artery, leading to death of brain cells and permanent loss of certain functions.
TIA
Artery temporarily blocked
Stroke
Artery completely blocked
Temporarily reduced function
Site of blockage
Area of brain cell death
Site of blockage
Carotid artery
The Washington Post

Stroke –
there's treatment if you act FAST.

Face
Face look uneven?

Arm
One arm hanging down?

Speech
Slurred speech?

Time
Call 911 NOW!

เจ็บป่วยฉุกเฉิน
1669
โทรฟรีแต่อย่าโทรเล่น

Controllable Atherosclerosis Risk Factors

- High blood pressure
- High blood cholesterol
- Smoking
- Diabetes
- Physical Inactivity
- Obesity
- Homocysteinemia
- Chronic inflammation (infection, autoimmune diseases, heavy metal intoxication, inflammatory diets)

Aspirin Was Not Beneficial in a Primary Prevention Trial

Gaziano JM et al. Lancet 2018 Aug 26

- In the ARRIVE trial, 12,546 patients with no history of CV disease who were deemed to be at moderate risk were randomized to receive daily aspirin (100 mg) or placebo.
- Inclusion criteria were age 55 or older plus two to four risk factors for men, and age 60 or older plus three or more risk factors for women. Patients with diabetes or previous gastro-duodenal ulceration or gastrointestinal bleeding were excluded. At baseline, 75% of participants were taking antihypertensive drugs, and 43% were taking statins.
- During median follow-up of 5 years, the incidence of the primary endpoint (CV-related death, myocardial infarction, unstable angina, stroke, or transient ischemic event) was similar in the aspirin and placebo groups (4.3% and 4.5%; *P*=0.6). No subgroup (according to sex, age, smoking status, body-mass index [BMI], or baseline calculated 10-year risk) clearly benefited from aspirin.
- Gastrointestinal bleeding occurred more frequently with aspirin than with placebo (1.0% vs. 0.5%; *P*=0.0007), but only a few were “severe.”

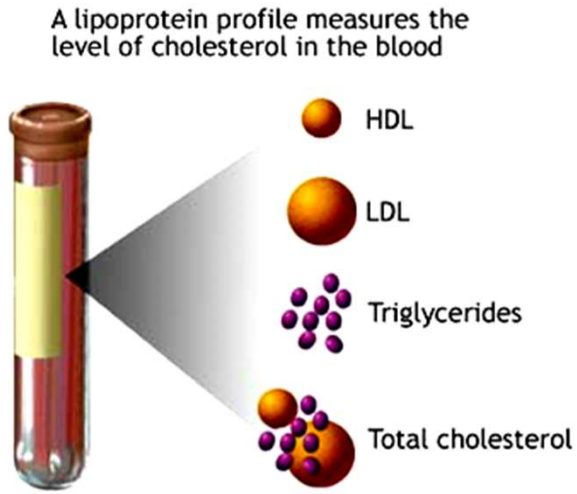
Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

N Engl J Med September 16, 2018

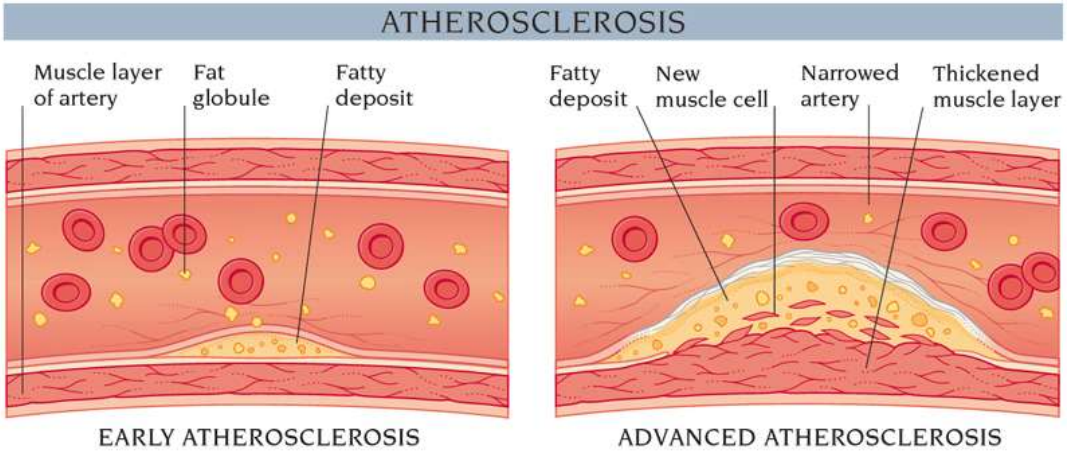
- Researchers randomized 19,000 healthy elders to 100-mg of aspirin or placebo daily.
- During a median follow-up of 4.7 years, the primary composite endpoint of death, dementia, or physical disability did not differ significantly between the groups. **Rates of cardiovascular disease also did not favor aspirin.**
- In terms of harms, however, major hemorrhagic events occurred more often with aspirin than with placebo (8.6 vs. 6.2 events per 1000 person-years).
- All-cause mortality was also higher with aspirin, likely due to more cancer-related deaths (6.7 vs. 5.1 per 1000 person-years).

Regular Lipid Profile

NIH and AHA recommend that everyone age 20 and older should have blood cholesterol measured at least once every five years
In Thailand most people have it checked every 3 month!



- **Total Cholesterol**
- **High-density lipoprotein cholesterol** (HDL-C) : often called “good cholesterol” because it removes excess cholesterol and carries it to the liver for removal.
- **Low-density lipoprotein cholesterol** (LDL-C): often called “bad cholesterol” because it deposits excess cholesterol in walls of blood vessels which can contribute to atherosclerosis.
- **Triglycerides**- measures all the triglycerides in all the lipoprotein particles; most is in the very low density lipoproteins (VLDL)

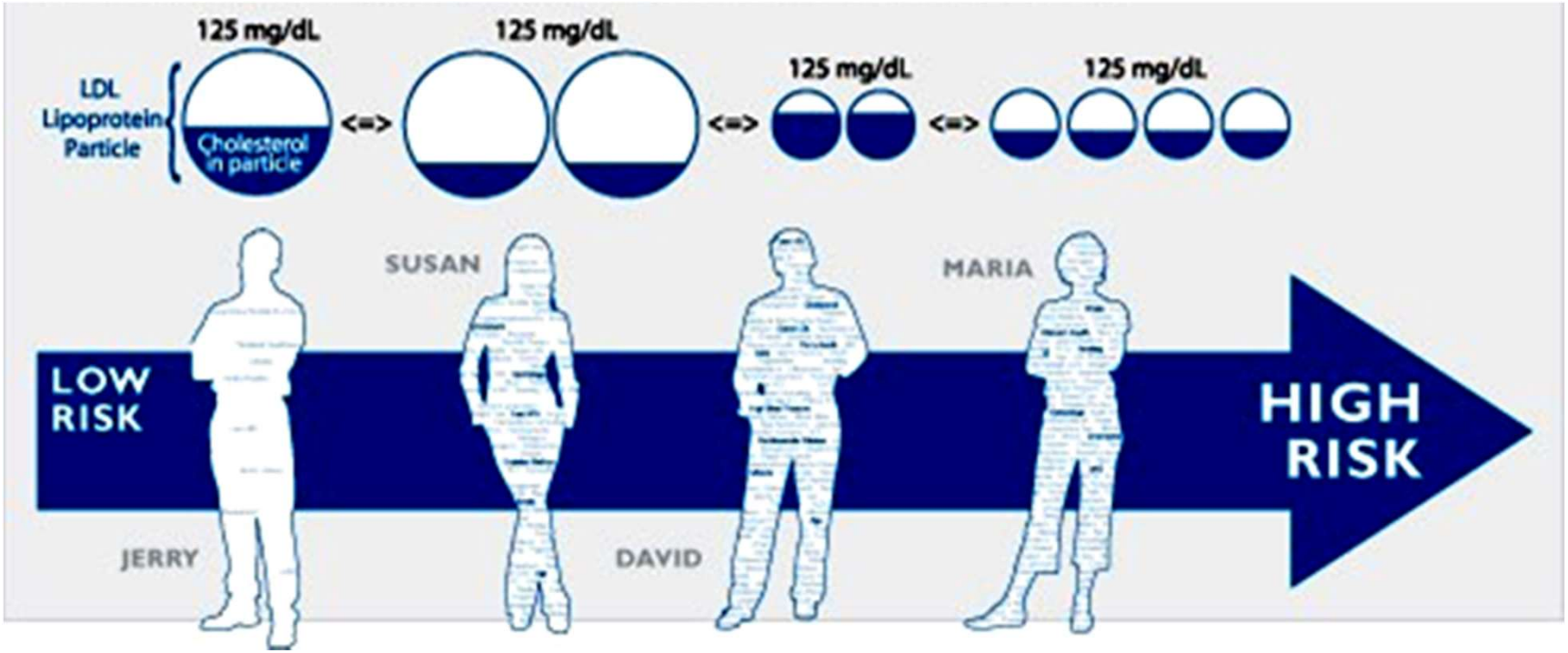


Why cholesterol became the culprit for atherosclerosis?

- The pathology of clogged up arteries showing cholesterol plague.
- The lower total cholesterol levels are a strong prediction of heart attack for both men and women.
- Among adults between ages 40 and 89, a reduction in total cholesterol of 39 mg/dL (or 1 mmol/L) was associated with about a 33% reduction in heart disease death. Among those aged 50 to 69 and 70 to 89, respectively, 1 mmol/L lower total cholesterol was associated with 34% and 17% reductions in the risk of death from heart disease.
- However, only cholesterol reducing agents that can reduce heart disease risk are STATIN.

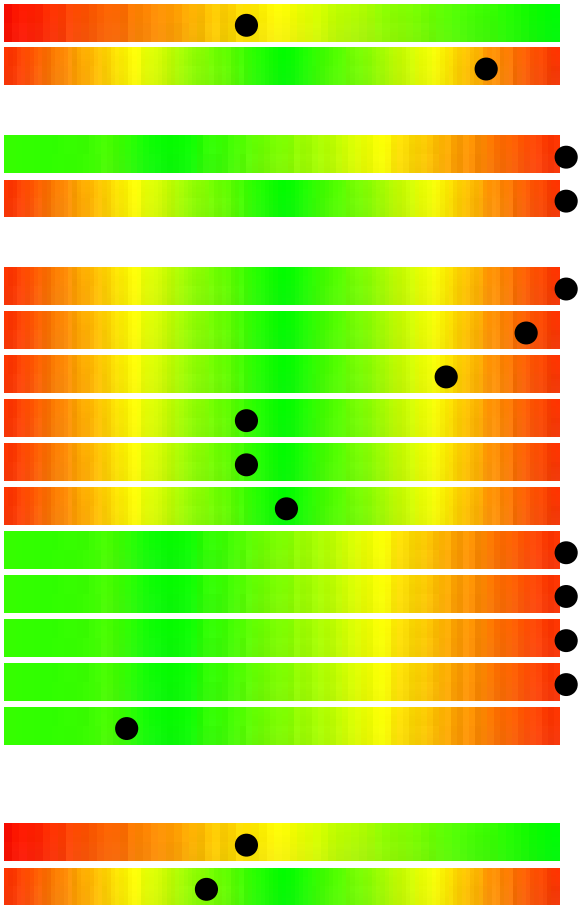
Liposcreen

- Determine the ratio of LDL-C/HDL-C (should be less than 3)
- Determine mean LDL particle size
- Determine the level of oxidized LDL-C



Liposcreen

LIPID STUDIES			
HDL(Protective)	***0.7* *L**	> 1.0	mmol/L
LDL(Atherogenic)	***3.7* *H**	0.5 - 3.5	mmol/L
Cholesterol/HDL Ratio	**8.1**		
LDL/HDL RATIO (Risk Factor)	***5.4* *H**	0.0 - 3.6	
Trig/HDL Ratio	***3.7* *H**	0.5 - 1.7	RATIO
LIPOSCREEN LDL Subfractions2			
Very Low Density Lipoprotein (VLDL)	***1.1* *H**	0.1 - 0.6	mmol/L
Intermediate Density Lipoprotein (IDL-1)	***0.7* *H**	0.1 - 0.6	mmol/L
Intermediate Density Lipoprotein (IDL-2)	**0.4**	0.1 - 0.4	mmol/L
Intermediate Density Lipoprotein (IDL-3)	**0.3**	0.1 - 0.6	mmol/L
Low Density Lipoprotein (LDL-1)	**0.56**	0.10 - 1.50	mmol/L
Low Density Lipoprotein (LDL-2)	**0.49**	0.10 - 0.80	mmol/L
Low Density Lipoprotein (LDL-3)	***0.38* *H**	0.00 - 0.20	mmol/L
Low Density Lipoprotein (LDL-4)	***0.41* *H**	0.00 - 0.01	mmol/L
Low Density Lipoprotein (LDL-5)	***0.38* *H**	0.00 - 0.01	mmol/L
Low Density Lipoprotein (LDL-6)	***0.08* *H**	0.00 - 0.01	mmol/L
Low Density Lipoprotein (LDL-7)	**0.00**	0.00 - 0.01	mmol/L
LDL Phenotype Pattern	TYPE B - ABNORMAL		
Mean Particle Size	***248.0* *L**	> 268.0	Angstrom
Oxidised LDL	**46.0**	26.0 - 117.0	IU/L

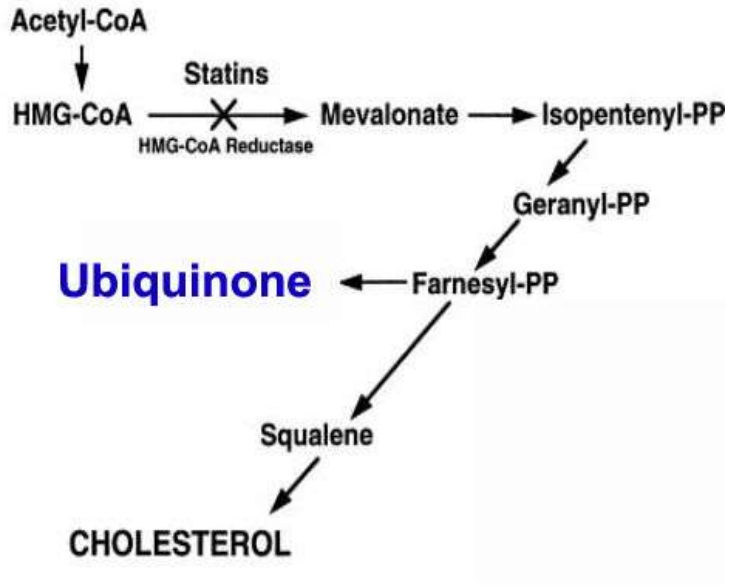


Are we ready to stop treating cholesterol levels and start treating risk?

