Did I Forget Anything?

Questions ?

Alcohol Intake, CAD events and Triglyceride in Women

- 15 gram alcohol (ethanol) =
- 12 oz beer = 5 oz wine = 1.5 oz distilled spirits
- 14,077 British women
  - those who consumed 1-14 drinks /wk compared with nondrinkers had reduced CAD events and lower TG and high HDL
- alcohol did not incr. TG nor incr. CAD

Ref: King AB, Practical Diabetology, p 29, March 2008

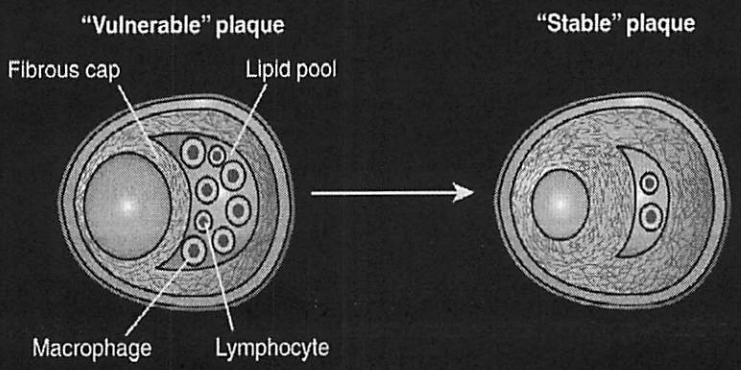
Alcohol: CHD Risk and Mortality

- Meta-analysis, 84 prospective cohort studies, > 1 million participants
  - active drinkers had significantly lower risks than nondrinkers for:
    - CV disease-related mortality, RR: 0.75
    - Incident CHD, RR: 0.71
    - CHD-related mortality, RR: 0.75
  - stroke risk was decreased only at $\leq$ 1 drink a day

BMJ 342: 671, Feb 22, 2011

VBWG

New therapeutic goal: Plaque stabilization

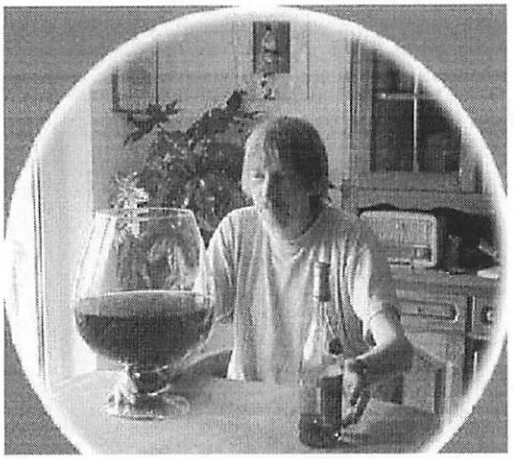


- Thin fibrous cap
- Large lipid pool
- Many inflammatory cells
- Few smooth muscle cells

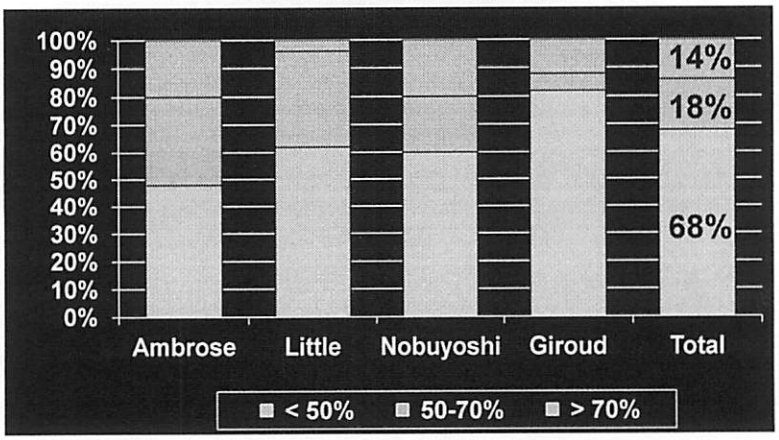
- Thick fibrous cap
- Smaller lipid pool
- Few inflammatory cells
- Dense extracellular matrix

Libby P, Aikawa M. *Nat Med.* 2002;8:1257-1262.

My ARNP said "Only 1 glass of alcohol a day". I can live with that.

