Primary Prevention: State of the Art

RM MSS
5/14/2010

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Lots on the menu…

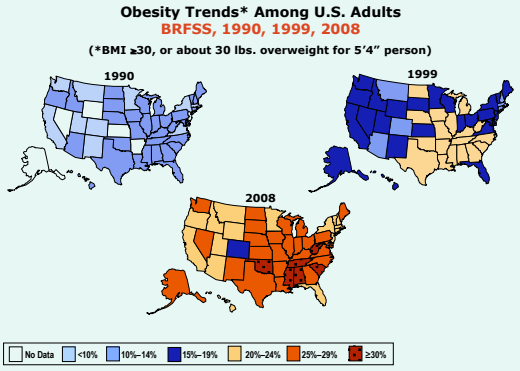
- How to achieve healthy lifestyle
  - Diet (and supplements)
  - Physical Activity
  - BMI < 25
  - Stop smoking
- Atherosclerosis biology and prevention
  - Target of Rx (LDL-C, statin pleiotropy, etc)
  - Primary vs Secondary Prevention
- Lessons from clinical trials
  - What have we learned?
  - What can't we learn?
- Guidelines for Primary prevention
  - Risk stratification
  - Coronary calcium screening
  - Statins (who and how)
  - Subgroups (v young, v old, women, DM, etc)
  - Hypertension
  - Diabetes
  - Aspirin
- Management dilemmas
- Patient expectations, treatment skeptics and enthusiasts, direct marketing to patients, "medicalising" poor lifestyle

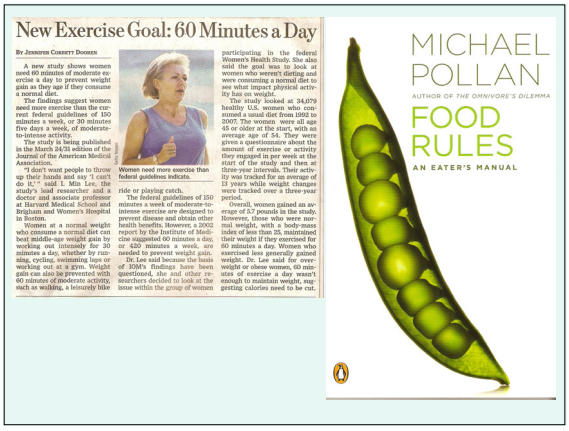
No shortage of recommendations:

- NCEP ATP III 2004 (update expected 2011) (www.nhlbi.nih.gov/guidelines/cholesterol/index.htm)
- USPHS Task force 2008: (www.ahrq.gov/CLINIC/uspstf/uspschol.htm)
- European 2007
- Canadian Cardiovascular Society 2008
- ACC/AHA Secondary Prevention 2006
- ASA: USPHSTF 2009
- ASA: ACCP Guideline 2008
- Women: AHA 2007 Guideline
- Children/Adolescents: AHA Guideline: 2007
- Diabetes: Endocrine Society 2008
- CAC Score: ACC/AHA Guideline 2007
- Coronary Screening: SHAPE Task Force 2005
- Coronary Screening: Expert Opinion: JACC 2010
- And Guideline Meta-Analysis: Arch Int Med 2010;170: 27-40)

But lets be pragmatic!

- Lifestyle, Lifestyle, and Lifestyle…
  - How to do we change the behavior of Homo sapiens whose paleolithic cortical wiring produces major (avoidable) health risks in the toxic environment of 2010?
- Statins (who and how)
  - Rx effect with earlier longer Rx
  - Long term safety
  - How to focus Rx
  - What's the target of Rx?





New Exercise Goal: 60 Minutes a Day

By Jennifer Corbett Dooren

A new study shows women need 60 minutes of moderate exercise a day to prevent weight gain as they age if they consume a normal diet.

The findings suggest women need more exercise than the current federal guidelines of 150 minutes a week, or 30 minutes five days a week, of moderate-to-intense activity.

The study is being published in the March 24/31 edition of the Journal of the American Medical Association.

"I don't want people to throw up their hands and say, 'I can't do this,'" said I-Min Lee, the study's lead researcher and a doctor and associate professor at Harvard Medical School and Brigham and Women's Hospital in Boston.