- Statins are the lipid lowering drugs with the strongest evidence of benefit.
- Statins reduce risk across the spectrum of LDL values. The first generation drugs reduce risk about 20% and the higher potency and high dose statins reduce it by about another 15%.
- But if you bluntly target only LDL, you will be:
  - treating some patients with low risk (those without other risk factors and LDL that is not exceptionally high)
  - neglecting some high-risk patients (those without elevations in LDL but with many other risk factors).
- Maybe it is time to decide about treatment based on risk for example statin in heavy smokers.
- The major trials tested fixed doses of drugs base only on LDL-C levels.

Statin

(simvastatin, pravastatin, atorvastatin, rosuvastatin)



- Statins inhibit HMG-CoA reductase which catalyzes the rate limiting step in cholesterol synthesis.
- Low density lipoprotein cholesterol (LDL) levels are lowered by inhibiting synthesis and up-regulating LDL receptors.
- **Statin inhibits ubiquinone (coenzyme Q-10) synthesis**
- Studies have demonstrated their ability to prevent coronary events and reduce mortality.
- **Those at highest risk benefit the most!**

Should we prescribe statin? When, Why, and How?

- Statin is used to prevent complications of **ATHEROSCLEROSIS**
- Recommended in patients with **higher risk** of having myocardial ischemia, stroke.
- **LDL number should not be the main factor in guiding treatment to prevent heart attack and stroke.**
- Risk of myopathy, kidney failure, hepatitis, diabetes, cerebral hemorrhage, and dementia.
- Lowering coenzyme Q10 levels, coenzyme Q10 supplementation is a must.
- BUT… don't stop the medicine abruptly if you haven't assessed the patients risks.
- **Don't stop statin in patients who previously had myocardial ischemia, cerebral ischemia, underwent coronary bypass surgery or having balloon angioplasty.**

STATIN and Drug Interaction

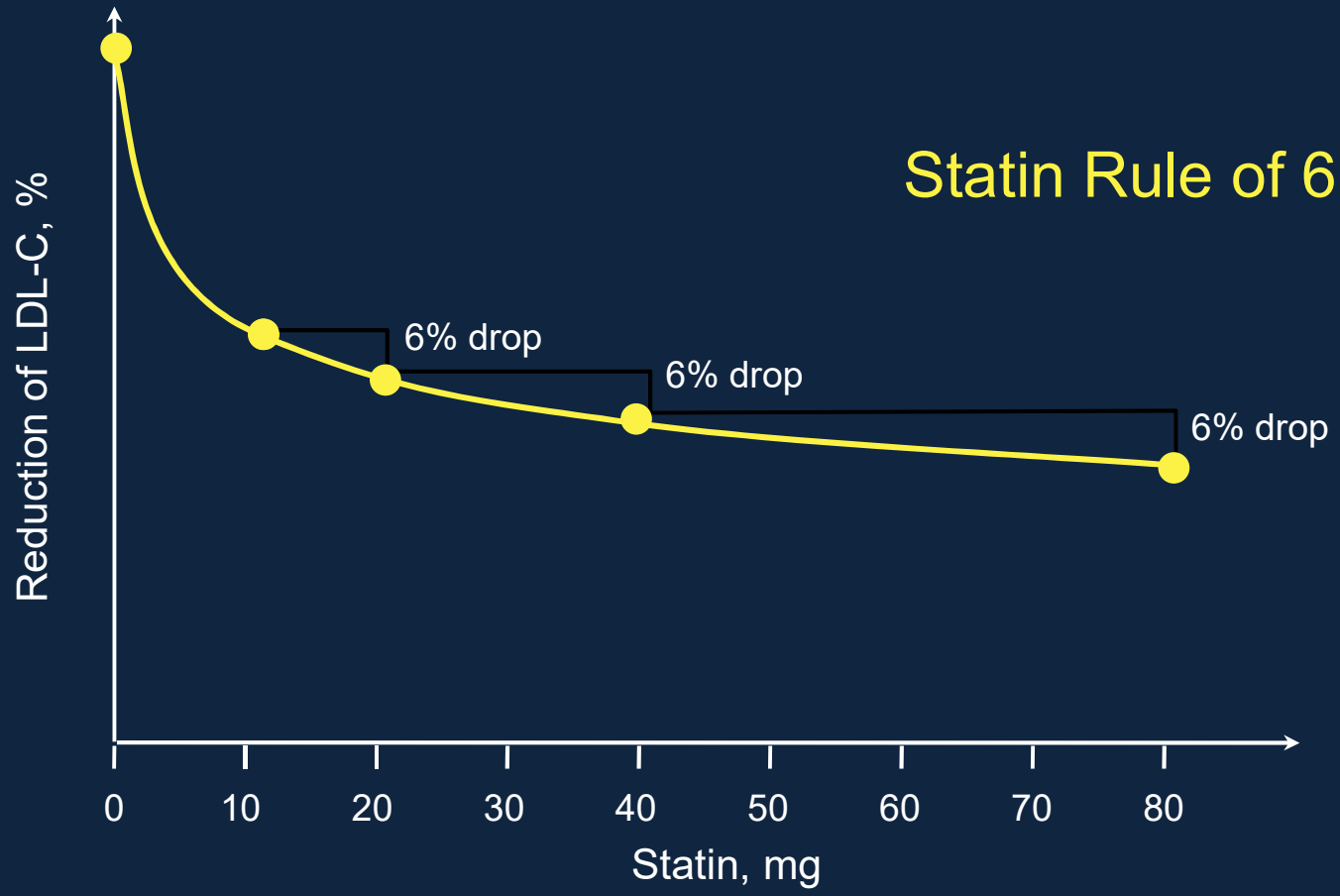
- When using these medicine, temporally stop statin to avoid serious side-effects
  - Antifungal drugs
  - Niacin
  - Fibrates
  - Cyclosporine
  - Erythromycin and Clarithromycin
  - Diltiazem and Verapamil
  - Amiodarone
  - HIV protease inhibitors
  - Omeprazole

Low cholesterol linked to higher risk of bleeding stroke in women

Neurology May 07, 2019; 92 (19)

- A prospective cohort study among 27,937 women enrolled in the Women's Health Study with measured total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), as well as triglycerides. Cox proportional hazards models to analyze associations between lipid categories and hemorrhagic stroke risk
- **Results** During a mean of 19.3 years of follow-up, 137 hemorrhagic strokes occurred. Compared to those with LDL-C levels 100–129.9 mg/dL, those with LDL-C levels <70 mg/dL had 2.17 times the risk (95% confidence interval [CI] 1.05, 4.48) of experiencing a hemorrhagic stroke.
- No significant increase in risk was seen for those with LDL-C levels 130–159.9 mg/dL.Women in the lowest quartile of triglycerides had a significantly increased risk of hemorrhagic stroke.
- No significant associations between total cholesterol or HDL-C levels and hemorrhagic stroke risk were observed.
- **Conclusion** LDL-C levels <70 mg/dL and low triglyceride levels were associated with increased risk of hemorrhagic stroke among women.

Doubling dose of statins will only decreases LDL-cholesterol levels by 6%



Adapted from Knopp RH. N Engl J Med. 1999;341:498–511; Stein EA. Am J Cardiol. 2002;89(suppl):50C–57C.

STATIN

- **Low Potency Statin (pravastatin-mevalotin, red yeast rice)**
  - Less side effects but efficacy for cardiovascular protection is uncertain.
  - Use for the purpose of cholesterol control only (psychological effect)
- **Intermediate Potency Statin (simvastatin-Zocor)**
  - Generic brands are the most popular; however, the efficacy is unproven.
  - Side effects may be higher than benefits.
- **Lipid soluble, high potency (atorvastatin-Lipitor, rosuvastatin-Crestor)**
  - High potency means higher risk of complications
  - Anti-inflammatory effects help preventing cardiovascular disease
  - To avoid side effects, non daily dosing is recommended.

An important question cardiologists never asked!

- Why cholesterol lowering agents besides statin never show benefit in reduction risk of cardiovascular disease?
- Would it mean statin benefit come from ‘pleiotropic effects’ but not ‘cholesterol lowering effect’?

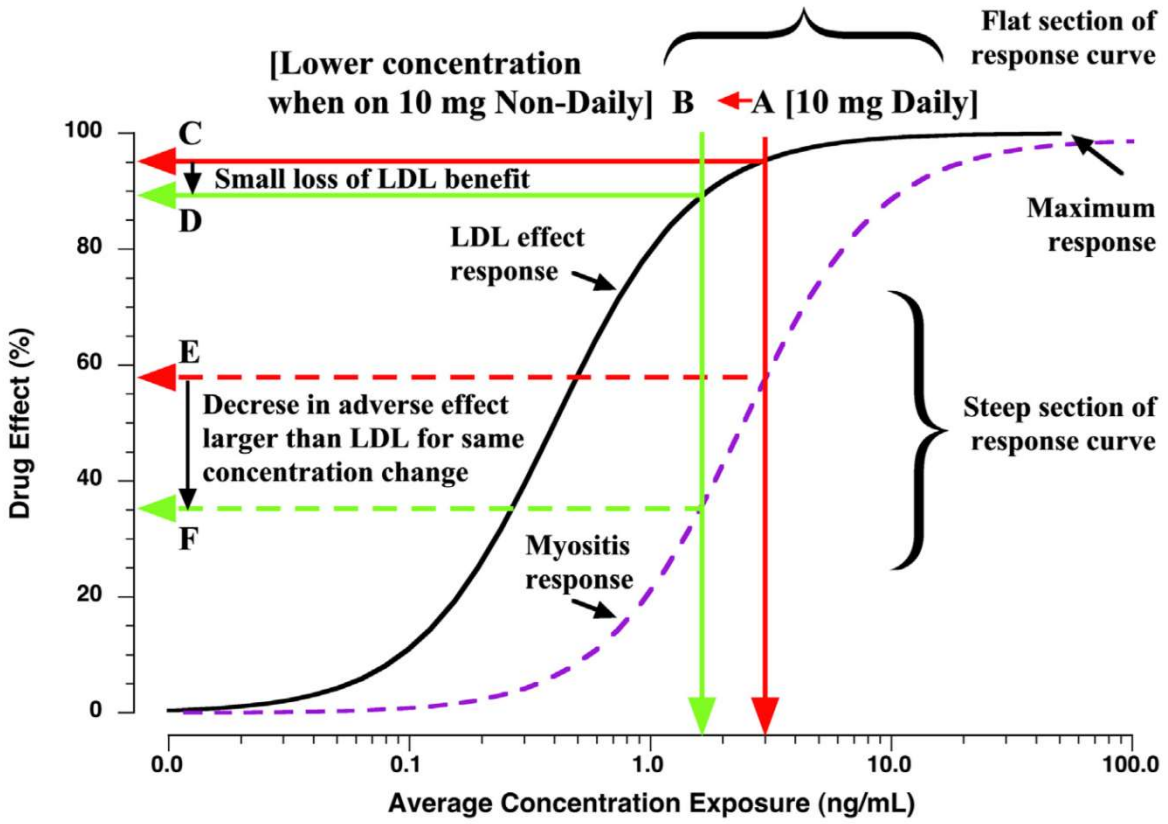
Pleiotropic Effects of Statin

- Up-regulate eNOS
- Inhibit vascular smooth muscle cell proliferation.
- Plaque stability
- Stem cell enhancement
- Lower hs-CRP
- Anti-inflammation

Nondaily Statin Dosing

Mechanisms of a potentially important approach to dealing with statin intolerance

Canadian Journal of Cardiology (2013) 29;895-898



Periodic Rosuvastatin or Atorvastatin Dosing Arrays (PRADA)

Drugs R D (2014) 14:221–225

- This retrospective study reviewed the medical records of patients with hyperlipidemia during an 8-year period in a private internal medicine practice. Periodic dosing was negotiated following several patients' refusal of statin therapy because of muscle aches or cost.
- Treatment was initiated by dispensing rosuvastatin or atorvastatin in a stepwise patient-directed approach (from two times/week to three times/week to every other day, up to five times/week).
- Chart review identified 46 patients who had been treated. Two patients with persistent myalgia terminated treatment before 12 weeks. Among the remaining 44 patients, 20 received doses of rosuvastatin from 15 to 100 mg per week, and 24 received atorvastatin from 20 to 140 mg per week.
- There was a significant decrease from pre-treatment in the mean TC/HDL-C ratio of 1.72 and mean LDL-C of 43.3 mg/dL.
- An independent samples t-test showed a non-significant reduction of the mean TC/HDL-C ratio and LDL-C with rosuvastatin versus atorvastatin.