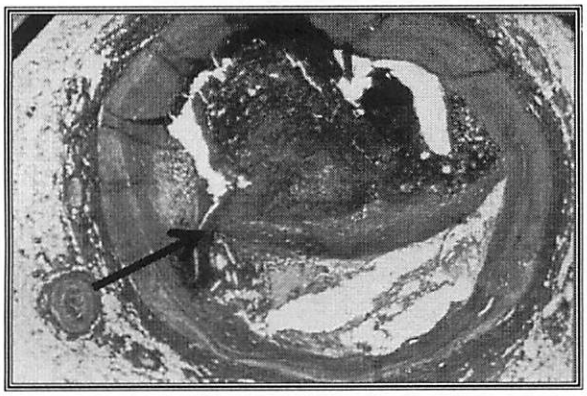


Coronary Stenosis Severity at the Time of MI



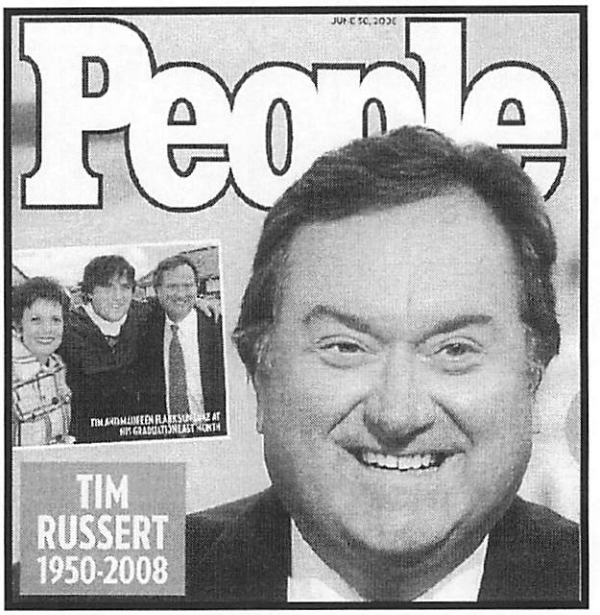
Falk et al, Circulation 92:657-71, 1995

Features of a Ruptured Atherosclerotic Plaque



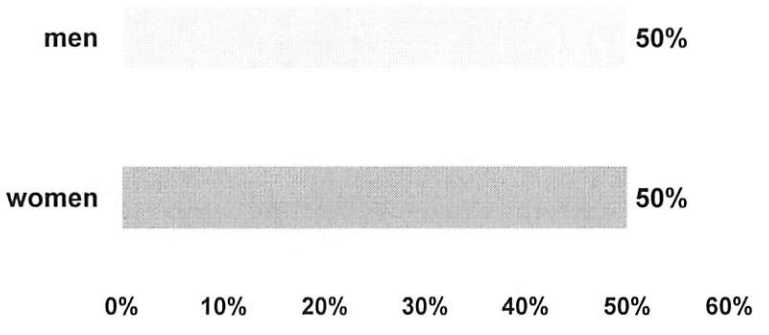
- eccentric, lipid-rich
- fragile fibrous cap
- prior luminal obstruction < 50%
- visible rupture and thrombus

Constantinides P. *Am J Cardiol.* 1990;66:37G-40G.



CHD diagnosis: often comes too late

MI or death as initial presentation of CHD



Fox Cs et al. Circulation 110:522-7, 2004

AIM-High Study

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes

- NIH sponsored, 3,414 pts, from US & Canada
- adding extended-release niacin to pts with stable coronary artery disease who are maintaining their LDL cholesterol below 80 mg/dL with intensive statin therapy.
- significant improvement in HDL & triglycerides
- trial was stopped 18 months earlier than planned due to increased ischemic stroke (28 strokes – niacin vs 12 strokes with statin only control arm), during 36 month f/u period

NEJM 365(24):2255-67, Dec 15, 2011

Bottom Line for Lipid Lowering

- put even <u>more</u> emphasis on using
  - statins
- and <u>less emphasis</u> on stain add-on therapies:
  - niacin
  - fibrates
  - ezetimibe
  - fish oil

The ACCORD Lipid Study

- Mean HDL levels inc: 38 to 41.2 (fenofibrate)
  38 to 40.5 (placebo)
- Mean TG levels dec: 160 to 122 (fenofib)
  160 to 144 (placebo)
- Cardiovasc events: 2.2% (fenofibrate)
  2.4% (placebo) **HR 0.92, P= 0.32**
- Dec in Glom Fil Rate: 2.4% (fenofibrate)
  1.1% (placebo)

"the burden of proof is firmly on advocates of the drug to justify the cost and risk to patients."