Women at a normal weight who consume a normal diet can beat middle-age weight gain by working out intensely for 30 minutes a day, whether by running, cycling, swimming laps or working out at a gym. Weight gain can also be prevented with 60 minutes of moderate activity, such as walking, a leisurely bike ride or playing catch.

Women need more exercise than federal guidelines indicate.

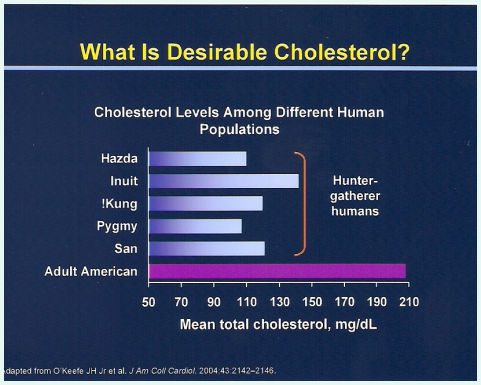
The federal guidelines of 150 minutes a week of moderate-to-intense exercise are designed to prevent disease and obtain other health benefits. However, a 2002 report by the Institute of Medicine suggested 60 minutes a day, or 420 minutes a week, are needed to prevent weight gain.

Dr. Lee said because the basis of IOM's findings have been questioned, she and other researchers decided to look at the issue within the group of women participating in the federal Women's Health Study. She also said the goal was to look at women who weren't dieting and were consuming a normal diet to see what impact physical activity has on weight.

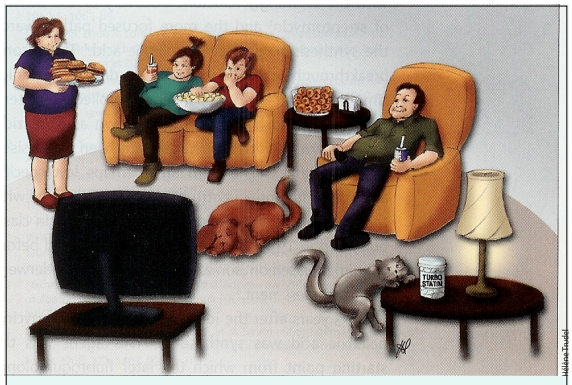
The study looked at 34,079 healthy U.S. women who consumed a usual diet from 1992 to 2007. The women were all age 45 or older at the start, with an average age of 54. They were given a questionnaire about the amount of exercise or activity they engaged in per week at the start of the study and then at three-year intervals. Their activity was tracked for an average of 13 years while weight changes were tracked over a three-year period.

Overall, women gained an average of 5.7 pounds in the study. However, those who were normal weight, with a body-mass index of less than 25, maintained their weight if they exercised for 60 minutes a day. Women who exercised less generally gained weight. Dr. Lee said for overweight or obese women, 60 minutes of exercise a day wasn't enough to maintain weight, suggesting calories need to be cut.

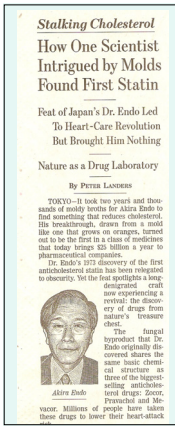
What Is Desirable Cholesterol?



Adapted from O'Keefe JH Jr et al. *J Am Coll Cardiol*. 2004;43:2142–2146.



Can the polypill save the world from heart disease? Lancet 2009; 373:1313



Stalking Cholesterol

How One Scientist Intrigued by Molds Found First Statin

Feat of Japan's Dr. Endo Led To Heart-Care Revolution But Brought Him Nothing

Nature as a Drug Laboratory

By Peter Landers

TOKYO—It took two years and thousands of moldy broths for Akira Endo to find something that reduces cholesterol. His breakthrough, drawn from a mold like one that grows on oranges, turned out to be the first in a class of medicines that today brings $25 billion a year to pharmaceutical companies.

Dr. Endo's 1973 discovery of the first anticholesterol statin has been relegated to obscurity. Yet the feat spotlights a long-denigrated craft now experiencing a revival: the discovery of drugs from nature's treasure chest.