If patients are unhappy with their cholesterol levels?

- Diet control and exercise is a “must do” advice, but sadly, it rarely works.
- Try plant stanol (Benecol)
- Try ezetimibe (Ezetrol)
- Use combination of anti-oxidants (coQ10 + C + lipoic acid) to reduce “oxidized” LDL-C
- Use periodic dosing interval of statins.
- Use red yeast rice
- Intermittent plasmapheresis to remove LDL-C

紅麴

紅曲

Red Yeast Rice

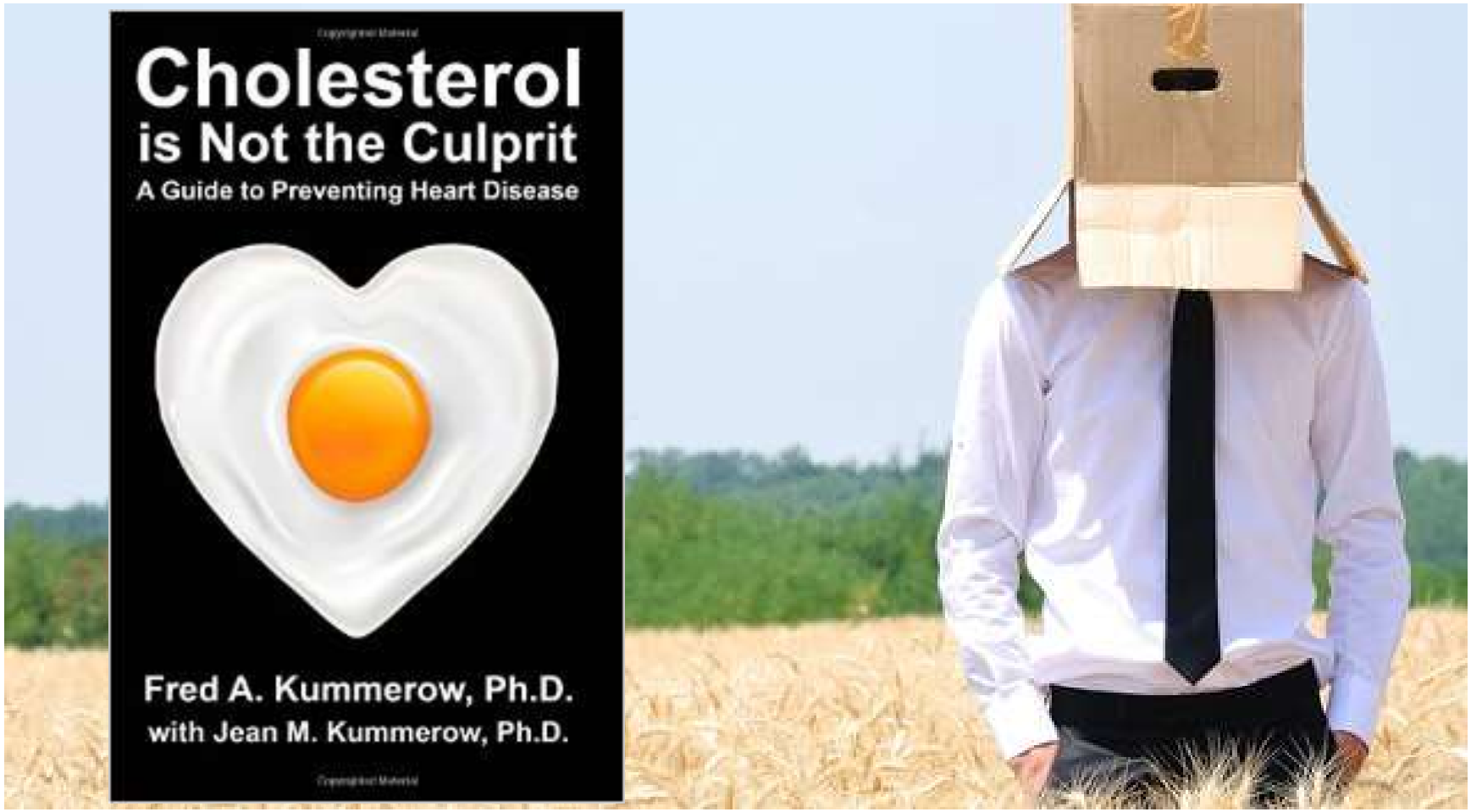
- *Hong qu* also known as red yeast rice, is rice that has been fermented with the yeast *monascus purpureus*.
- The fermentation process changes the color of the rice from white to red, thereby giving it the name "red yeast rice."
- For centuries, *hong qu* has been used in China as as a coloring agent to prepare fish, fish sauce, fish paste, rice wine, and red soybean curd.
- In the late 1990s, it was introduced and used in the U.S. as a dietary supplement to promote healthy cholesterol levels.
- Active gradient in red yeast rice is **lovastatin** (another statin).

Red Yeast Rice for Dyslipidemia in Statin-Intolerant Patients

Ann Intern Med.2009;150:830-839.

- 62 patients with dyslipidemia and history of discontinuation of statin therapy due to myalgia were assigned to receive red yeast rice 1800 mg or placebo twice daily for 24 weeks.
- All patients were enrolled in a 12 week therapeutic lifestyle change program
- Results: Red yeast rice and therapeutic lifestyle change decrease LDL-C without increasing CPK or pain levels.

To prevent atherosclerosis
we have to think outside the box.



Meta-analysis shows little association between egg consumption and coronary heart disease or stroke

BMJ 2013 Jan 7; 346:e8539.

- To lower blood cholesterol and cardiovascular disease risk, the American Heart Association (AHA) recommends consuming <300 mg of cholesterol daily (Circulation 2006; 114:82). Because chicken eggs are high in cholesterol (about 200 mg each), clinicians commonly advise patients with elevated blood cholesterol to avoid eating them.
- The analysis included nine reports on coronary heart disease (CHD) and eight reports on stroke, with 10 to 20 years of follow-up in most studies. **No associations between egg consumption and risk for CHD or stroke were observed.**
- However, subgroup analyses of diabetic patients in which highest and lowest egg consumption were compared showed excess risk for CHD (relative risk, 1.5) and less risk for hemorrhagic stroke (RR, 0.8).

Nutritional value of one whole egg (50 gm)

Energy	78 kcal	Calcium	25 mg (5%)
Carbohydrates	0.56 gm	Iron	0.6 mg (10%)
Fat	5.3 gm	Magnesium	5 mg(3%)
Protein	6.3 gm	Phosphorus	86 mg (25%)
Vitamin A	70 µg (16%)	Potassium	63mg (5%)
Thiamin	0.033 mg (5%)	Zinc	0.5 mg (10%)
Riboflavin	0.25 mg (33%)	Cholesterol	212 mg
Pantothenic	0.7 mg (28%)	Choline	113 mg
Folate	22 µg (11%)		

Dietary Guidelines for Americans, 2015

Nutrient Intakes and Nutrients of Concern

- Based on intake data, together with nutritional biomarker and health outcomes data, identified nutrients that may pose a public health concern:
  - Vitamin D, calcium, potassium, and fiber are underconsumed across the entire US population.
  - Iron is underconsumed for adolescent and premenopausal females.
  - Sodium is overconsumed across the entire US population
  - Saturated fat is overconsumed and may pose the greatest risk to those > 50 years old.

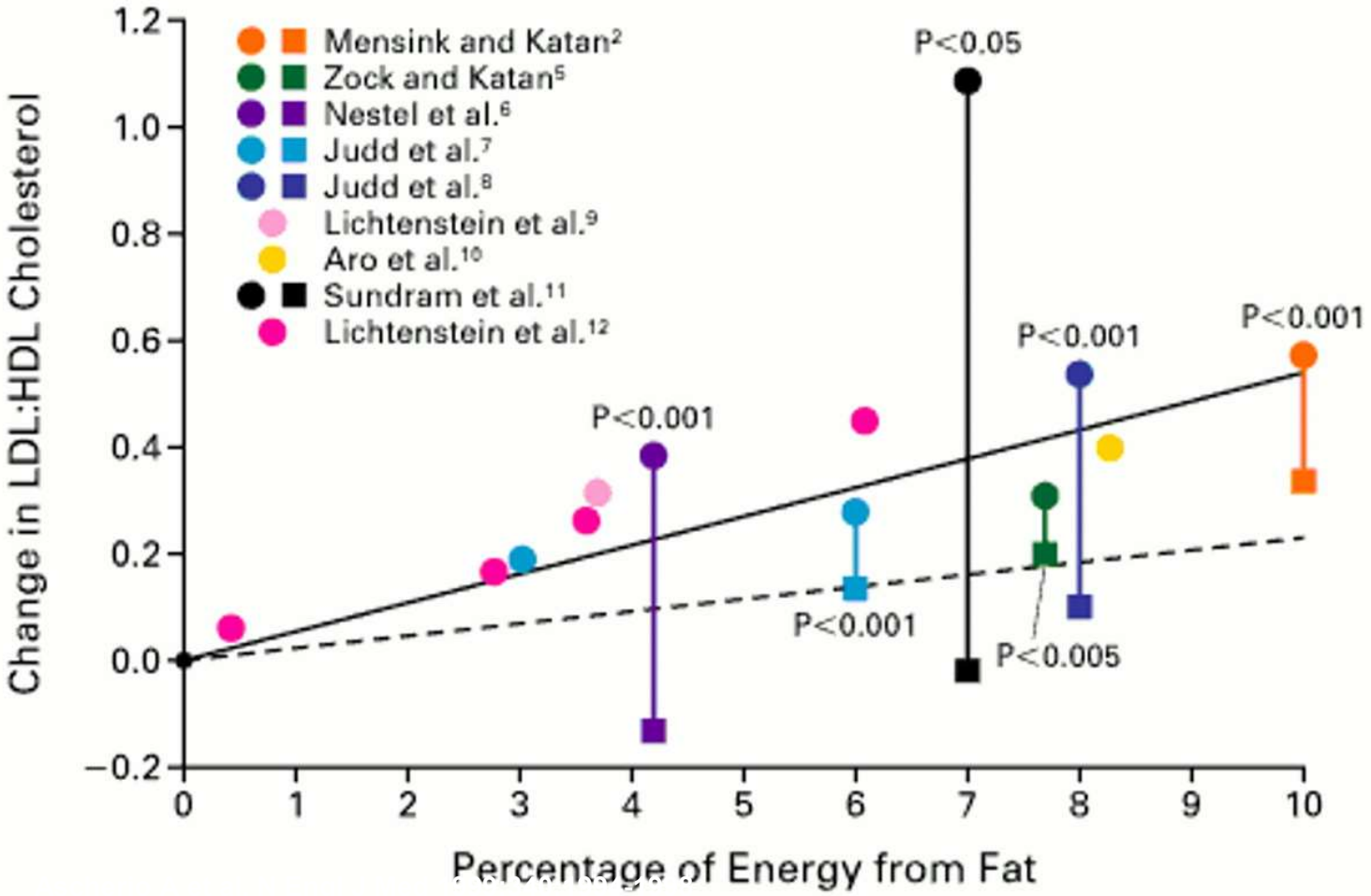
- Cholesterol is not considered a nutrient of concern for overconsumption.

TRANS FAT

The leading cause of high blood cholesterol?