ACCORD Study **Group. N Engl J Med 362:1563-1574April 29, 2010**

Doubt Cast

on the "Good"

in "Good Cholesterol"

Fibrates and Heart Disease in Diabetics

The ACCORD Lipid Study

- Goal: to study whether adding fenofibrate to statin therapy prevents adverse cardiovascular events in pts with Type 2 diabetes,
- > 5000 pts, mean age 62 yrs, 31% women, 4.7 yrs; Hg A1C: ≥ 7.5%, LDL: 60-180 mg,
- HDL: <55 (women/blacks), <50 (men/others)
  - all received simvastatin,
  - fenofibrate 160 mg/day or placebo

ACCORD Study Group. N Engl J Med 362:1563-1574April 29, 2010

Fish Rich in Omega-3 Associated with Moderate Reduction in CVA

- 26 prospective cohort studies
- 12 randomized controlled trials
  - 794,000 participants
  - 35,000 CVAs
- 2-4 servings omega-3-rich fish (RR:0.94)
- ≥5 servings omega-3-rich fish (RR:0.88)
- Omega-3-supplements: no significant effect

BMJ October 2012

FISH	MERCURY	OMEGA-3
Tilefish	1.45	0.90
Shark	0.98	0.83
Swordfish	0.97	0.97
King mackerel	0.73	0.36
Tuna (fresh, frozen)	0.39	0.2
Halibut	0.24	0.5
Tuna (canned, light)	0.13	0.24
Cod	0.11	0.1
Pollock	0.03	0.5
Salmon (fresh, frozen)	.022	1.9
Crab	.06	0.3
Salmon (canned)	0	1.0
Shrimp	0	0.29

Sources: U.S. Department of Agriculture Nutrient Database for Standard Reference; U.S Food and Drug Administration; American Heart Association

Cleveland Clinic Men's Health Advisor March 2013, pg 6

Guidelines for Cardiovascular Disease in Women – Omega-3 Fatty Acids

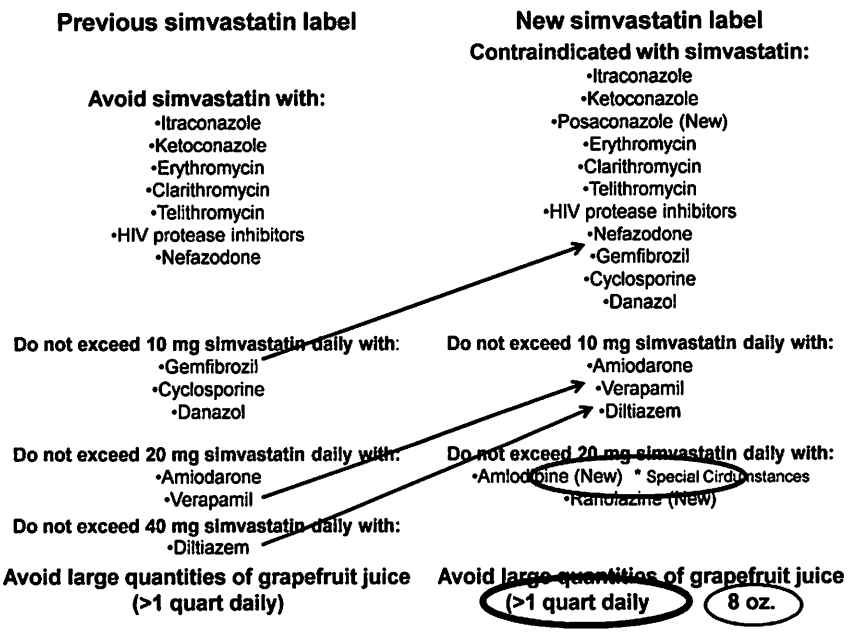
- consumption of O-3FA in fish or in capsule form:
  - 1800 mg/d eicosapentaenoic acid
- may be considered for primary or secondary prevention of CV events in women with hypercholesterolemia, hypertryglyceridemia or both

American Heart Association. Circulation Feb 16, 2011

Omega-3s: has the tide turned?

- meta-analysis 68,680 participants, 24 year time frame
- fish oil = omega-3 polyunsaturated fatty acids
- usual dietary sources: nuts, seeds, salmon, mackerel, herring and sardines
- average fish oil dose: 1000 mg/day
- fish oil supplements don't prevent heart attacks.

JAMA 309(1):20, Sept 12, 2012



06-08-2011 The U.S. Food and Drug Administration (FDA)

Do statins benefit very elderly pts?

- very elderly = ≥80 yrs old
  - each 40 mg/dL drop in LDL lowers cardiovascular risk for 1 year
    - regardless of age
- continue to use statins in the elderly unless the pt is not expected to survive a year or more.
- keep in mind that a patient who survives to 80 yrs will live another 8 years on average.

Presciber's Letter pg 10, February 2012

Statin Associated
Myalgia, Stiffness and Joint Pains
No or few elevations in Enzymes

Niacinamide

- Start with 500 mg.
- Most make it on 1000 mg or higher per day
- This is the cheapest therapy available
- No flushing, no itch, no fall in triglycerides or rise in HDL

L- Carnitine

- Use 500 mg
- Relatively expensive

Coenzyme Q10

- Use 200-500 mg
- Very expensive

Vitamin D

- 1000 IU a day

Caso, G, Am J Cardiol 2007; 99: 1409-1412
Dr. William Castelli

FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury

This information has been updated in the December 15, 2011, FDA Drug Safety Communication: Revised dose limitation for Zocor (simvastatin) when taken with amiodarone[1].

Safety Announcement
[06-08-2011] The U.S. Food and Drug Administration (FDA) is recommending limiting the use of the highest approved dose of the cholesterol-lowering medication, simvastatin (80 mg) because of increased risk of muscle damage. Simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy). Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug. In addition to these new limitations, FDA is requiring changes to the simvastatin label to add new contraindications (should not be used with certain medications) and dose limitations for using simvastatin with certain medicines.

Incident Diabetes with Statin Therapy

- JUPITER Trial, 17,000 pts, no CVD, CRP ≥2
- Looked at baseline diabetes risk factors:
  - 11, 508 pts with at least 1: metabolic syndrome, impaired fasting glucose, BMI ≥ 30, AIC> 6%
    - 54 more on rosuvastatin received a diagnosis of diabetes compared to placebo
  - 6095 pts without diabetes risk factors
    - no more likely than placebo recipients to receive a new diabetes diagnosis

Lancet 380:565, Aug 11, 2012

Factors That Increase the Risk of Statin-Induced Myopathy

Patient Characteristics

- Increasing age
- Female gender
- Renal insufficiency
- Hepatic dysfunction
- Hypothyroidism
- Diet (ie, grapefruit juice)
- Polypharmacy

Statin Properties

- High systemic exposure
- Lipophilicity
- High bioavailability
- Limited protein binding
- Potential for drug-drug interactions metabolized by CYP pathways (particularly CYP450 3A4)

CYP450 = cytochrome P450.
Rosenson RS. *Am J Med.* 2004;116:408-416.

Statin-Induced Cognitive Impairment

- memory loss, forgetfulness, amnesia, confusion, memory impairment
- generally not serious and reversible upon statin discontinuation:
  - does not lead to significant decline later
- time to onset of symptoms:
  - 1 day to years
- symptom resolution:
  - median of 3 weeks

htttp://www.fda.gov/Drugs/Drug Safety/ucm293101.htm

Risk for Diabetes Increases: Statin Dose

- Meta-analysis of 5 randomized statin trials,
- 32K participants without diabetes at baseline, intensive vs moderate statin doses: 80 vs 20 mg
- mean f/u 4.9 yrs:
  - 8.4% developed diabetes: intensive dose Rx
    - NNT: 498 pts x 1 yr for 1 pt: diabetes
    - lower diabetes incidence, moderate dose
  - CV events lowered by statins16%
    - NNT: 155 pts for 1 pt to benefit

JAMA 305:2556, June 2011

Standards of Medical Care in Diabetes - 2013

"statins should be prescribed:

- regardless of lipid levels in patients with diabetes and cardiovascular disease
- in diabetics who have multiple concomitant cardiovascular risks."

http/care.diabetesjournals.org/content/36/Supplement_1/S11.

February 28, 2012 FDA Statin Safety Label Changes

- removing the recommendation for periodic monitoring of liver enzymes
  - Liver injury cannot be prevented with routine monitoring
- adding a warning regarding the potential and non-life threatening side effect of memory loss
- adding a warning about the potential for increased blood sugar and hemoglobin A1C levels

htttp://www.fda.gov/Drugs/Drug Safety/ucm293101.htm

ATP III Update – July 2004

Risk Category	LDL-C goal	Consider drug treatment
High risk: CHD or CHD risk equivalents (10-yr risk > 20%)	< 100 mg/dL (optional goal: < 70 mg/dL)	> 100 mg/dL (consider drug Rx if LDL-C < 100 mg/dL)
Moderately high risk: 2+ RF (10 yr risk 10-20%	< 130 mg/dL (optional goal: < 100 mg/dL)	> 130 mg/dL (consider drug Rx if LDL-C 100-129 mg/dL)