- **Occur in small quantities in meat and dairy products.**
- **Industrially created by partial hydrogenation of plant.**
- **The process developed in the early 1900s and first commercialized as Crisco in 1911.**
- **Considered to be more of a health risk than saturated fat.**

Results of Randomized Studies of the Effects of a Diet High in Trans Fatty Acids (Circles) or Saturated Fatty Acids (Squares) on the Ratio of LDL Cholesterol to HDL Cholesterol



The NEW ENGLAND JOURNAL of MEDICINE

Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies

BMJ 2015;351:h3978

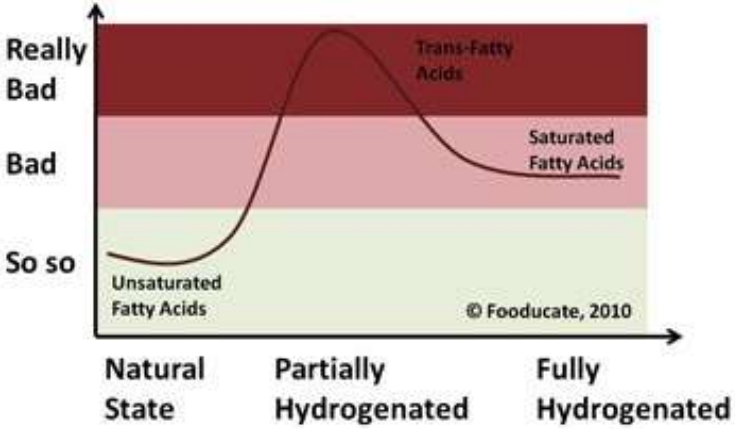
- Saturated fat intake doesn't translate readily into higher cardiovascular risk, but increased trans fat intake does, a *BMJ* meta-analysis confirms.
- In an attempt to better quantify risks associated with dietary fats, researchers pooled results of several observational studies. They focused on results comparing the highest versus lowest levels of fat intake (measured, for the most part, with dietary recall).
- **Saturated fat wasn't associated with all-cause mortality, total coronary heart disease (CHD), stroke, or diabetes. Trans fat, on the other hand, was associated with increased risks for all-cause mortality (relative risk for highest vs. lowest intake, 1.34), CHD mortality (1.28), and total CHD (1.21) — but not stroke or diabetes.**

Trans-fat ban linked to reduction in New York cardiovascular disease admission

JAMA Cardiology April 12, 2017

- Researchers compared admission rates for the composite of myocardial infarction and stroke between New York counties implementing the ban in its eateries versus those that did not. The restricting counties showed an additional 6% drop in admissions relative to non-restricting counties after adjustment for an already-declining trend across the state. The difference became significant 3 years after implementation of the bans and benefitted men and women equally.
- Of note, in 2015, the FDA mandated that food manufacturers remove partially hydrogenated oils from their products by mid-2018. Those oils are the major dietary source of trans-fatty acids.

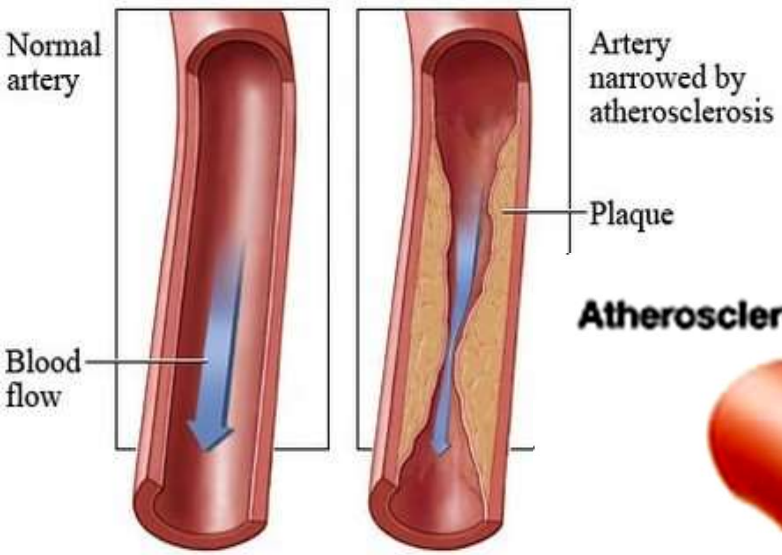
Full vs. Partial Hydrogenation

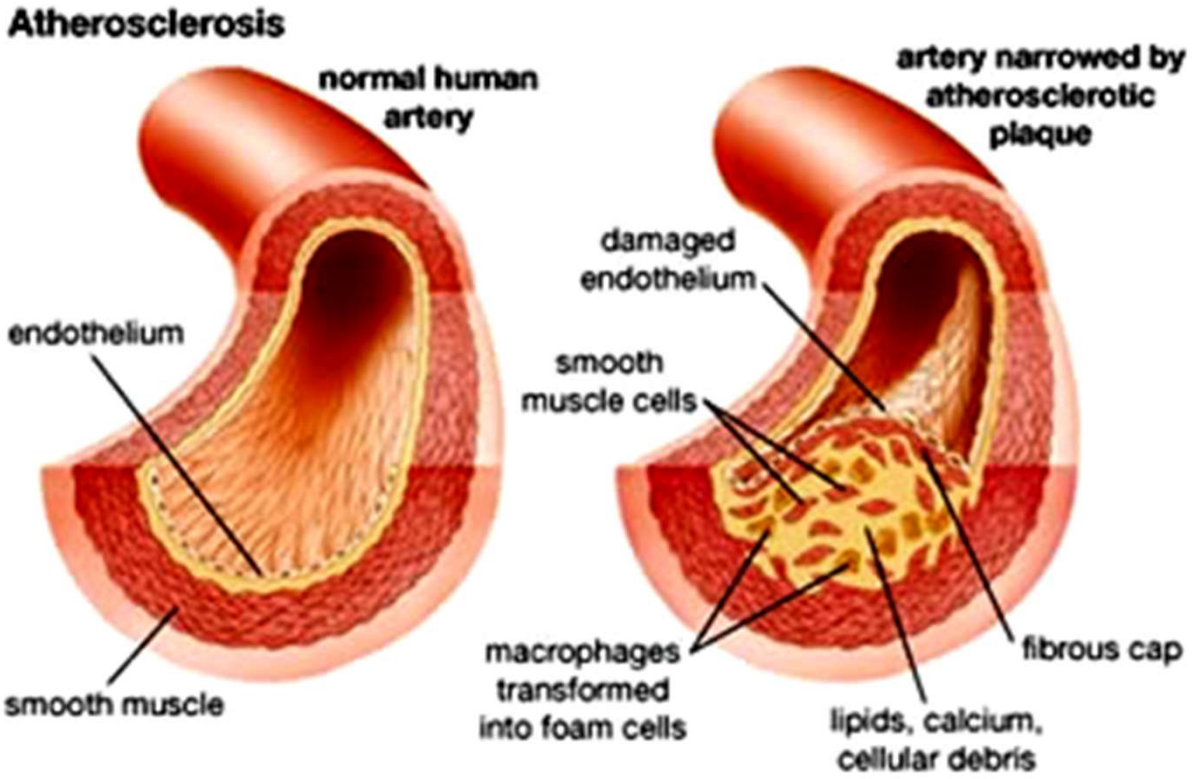


However,…
Crisco is claiming that trans fat is partially hydrogenated oil but Crisco is fully hydrogenated oil, totally saturated fatty acids

- The chemical structure of the unsaturated fatty acids after the partial hydrogenation turns them into **trans-fatty acids**.
- But if go all the way, they turn into the more familiar **saturated fatty acids**.
- That doesn't mean this processed artificial fat is healthy!

Atherosclerosis is a chronic inflammation of the artery that leads to vascular thrombosis

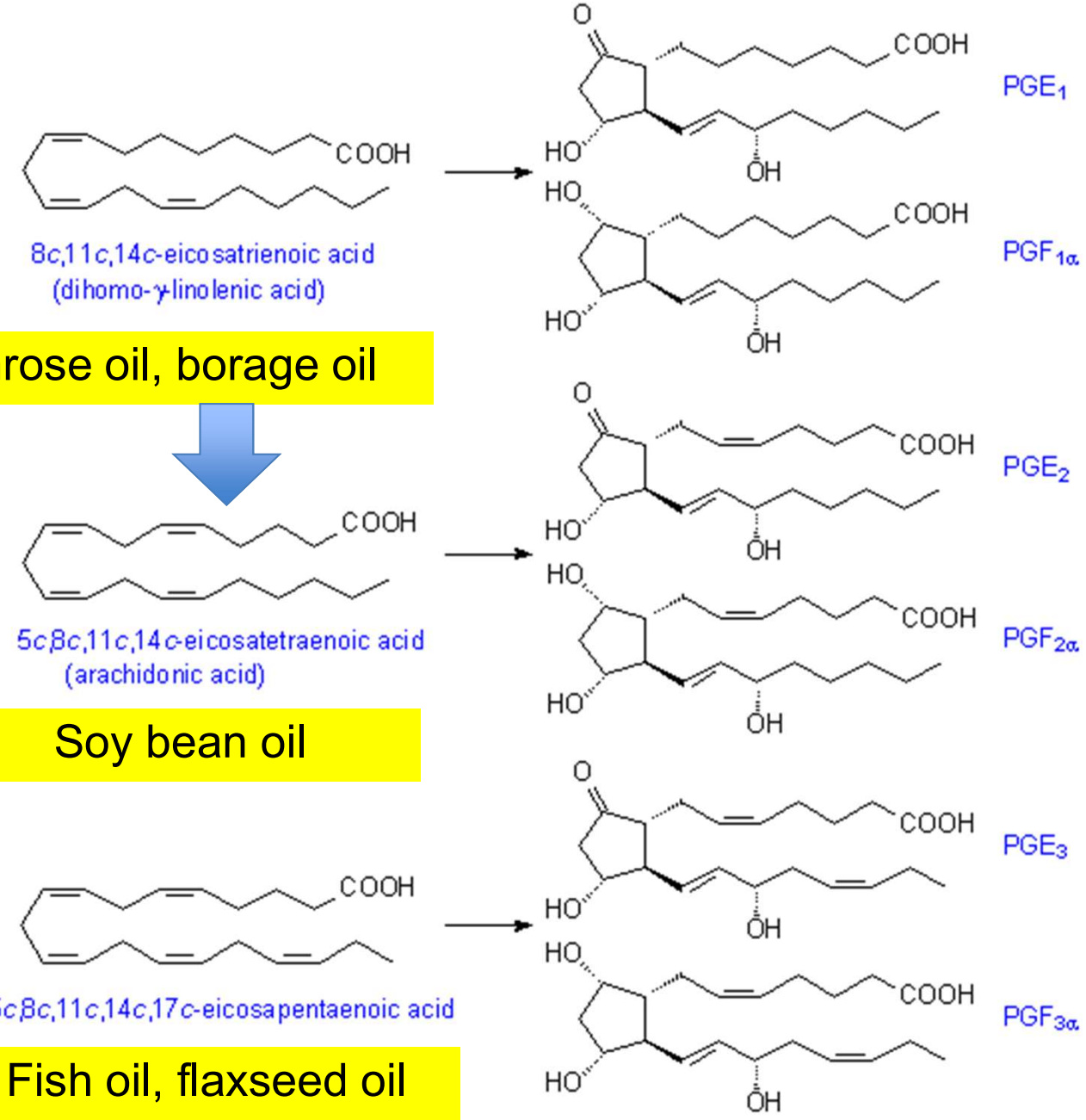




Three types of unsaturated fat: Omega 3, Omega 6, and Omega 9

Omega-6 fatty acids	**Food sources**
LA, linoleic acid 18:2ω6	Vegetable oils (corn, soybean), animal
AA, arachidonic acid 20:4ω6	Animal sources (meat, milk)
Omega-3 fatty acids	**Food sources**
ALA, alpha-linolenic acid 18:3ω3	Flaxseed, canola oil, walnuts
EPA, eicosapentaenoic acid 20:5ω3	Marine sources, fish oils
DHA, docosahexaenoic acid 22:6ω3	Marine sources, fish oils, egg, dairy products
Omega-9 fatty acids	**Food sources**
Oleic acid 18:1ω9	Olive oil, rice bran oil