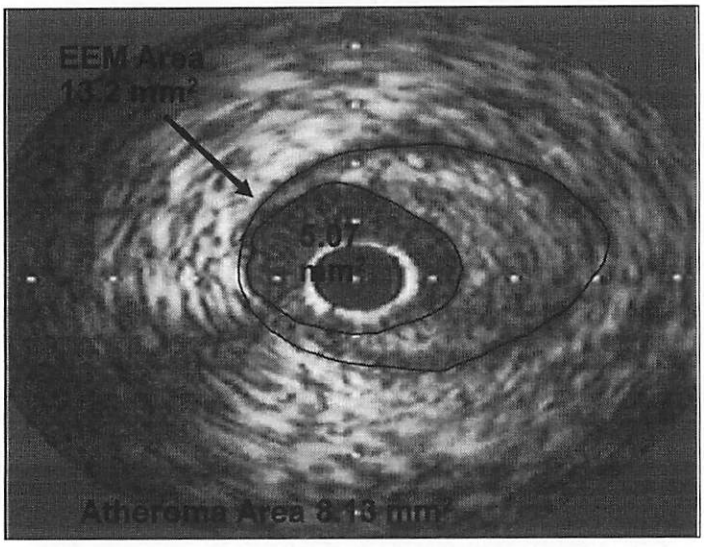
Circulation 110:227-239, 2004

American Heart Association/American College of Cardiology (AHA/ACC) Guidelines

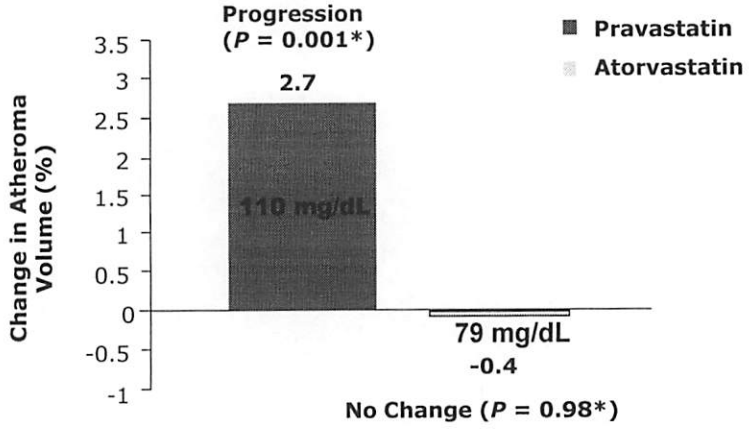
- LDL-C Goal:
  - < 100 mg/dL in CHD patients
    - goal of <70 mg/dL is reasonable
      - (even where baseline LDL-C < 100 mg/dL)

Smith et al, J Am Coll Cardiol 47:2130-39, 2006

IVUS – Intravascular Ultrasound

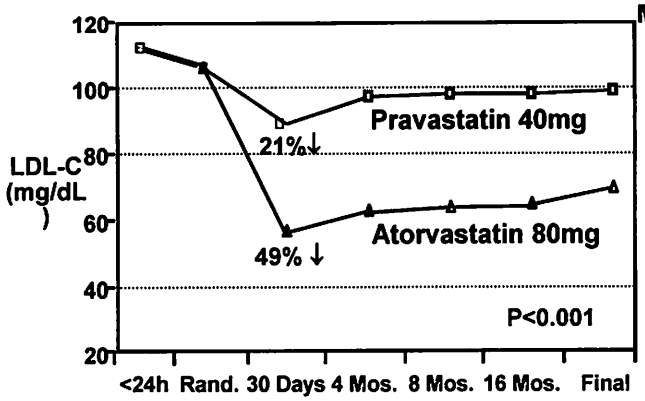


REVERSAL Primary End Point:
Percent Change in Atheroma Volume



*Wilcoxon signed rank test.
†Wilcoxon rank sum test.
Nissen. American Heart Association Scientific Session; 11/10/03; Orlando, FL.

PROVE-IT Trial
Changes from (Post-ACS) Baseline in Median LDL-C

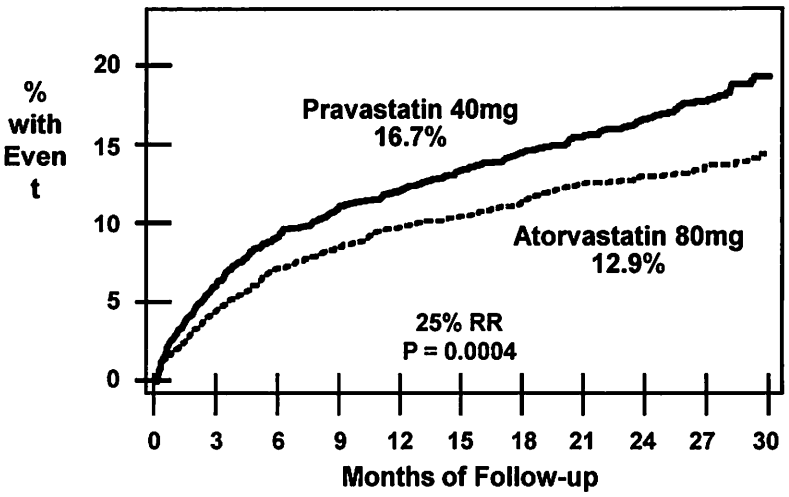


Median LDL-C (Q1, Q3)
95 (79, 113)
62 (50, 79)