Three sources of C20 prostaglandins



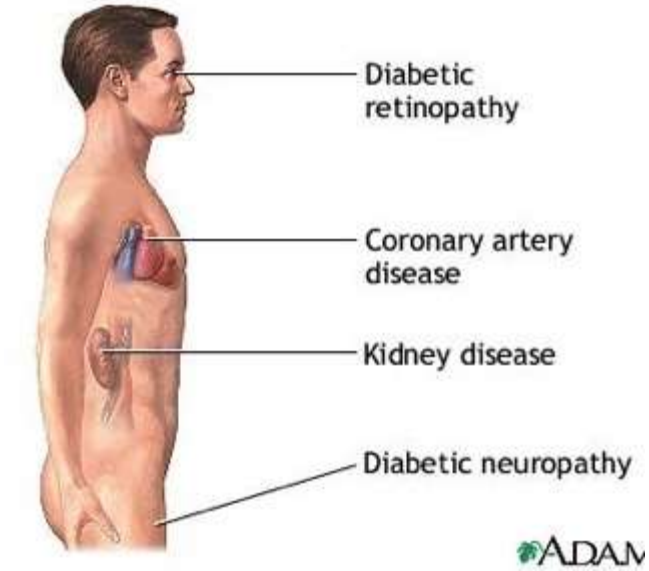
Mediterranean Diets

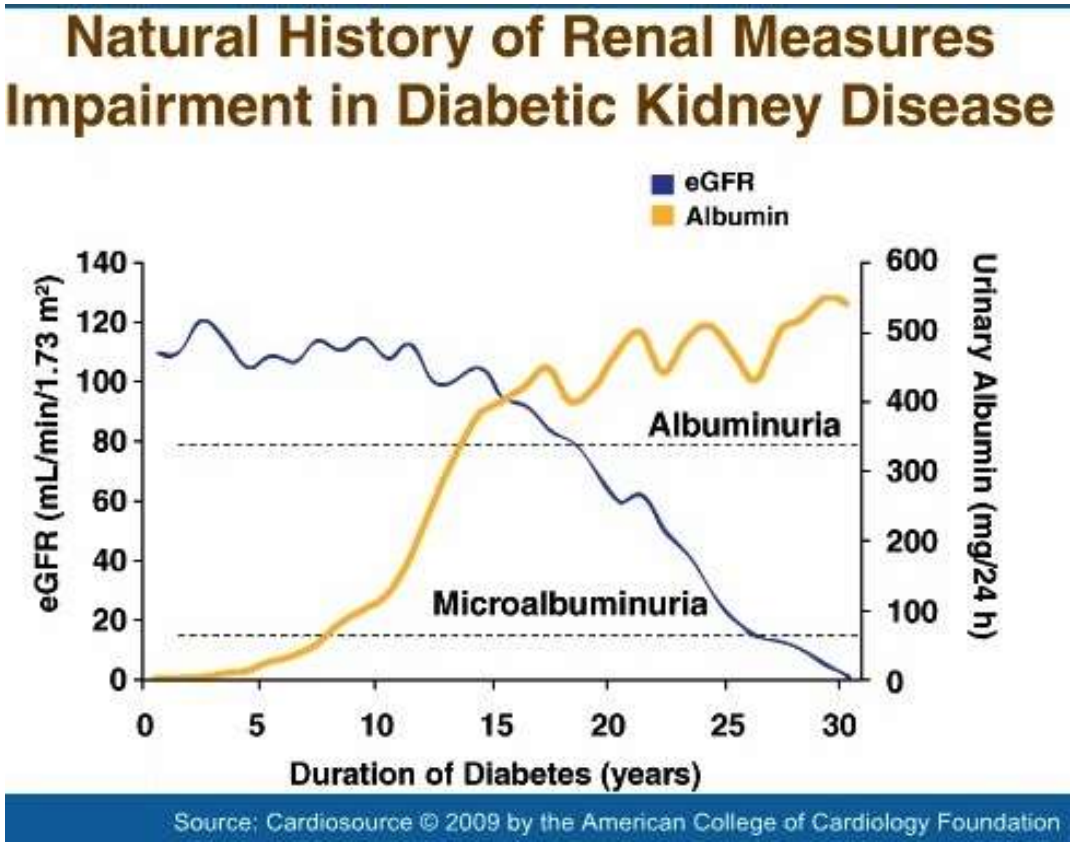
Olive Oil

The Anti-inflammatory Oil

OLIVE OIL: FAT COMPOSITION	
Saturated Fat	Palmitic acid 7.5% -20% Stearic acid 0.5%-5%
Monounsaturated Fat	**Oleic acid 55%-83%**
Polyunsaturated Fat	Linoleic acid 3.5%-21% Linolenic acid <1.5%

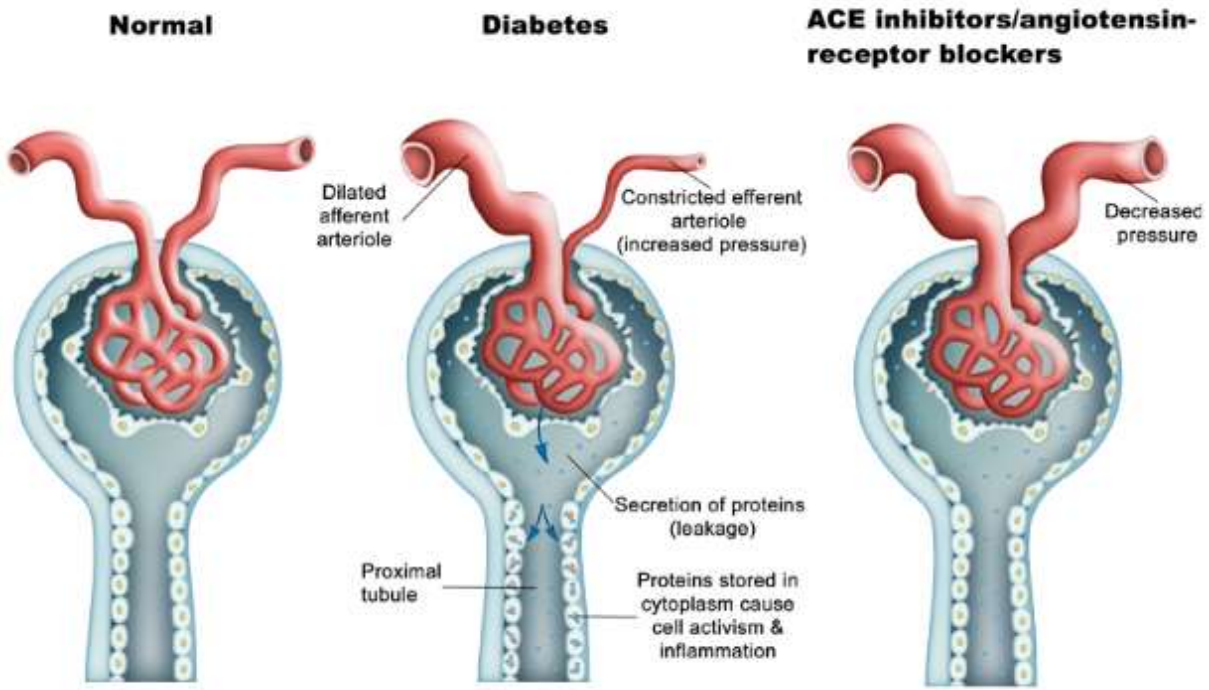
Diabetes is the most common cause of ESRD
Early detection for microalbuminuria and serum creatinine test.





Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are the best antihypertensive agents to reduce proteinuria and prevent CKD progression in the early stage.
The side effect is hyperkalemia and worsening renal function in late stage CKD.

Local effects of ARBs and ACEIs in the kidney in the patient with type-2 diabetes. Vasoconstriction in the efferent arteriole is reduced and less protein crosses the glomerular filter into the tubule of the nephron



Chronic Kidney Disease (CKD)
Early Detection is IMPORTANT

- **People who have chronic kidney disease at the early stage won't have any symptoms.**
- Kidney failure symptoms happen when there are less than 25% of functioning nephrons left
- **To prevent CKD, we need early detection by routine urine analysis and creatinine level testing.**
- **But the question is can nephrologist prevent the progression of CKD or do they make thing worse?**

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60 - 89
3	Moderate ↓ GFR	30 - 59
4	Severe ↓ GFR	15 - 29
5	Kidney failure	< 15 (or dialysis)

Medicine

The most common cause of CKD that most nephrologists don't know!

- Non-steroid anti-inflammatory drugs (NSAIDS)
- Paracetamol
- Sulfonylurea
- Statin
- Proton Pump Inhibitor
- Diuretics
- Phosphate containing enema
- Calcium supplements

Sulfonylurea: Friends of Foes?

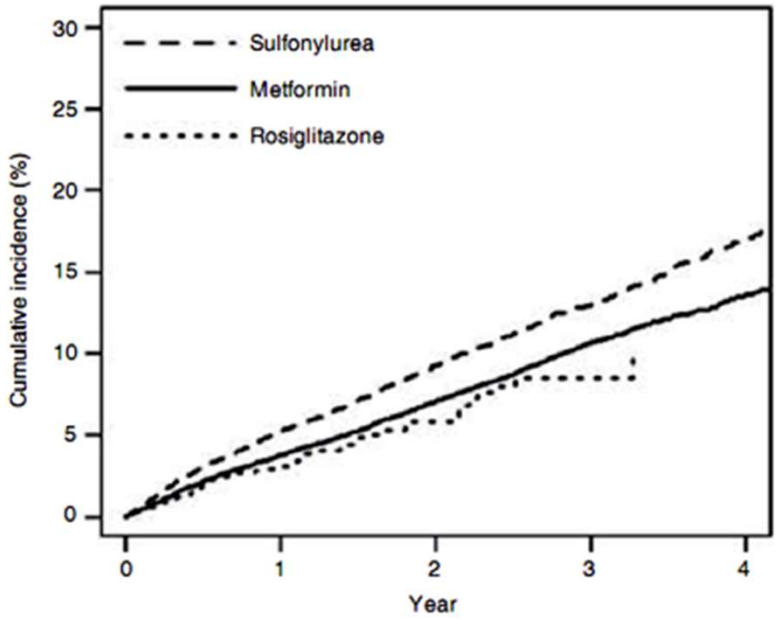
Glipizide, Gliclazide, Glibenclamide, Glimepiride

- Bind to ATP-dependent K^+ (K_{ATP}) channel on the cell membrane of pancreatic beta cells
- Most common medicine used in diabetes.
- Promote insulin release by binding to sulfonylurea receptor can result in hypoglycemia, weight gain, and beta cell apoptosis.
- The binding to the same receptor at myocardial cell impairs ischemic preconditioning and has arrhythmogenic effects.
  (Leibowitz Diabetologia 1996;39:503-514)

- **Increase overall mortality.**
  (Simpson et al. CMAJ 2006;174:169-174)

- **Compared to metformin, sulfonylurea users had an increased risk for persistent declined in GFR, end stage renal disease, and death**
  (Kidney Int 2012;81:698-706)

Studies show people who have higher HbA1c will have more chance of renal failure, but they didn't say that giving more drugs to control blood sugar will prevent CKD. **Can these studies be explained that patients with higher HbA1c received more drugs and the renal failure came from drugs and not from the diabetes!**



Compared to metformin, sulfonylurea users had an increased risk for persistent declined in GFR, end stage renal disease, and death.
(Kidney Int 2012;81:698-706)

Use of proton-pump inhibitors (PPIs) is associated with a 20% to 50% increased risk for developing chronic kidney disease (CKD)

Lazarus B. et al. *JAMA Intern Med*. January 11, 2016

- In the main, population-based cohort, researchers followed over 10,000 people without CKD at baseline. Over roughly 14 years, nearly 14% developed CKD. Rates of CKD were higher among patients using PPIs at baseline, compared with nonusers (14.2 vs. 10.7 events per 1000 person-years). PPI users also had higher rates of acute kidney injury than did nonusers. Similar associations were observed in a larger replication cohort.
- Add to increasing concerns about PPI use, including excess risks for *Clostridium difficile* infections, pneumonia, and fractures, and less platelet inhibition when PPIs are used concomitantly with clopidogrel.

Use of proton pump inhibitors (PPIs) is associated with increased risk for death from CVD, CKD, and gastric cancer

BMJ 2019;365:l1580

- Using Veterans Affairs records, researchers compared mortality outcomes between 158,000 adults who were newly prescribed a PPI for more than 90 days and 57,000 newly prescribed a histamine-2 blocker.
- During a median 10 years' follow-up, 37% of participants died. There were 46 excess deaths per 1000 PPI users in that time. PPIs were associated with excess mortality from cardiovascular disease (CVD) and chronic kidney disease (CKD). Patients without indications for PPI use had higher mortality risk from CVD, CKD, and also upper gastrointestinal cancer. Longer duration of use was associated with greater risk.
- The authors conclude: "PPIs should be used only when medically indicated and for the minimum duration necessary."

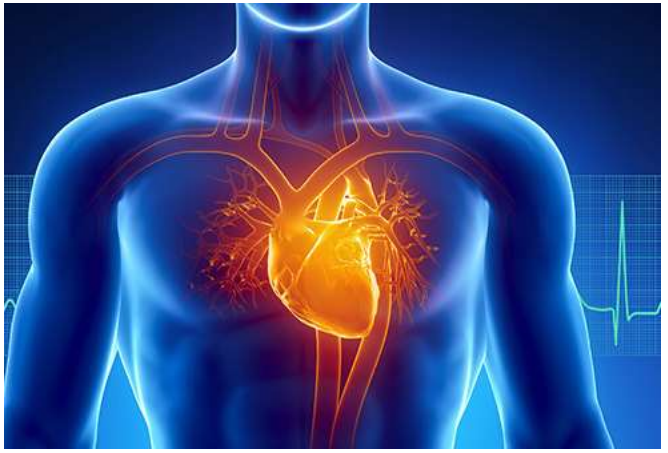
Proton-pump inhibitor use is associated with increased mortality risk

Xie Y et al. BMJ Open August 10, 2017

- Using data from the U.S. Department of Veterans Affairs, researchers examined health records of new users and nonusers of acid suppression therapy.
- During a median 6 years' follow-up, use of PPIs was associated with increased risk for death, relative to use of H2 blockers (adjusted hazard ratio, 1.25).
- Risk was also increased among patients taking PPIs, compared with those not taking acid suppression therapy, and among those taking PPIs who did not have a gastrointestinal condition that would warrant a PPI prescription.