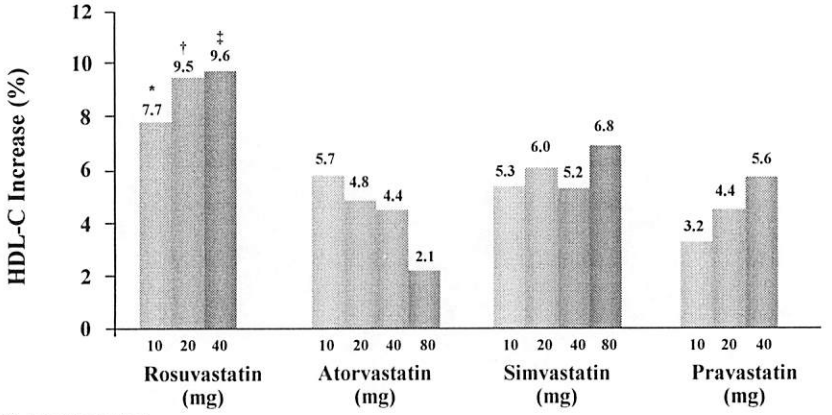
Note: Changes in LDL-C may differ from prior trials:

- **25% of patients on statins prior to ACS event**
- **ACS response lowers LDL-C from true baseline**

All-Cause Death, Non-Fatal MI, or Urgent Revascularization



Percentage Change from Baseline in HDL-C at Week 6 by Dose



ITT = intention-to-treat.
* $P<0.002$ vs pravastatin 10 mg.
† $P<0.002$ vs atorvastatin 20 mg, 40 mg, 80 mg; simvastatin 40 mg; pravastatin 20 mg, 40 mg.
‡ $P<0.002$ vs atorvastatin 40 mg, 80 mg; simvastatin 40 mg; pravastatin 40 mg.
Adapted from Jones PH, et al. *Am J Cardiol.* 2003;92:152-160.

Which statins should be taken in the evening?

We usually tell patients to take statins in the evening because most cholesterol is produced at night.

It's true that *Mevacor* and *Zocor* are slightly more effective for lowering cholesterol when they're taken in the evening instead of the morning.

Lescol is also recommended to be taken in the evening.

But *Lipitor*, *Crestor*, and *Pravachol* can be taken at any time of the day...probably because they have a longer half-life.

Recommend evening dosing when possible for *Mevacor*, *Altocor*, *Zocor*, and *Lescol*.

Tell patients they can take *Lipitor*, *Crestor*, or *Pravachol* whenever they take their other meds.

References(s):

BMJ 2003;327:788. Am J Cardiol 2002;90:784.

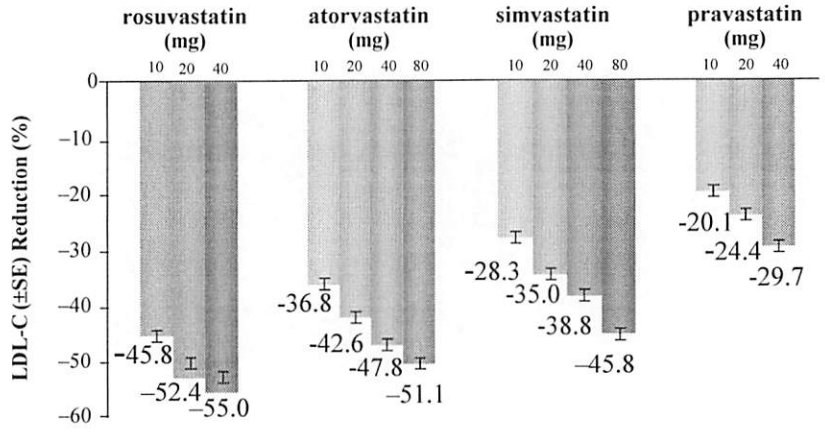
Prescribers Letter p. 2, Dec. 03

NCEP III Guidelines

• Risk category	• LDL goal (mg/dL)
– **CHD or CHD risk equivalents (10-yr risk > 20%)**	**< 100**
– **2+ risk factors (10-yr risk ≤ 20%)**	**< 130**
– **0-1 risk factors**	**< 160**