HYPERURICEMIA

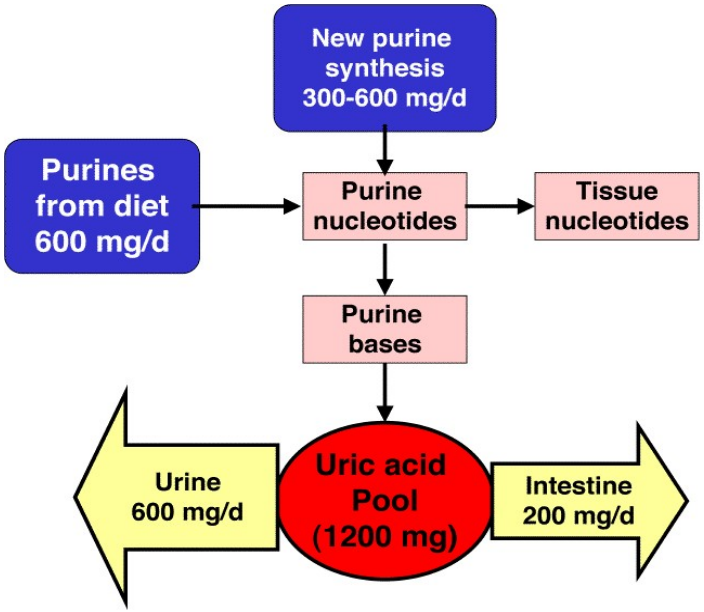
- Hyperuricemia is the cause of gout, kidney stone, endothelial dysfunction, cardiovascular, and chronic kidney disease.
- Controlling uric acid level is proven to slow progression of chronic kidney disease.
- Normal Uric acid levels are 2.4-6.0 mg/dL (female) and 3.4-7.0 mg/dL (male).
- Uric acid precipitation may occur when the blood uric acid level rises above 7 mg/dL or under acid condition.



Causes of Hyperuricemia

- Genetics
- Drugs (diuretics, salicyltes, pirazinamide, cyclosporine, nicotinic acid)
- Excess intake of purine rich foods such as meats, poultry, and animal internal organs.
- Alcohols
- Malignancies
- Lead Toxicity
- Chronic Kidney Disease
- **High dietary fructose intake**

Uric Acid Homeostasis



- Our body can make uric acid, stop eating chicken may not make much difference.
- 70% of uric elimination occurs through the kidney and the rest via gastrointestinal tract.
- One of the most important cause of hyperuricemia that most doctors don't know is fructose found in soft-drink and fruit juice.

Dietary purine intake and serum uric acid levels

Is it time to change your mind?

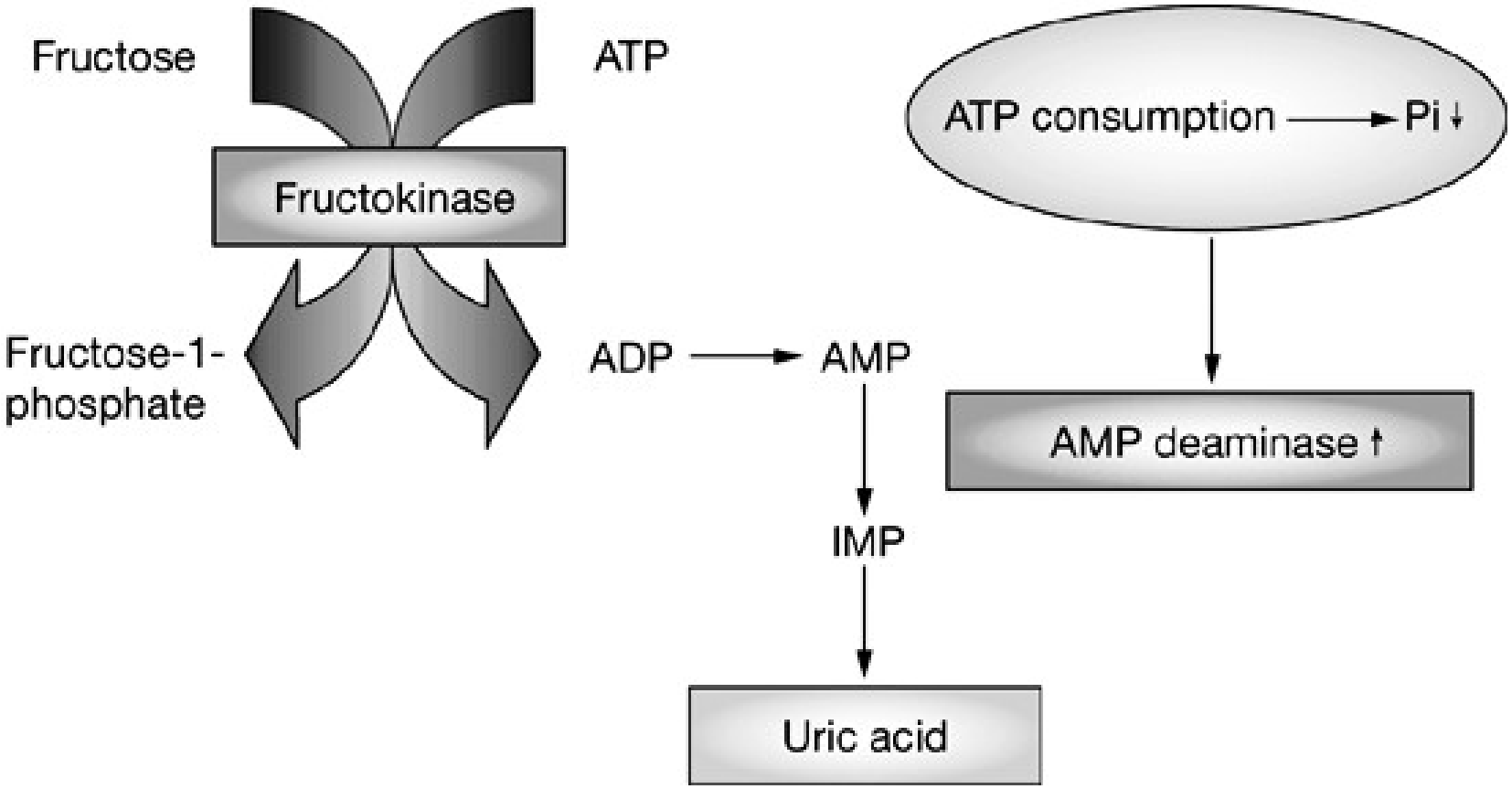
- Severe reduction in dietary purine intake can accomplish NO MORE THAN a 1 mg/dL decrease in serum uric acid.
- High consumption of purine-rich vegetables has NO association with serum uric acid.
- Fructose is the only carbohydrate that influences purine metabolism. So, apple cider is NOT good for gout. Ingestion of 5 apples resulted in 35% increase in serum uric acid within 6 hours!

Choi HK et al. NEJM 2004;350:1093-1101
Choi HK et al. Lancet 2004;353:1277-1281
Lotito SB and Frei B Free Radic Biol Med 2004;37:251-258

One Bottle of Soda Contains 35 Gram of Fructose

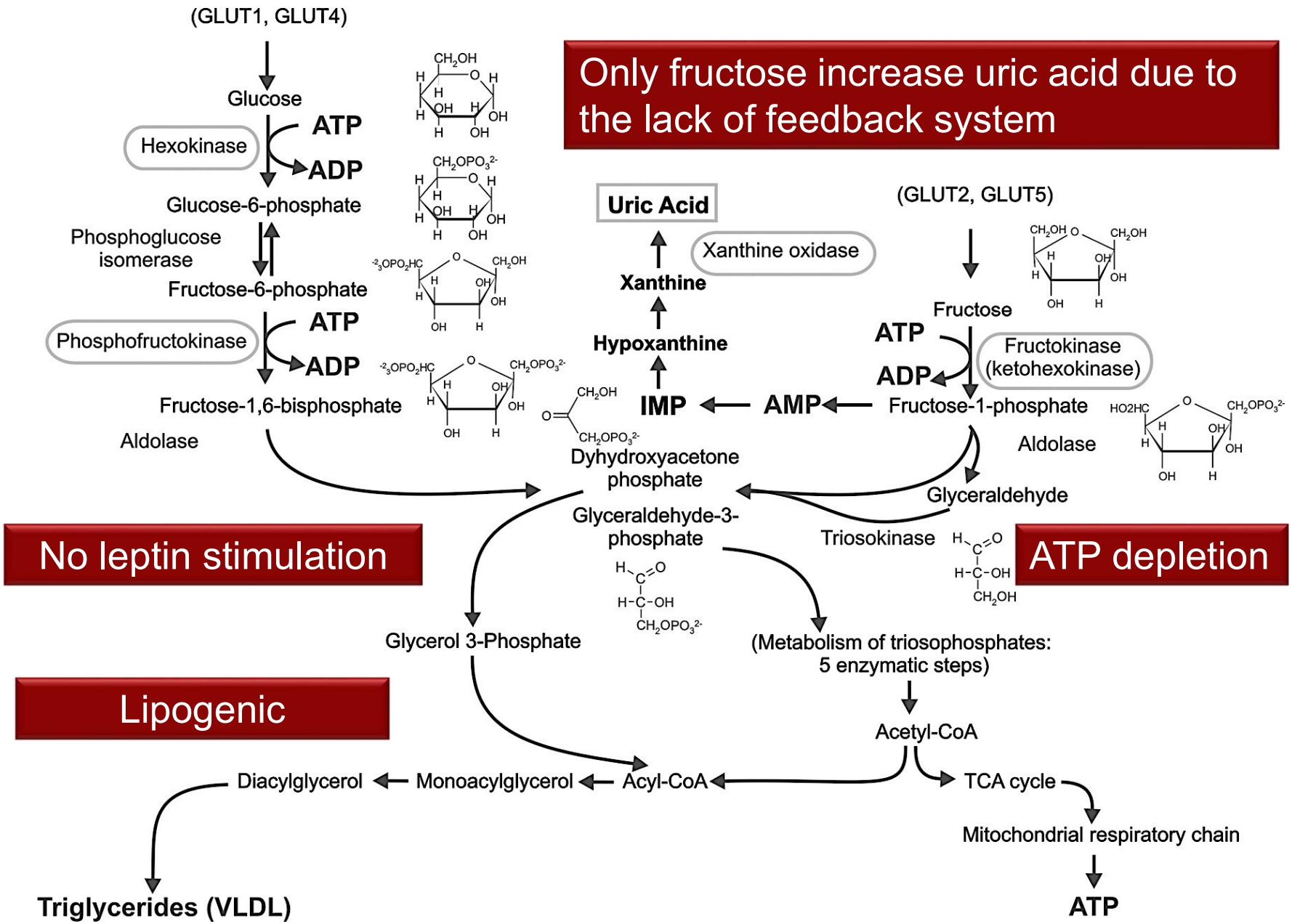
Diets	35 gram of fructose
Soda beverage	1 bottle = 20 Oz
Honey	4 oz
Mango	2 mangoes
Apple	3 apples
Date	4 dates
Banana	5 bananas
Peach	6 peaches
Mandarin orange	7 oranges
Pineapple	8 slices
Strawberries	9 cups

Fructose-induced production of uric acid in the hepatocyte



Nakagawa T *et al.* (2005) Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome *Nat Clin Pract Neprol* **1:** 80–86 doi:10.1038/ncpneph0019

Fructose metabolism.

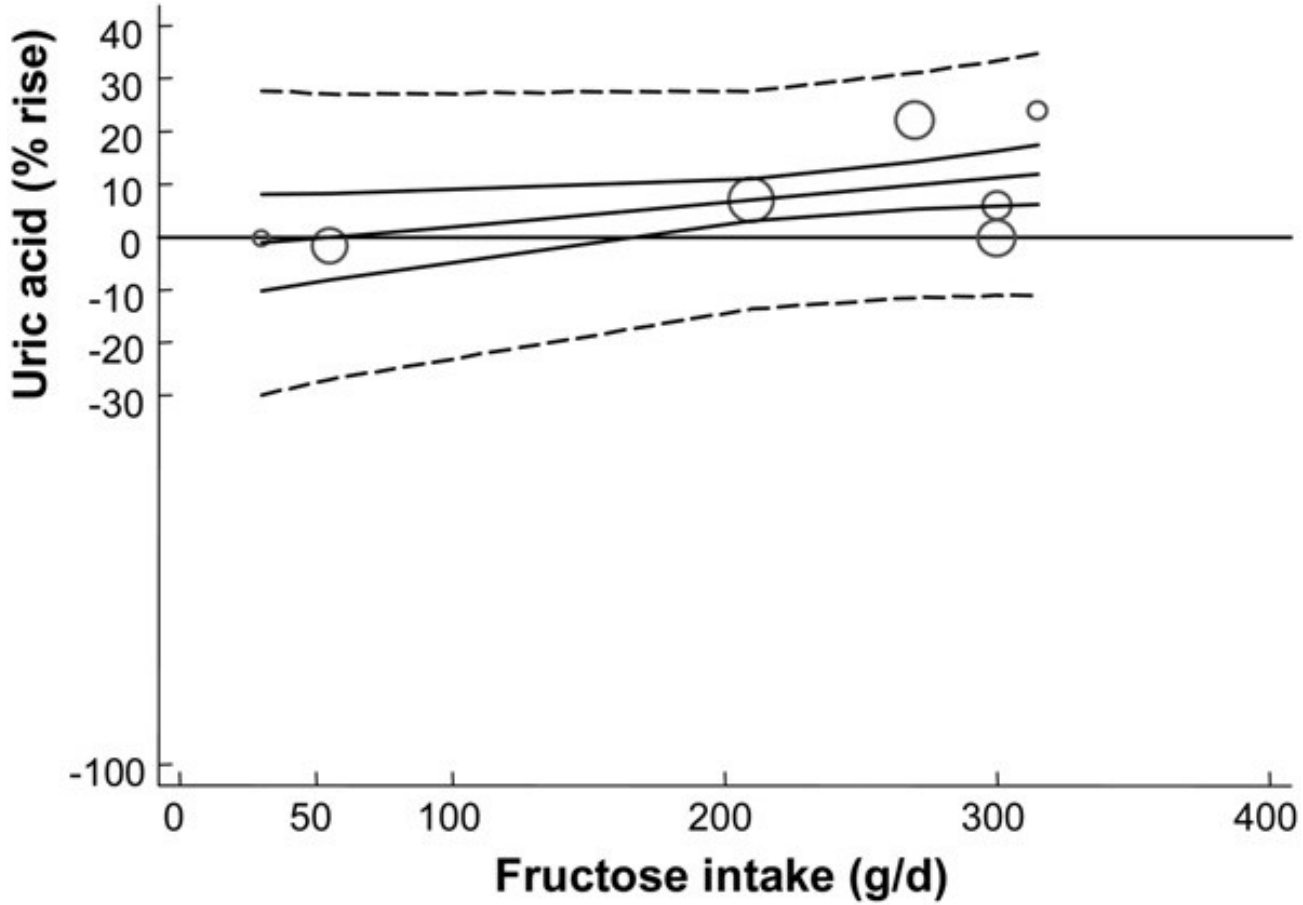


Johnson R J et al. Endocrine Reviews 2009;30:96-116

Fructose Over-Consumption Can Cause Hyperuricemia

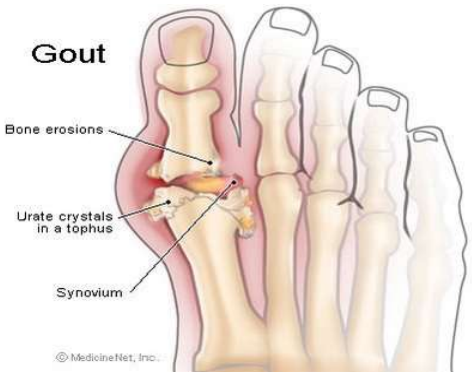
Uric Acid Level and Fructose Consumption

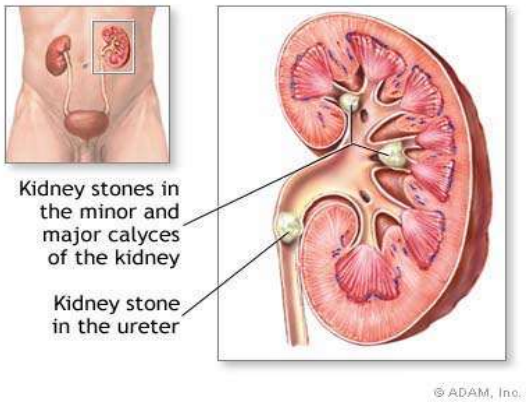
J Nutr 2009; 139:1246S

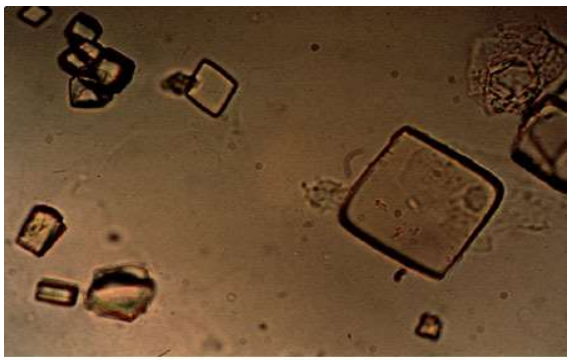


Consequences of Hyperuricemia

- Gout
- Uric Acid Stone
- Uric Acid Nephropathy
- Endothelial Dysfunction
- Hypertension
- Chronic Kidney disease







Uric Acid and Hypertension

(N Engl J Med 2008;359:1811-21)

- Elevated uric acid level predicts the development of hypertension
- Elevated uric acid level is observed in 25%-60% of patients with essential hypertension.
- Elevated uric acid level is observed in nearly 90% of adolescents with essential hypertension.
- Raising uric acid level in rodents results in hypertension.
- Reducing uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset.

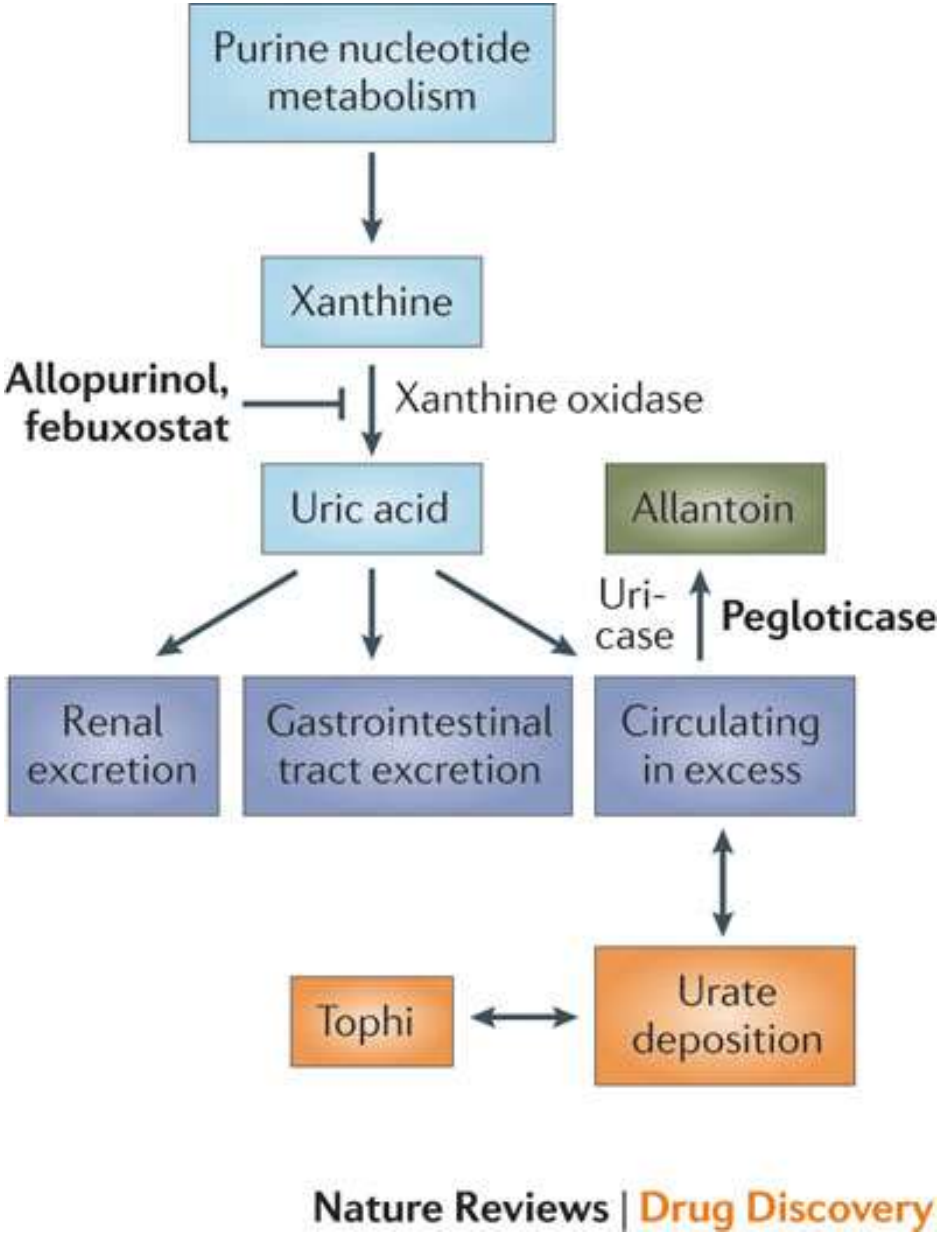
Uric Acid Levels and Chronic Kidney Disease

(World J Nephrol 2013;2:17-25)

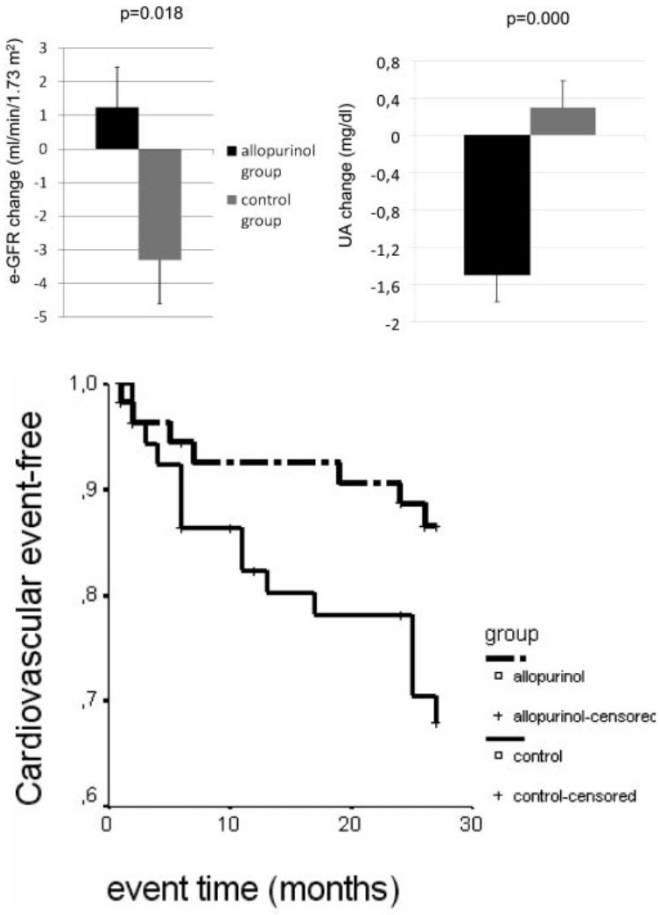
- Uric acid > 7 mg/dL increased CKD risk 2.14 fold in men and 3.12 fold in women.
- Uric acid > 8 mg/dL increased CKD risk three fold in men and 10 fold in women.
- Each 1 mg/dL increase in uric acid increase risk of CKD 7%-11%
- Each 1 mg/dL increase in uric acid associated with 1.28 odds ratio of reduced eGFR at 5 years.
- Uric acid > 6.5 mg/dL in men and > 5.3 mg/dL in women, associated with hazard ratio of 1.36 for all cause mortality and 2.14 for incident CKD

- Allopurinol, xanthine oxidase inhibitor, is a potent drug used for treatment of hyperuricemia

- Uricase further oxidates uric acid into allantoin, a more soluble molecule; however, the mutation in human uricase gene causes the enzyme to be non-functional.



Allopurinol slows down the progression of renal disease in patients with CKD, and reduces cardiovascular risk and hospitalization.
(Clin J Am Soc Nephrol 2010; 5: 1388-1393)