JAMA 285(19):2487, 5/16/01

Percentage Change in LDL-C: Pair-wise Comparisons (Stellar Trial)



*P 0.001 vs atorvastatin 10 mg; simvastatin 10 mg, 20 mg, 40 mg; pravastatin 10 mg, 20 mg, 40 mg.
†P<0.002 vs atorvastatin 20 mg, 40 mg; simvastatin 20 mg, 40 mg, 80 mg; pravastatin 20 mg, 40 mg.
‡P<0.001 vs atorvastatin 40 mg; simvastatin 40 mg, 80 mg; pravastatin 40 mg.
Jones PH, et al. *Am J Cardiol.* 2003;92:152-160.

Cardiovascular Risk in Women

- women with a 10-year predicted risk for cardiovascular disease (CAD) of ≥10% are now considered at high risk,
- in past:
  - –10-year risk for CAD of ≥ 20%
    - Framingham data

American Heart Association. Circulation Feb 16, 2011

U.S. Serum Lipid Levels (in mg/dL)

	NHANES 1988-1994	NHANES 1999-2002	NHANES 2007-2010
Total Cholesterol	206	203	196
LDL Cholesterol	128	124	119
HDL Cholesterol	50.7		52.5
Triglycerides	118	123	110
Lipid-lowering medication use	3.4%	9.3%	15.5%

JAMA 308:1545-54, 2012

Guidelines for Cardiovascular Disease in Women

- Mosca, Laurie et al, Circulation Feb 16, 2011
- Effectiveness-based guidelines for the prevention of cardiovascular disease in women - 2011 update: A guideline from the American Heart Association.

Women's Cardiovascular Health Classification System

1. "high risk"
2. "at risk"
3. "ideal cardiovascular health"

American Heart Association. Circulation Feb 16, 2011

If 2 or more RF, conduct a 10-year risk assessment

FOR MEN

50 yo male
overweight
BP 140/78
on HCTZ
FBS 112
T chol 201
TG 180
HDL-C 39
LDL-C 126
smoker
No CHD

Age

Years	LDL Pts
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	**6**
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Systolic Blood Pressure

	Untreated	Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	**2**
≥ 160	2	3

HDL-C

(mg/dL)	Pts
> 60	-1
50-59	0
40-49	1
< 40	**2**

Total Cholesterol

(mg/dL)	20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	**3**	1	0
240-279	9	6	4	2	1
>280	11	8	5	3	1

Cigarette Smoking

Nonsmoker	0	0	0	0	0
Smoker	8	5	**3**	1	1

CHD Risk

Pts	10-Yr CHD Risk
< 0	< 1%
0	1%
1	1%
2	1%
3	1%
4	1%
5	2%
6	2%
7	3%
8	4%
9	5%
10	6%
11	8%
12	10%
13	12%
14	16%
15	20%
16	**25%**
≥ 17	≥ 30%

JAMA 2001; 285: 2486-2497

Estimate of 10-Year Risk for Women
(Framingham Point Scores)

1

Age, y	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

3

Systolic BP mm Hg	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

4

HDL mg/dL	Points
≥60	-1
50-59	0
40-49	1
<40	2

5

	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

2

Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

6

Point Total	10-Year Risk, %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥30

NCEP-ATP-III. JAMA. 2001; 285:2486-2497.

Friedwald Formula

- LDL = TC – HDL –TG/5
- 98 = 198 – 40 – 300/5 (60)
- 118 = 198 – 40 – 200/5 (40)

Non-HDL cholesterol = Tot chol - HDL

Friedewald Equation reliability in elevated triglyceride setting - SLP

Triglycerides (mg/dL)	% correct (within +/- 10%)	% incorrect (outside +/- 10%)
<200	85	15
201-300	77	23
301-400	59	41
401-600	41	59

SIP – Standard Lipid Panel

McNamra et al, Clin Chem 36:36-42, 1990

AHA/NHLBI
The Metabolic Syndrome

- abdominal obesity – waist diameter
  - men: > 40 inches/102 cm > 37 inches
  - women: > 35 inches/88 cm > 32 inches
- triglycerides: ≥ 150 mg/dL (1.69 mmol/L)
- HDL cholesterol
  - men: < 40 mg/dL (1.03 mmol/L)
  - women: < 50 mg/dL (1.28 mmol/L)
- blood pressure: ≥ 130/> 85 mm Hg
- fasting glucose: ≥ 100 mg/dL (5.56 mmol/L)

JAMA 285(19):4287, 5/16/01; **Grundy et al. *Circulation* 2005;112:2735-2752.;**

LIPID PANEL **Final**

I will discuss the lab results with the patient at his office visit next week

Test	Result	Flag
TRIGLYCERIDES	228 MG/DL	H
CHOLESTEROL, TOTAL	167 MG/DL	
HDL CHOLESTEROL	41 MG/DL	
LDL-CHOLESTEROL	80 MG/DL CALC	

Desirable range <100 mg/dL for patients with CHD or diabetes and <70 mg/dL for diabetic patients with known heart disease.