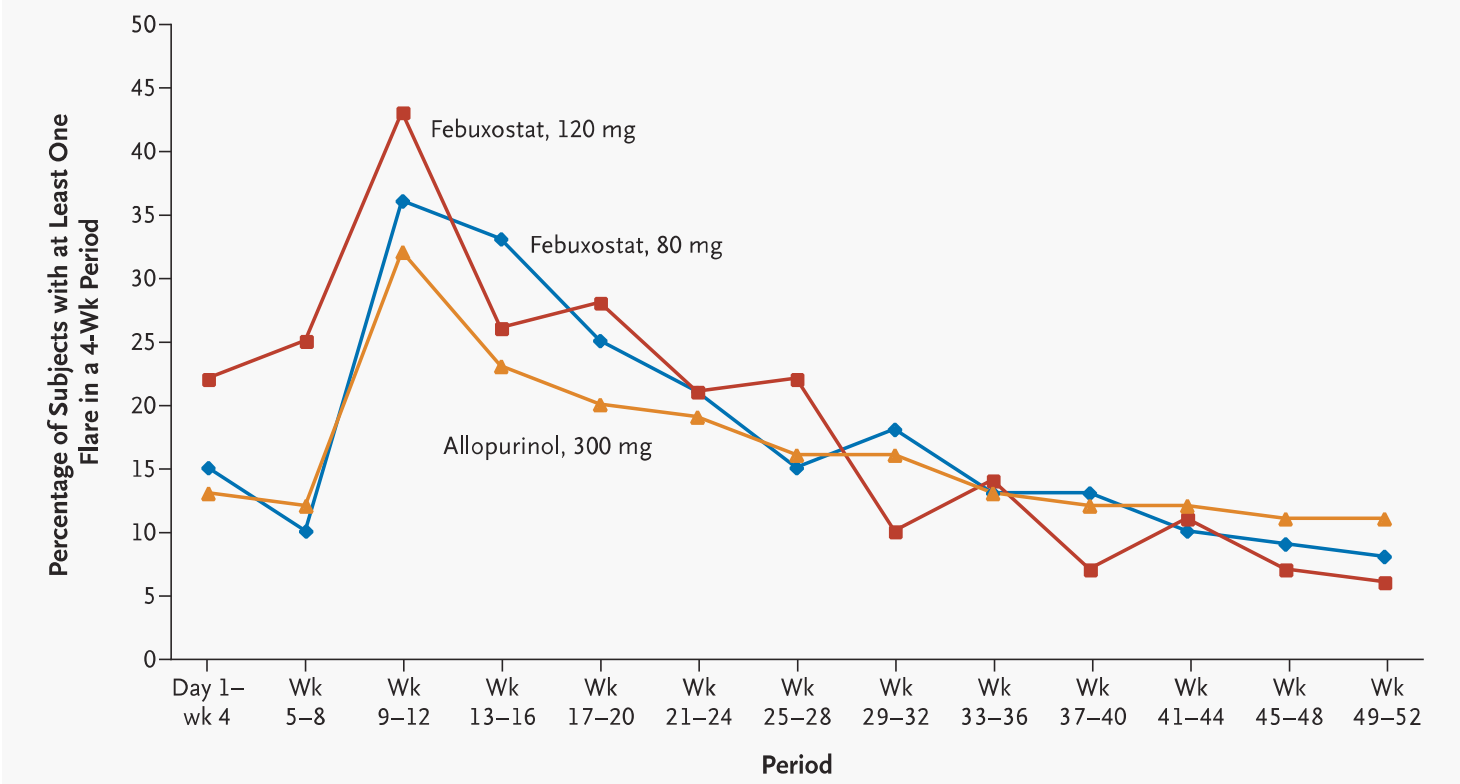
- 113 patients with eGFR < 60 ml/min were randomly assigned to treatment with allopurinol 100 mg/d or the usual therapy for 24 months.
- The result showed that allopurinol treatment slowed down renal disease progression independently of age, gender, diabetes, albuminuria, and renin-angiotensin system blockers use.
- In addition, 15 cardiovascular events occurred in the control group and only 7 events in allopurinol treatment group.

Allopurinol Used for Gout Lower CKD Risk

Vargas-Santoz A.B. et al. *JAMA Intern Med.* October 8, 2018; 4463

- Using a U.K. primary care database, researchers matched roughly 4800 users of allopurinol (at least 300 mg/day) to nonusers. All patients were newly diagnosed with gout and didn't have CKD (stage 3 or higher) at baseline.
- During 4–5 median years' follow-up, fewer people taking allopurinol were diagnosed with stage 3 or higher CKD than people not taking the drug (579 vs. 623). Lower doses did not yield a similar effect.

Febuxostat
Nonpurine Selective Inhibitor of Xanthine Oxidase
(N Engl J Med 2005;353:2450-2461)



Guidelines for management of hyperuricemia

- Patient education on diet (including fructose reduction) and lifestyle is recommended.
- Xanthine oxidase inhibitor therapy with allopurinol or febuxostat is recommended
- Target serum urate level should be lower than 6 mg/dl
- Prior to initiation of allopurinol, HLA-B*5801 testing should be considered.
- In patients who can not tolerate allopurinol, febuxostat can be another alternative.

Sodium Bicarbonate ($NaHCO_3$)
Uric Acid Excretor and CKD Protector

- An inexpensive, safe, and effective, but for unknown reason, is not a part of hyperuricemia treatment guidelines?.
- It can prevent renal calculi for both uric acid stones and calcium stones.
- Taste like salt but it is not NaCl so won't cause rising in blood pressure.
- Numerous evidence now indicated that $NaHCO_3$ can delay progression of CKD and should be prescribed in all cases of CKD regardless of serum bicarbonate.
- Should not be taken with milk or calcium.

If we wait for patients to develop acidosis before prescribing sodium bicarbonate, it will be too late!

Correlation between serum bicarbonate and changes in serum creatinine

Renal dysfunction	Creatinine	HCO3	Chloride
Moderate	2-4	22+/-1.2	106+/-1.0
Severe	4-14	19+/-0.5	107+/-0.6
Control	0.6-1.7	28+/-0.3	102+/-0.3

- Delay progression of CKD into end stage kidney disease should be done early (Cr < 3); however, at this stage bicarbonate levels will remain normal since the kidney is working harder to compensate.
- Sodium bicarbonate prescription need to be done early for better results.

Sodium bicarbonate and sodium chloride: effects on blood pressure and electrolyte homeostasis in normal and hypertensive man

J Hypertens. 1990 Jul;8(7):663-70.

- A randomly allocated, placebo-controlled, crossover trial in 10 mildly hypertensive and 10 normal subjects were studied.
- The subjects ingested a fixed daily basal diet of 60 mmol sodium and chloride, 60 mmol potassium and 14 mmol calcium. After balance was achieved (4 days), the subjects were randomly assigned to drink 3 liters/day of a NaHCO3-containing mineral water (26.2 mmol/l sodium and 33.03 mmol/l HCO3) or a control solution containing equimolar amounts of cations as the chloride salt for 7 days (total daily sodium 138 mmol). All urine was collected. Blood pressure was determined by an automated device. One month later the opposite regimen was followed.
- NaCl did not influence blood pressure, whereas NaHCO3 decreased systolic blood pressure (by 5 mmHg) in the hypertensive subjects.
- Urinary calcium excretion, which was greater in hypertensives than in normotensives, and greater in white than in black subjects, increased consistently with NaCl but not with NaHCO3.

Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study.

Am J Kidney Dis. 2013 Oct;62(4):670-8.

- 3,939 participants with CKD stages 2-4 who enrolled in the Chronic Renal Insufficiency Cohort (CRIC) between June 2003 and December 2008.
- During a median follow-up of 3.9 years, 374 participants died, 767 had a renal outcome, 332 experienced an atherosclerotic event, and 391 had a congestive heart failure event.
- **In adjusted analyses, the risk of developing a renal end point was 3% lower per 1-mEq/L increase in serum bicarbonate level. The association was stronger for participants with eGFR >45 mL/min/1.73 m(2).**
- The risk of heart failure increased by 14% per 1-mEq/L increase in serum bicarbonate level over 24 mEq/L.
- **Serum bicarbonate level was not associated independently with atherosclerotic events and all-cause mortality.**

Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with CKD

Kidney Inter 2012; 81: 86-93

- A number of studies have shown beneficial effects of alkali supplementation in slowing the progression of kidney disease.
- After intake of oral sodium bicarbonate, or fruits and vegetable in amounts that reduce dietary acid by half for one month, there were reduction in dietary acid decreased kidney injury measured by using urine indices of kidney injury (albumin, N-acetyl-glucosaminidase, TGF-b).
- Fruits and vegetables appear to be as effective as sodium bicarbonate in preventing kidney damage in CKD.
- The benefits of alkali supplementation in patients with normal serum bicarbonate is still clearly demonstrated.

Do not restrict fluid or prescribe diuretic in CKD patients who don't have volume overload

- Recent observational studies suggest a strong, direct association between preservation of renal function and fluid intake (Kidney Int. 2013;84:45-53).
- A prospective cohort of 2148 apparently normal participants from a Canadian community was followed for 6 years. Individuals with the highest rates of daily urine excretion had the lowest rates of decline in eGFR (Clin J Am Soc Nephrol 2011; 6: 2634).
- 2744 individuals were surveyed in cross- sectional manner. Compared with the reference group, which had a mean of daily fluid intake of 1.8 l, the groups averaging 2.4 and 3.2 l had, respectively, 30% and 50% reductions in CKD prevalence (Nephrology (Carlton) 2011; 16: 326).
- Unfortunately, most nephrologists will routinely ask CKD patients to restrict fluid intake and prescribe diuretics. Such practices lead to decrease in GFR and the progression of CKD to end stage renal disease.

Reverse Osmosis: The Toxic Water

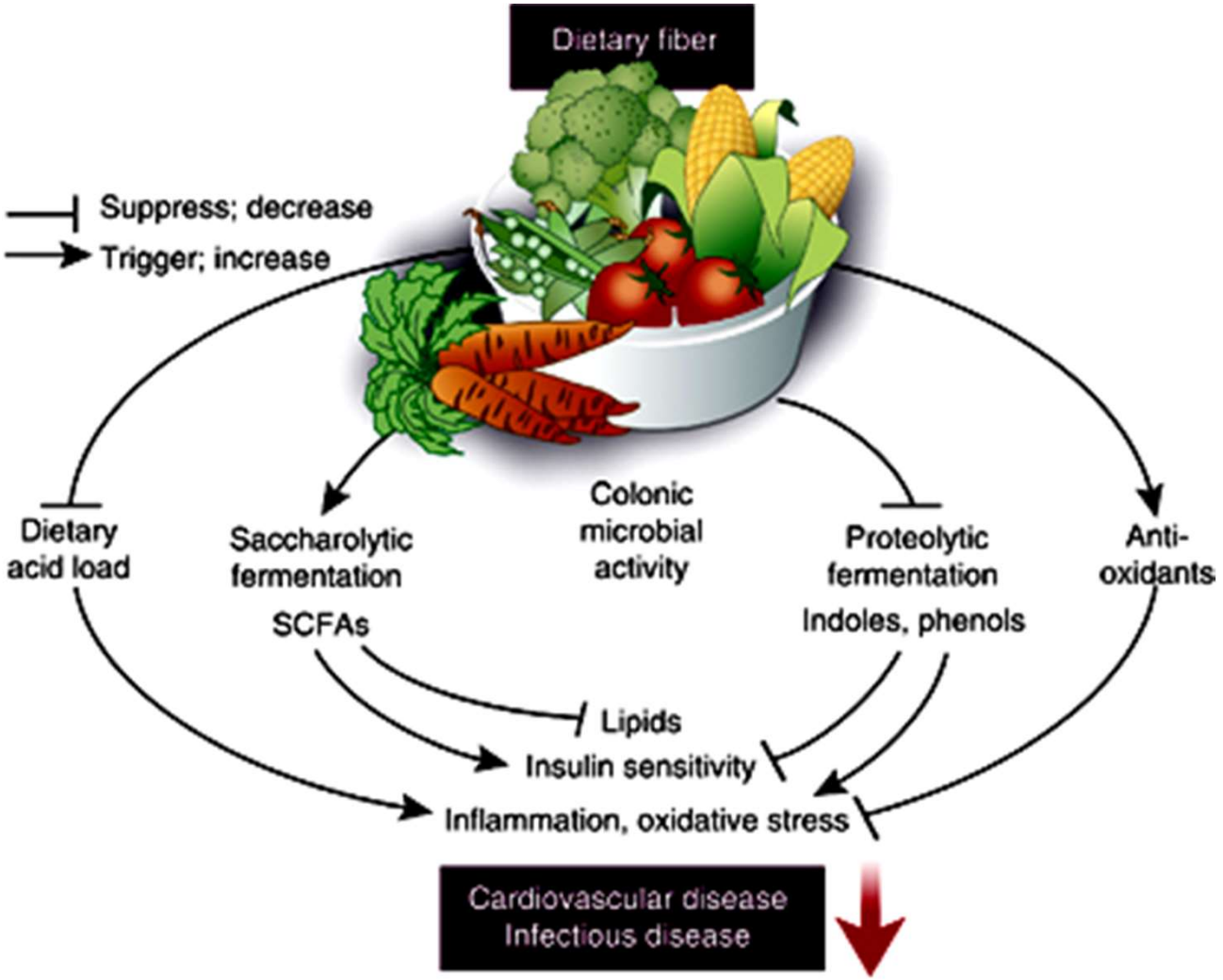
- In Thailand, many hotels, restaurants, and hospitals will serve their clients with “reverse osmosis” or RO water.
- This type of water will have pH less than 6.5 and mineral free leading to systemic acidosis and can be the cause of mineral deficiencies, cancer, osteoporosis, atherosclerosis, and kidney failure.

Dietary Guidelines for CKD patients come from TEXTBOOK OF THE DEAD KIDNEY Don't listen any dietary advice from any nutritionist who don't understand anti-aging medicine

- Most of dietary guidelines for CKD patients are written by nutritionists who so confused about the term CKD and ESRD.
- Advice for ESRD patients can not be used for CKD patients
- They cause more harm, resulting in nutritional depletion and speed up the progression of CKD and should be discarded.

High dietary fiber intake is associated with decreased inflammation and all cause mortality in patients with CKD

Kidney Inter 2012;81:300-306



Dietary Advice in CKD Patients

They are also healthy anti-aging food for everybody!

- Choose alkaline diets
- Less sugar, grains are good carbohydrate
- High fibers
- Less meat. Fish is meat as well as meat soup!
- Avoid meat soups, they contain meat, acid, toxins, and MSG!
- Eat at both white egg and yolk. Two eggs per day is enough.
- No all kinds of milk due to high phosphorus contents.
- Avoid any soft drink including sugar-free kinds since they are phosphoric acid
- Choose olive oil or rice bran oil.
- Consume fruits, vegetables, nuts, and grains in moderate amounts
- Be moderate, nothing good if you eat too much.
- Drink more water, avoid RO water, mineral water is preferable.