CHOL/HDLC RATIO	4.1 CALC	
NON-HDL CHOLESTEROL	126 MG/DL CALC	

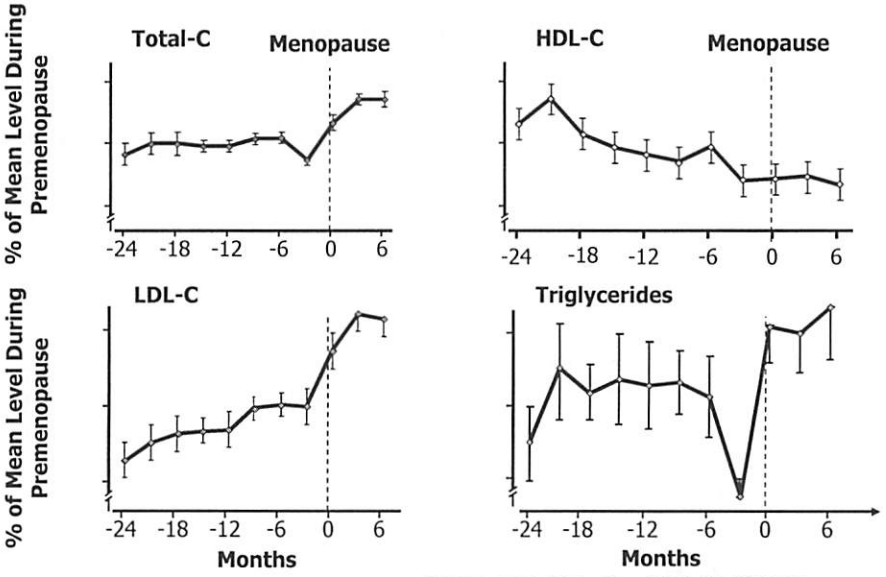
Target for non-HDL cholesterol is 30 mg/dL higher than LDL cholesterol target.

Menopause Before Age 46 Double CVD Risk Later In Life

- NIH funded MESA – Multi-Ethnic Study of Atherosclerosis, 2,509 women, late 1818 pts
- early menopause < 46 yrs old, 693 pts,
  - 446 (64%) natural menopause
  - 247 (36%) surgical menopause
- baseline age 45-84, followed 7 yrs,
- CVD events (MI with/out death, CVA, angina)
  - early menopause 41/693 (5.9%)
  - non-early menopause 47/1818 (2.6%)

Wellons & Vaidya Menopause, October 2012

Change in Lipids After Menopause, N=10



Jensen et al. *Maturitas.* 1990;12:321-331.

CVD Women: Some Facts

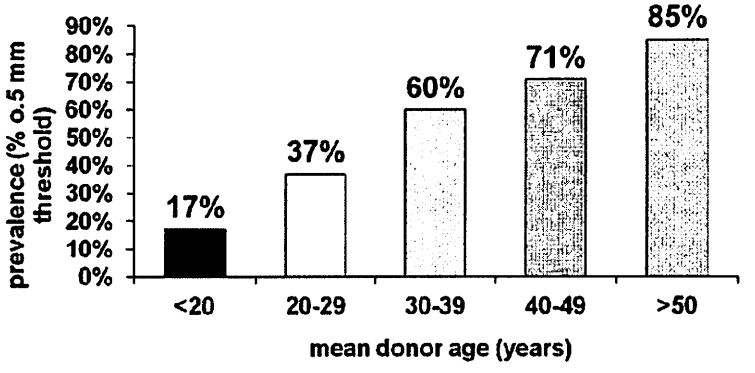
- Since 1984:
  - CVD has killed more American women/yr than men.
- 1 in 2 women will die of heart disease.
  - 1 in 25 women will die of breast cancer.
- 2/3 of women who die suddenly have
  - no previously recognized symptoms.

www.cdc.gov

Lipid Disorders

H. James Brownlee, Jr., M.D.

Atheromas In Teenagers
IVUS in 252 heart transplant donors



Tuzcu EM et al, Circulation 103:2705, 2001