The fungal byproduct that Dr. Endo originally discovered shares the same basic chemical structure as three of the biggest-selling anticholesterol drugs: Zocor, Pravachol and Mevacor. Millions of people have taken these drugs to lower their heart-attack

Akira Endo

Akira Endo discovers and Compactin in 1973

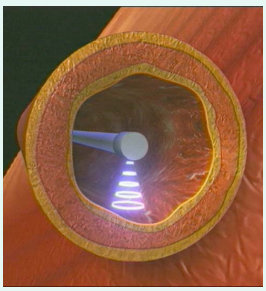
Mevacor FDA approved 1987

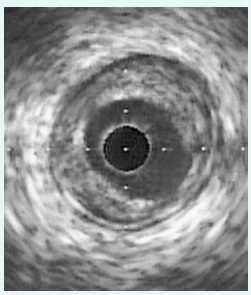
Statins Work!

Meta-analysis of Primary Prevention trials BMJ 2009;338b:2376

- RCT's > 1 year duration, at least 80% of enrollees without CVD or reported separately for 1– or 2– prevention
- 10 studies, 70,388 people, median age 55-65
- 34% women, 23% with DM
- Moderate intesnsity LDL lowering (from Prava 20-40, Lova 20-40, Atorva 10 to max Simva 40 and Rosuva 20)
- Mean in trial f/u 4.1 years

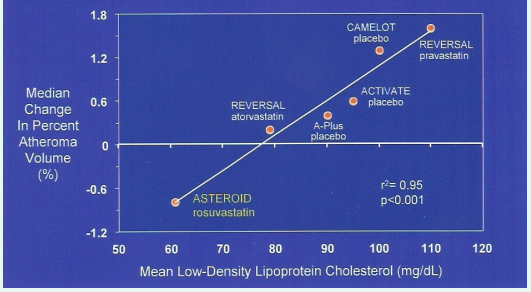
Outcome	Odds Ratio	Confidence Interval
All cause mortality	.88	.81-.96
Major coronary events	.70	.61-.81
Major cerebrovascular events	.81	.71-.93
Cancer	.97	.89-1.05
Major coronary events men	.72	.61-.86
Major coronary events women	.79	.56-1.13
Major coronary events age < 65	.62	.42-.87
Major coronary events age > 65	.86	.67-1.09



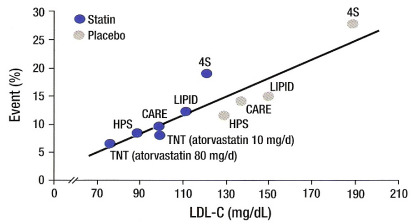


Recent Coronary IVUS Progression Trials

Relationship between LDL-C and Progression Rate



Relationship Between LDL-C and Event Rates in TNT and Other Statin Trials



TNT = Treating to New Targets; HPS = Heart Protection Study;
CARE = Cholesterol and Recurrent Events Trial;
LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease;
4S = Scandinavian Simvastatin Survival Study

LaRosa JC et al. *N Engl J Med.* 2005;352.

Atherosclerosis Biology

- Disease begins early
- LDL-C is an important treatment (but not the only) target
  - Non-HDL-C, LDL particle number
  - hsCRP
  - HDL-C
- Residual risk with statin primary and secondary prevention: wrong target or too little, too late?
- For secondary prevention LDL-C levels of 60 mg/dl or less are associated with “no progression on IVUS”: Lower is better

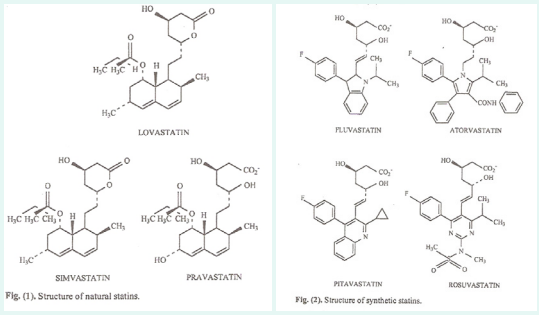
Primary vs Secondary Prevention

- Primary (lower short-term risk) vs Secondary prevention (higher short-term risk)…where Rx benefit risk is clearer in higher risk
- Why?
  - Just earlier, less plaque, and same issues as secondary prevention or…
  - Different biology: lower risk plaque fracture and thrombosis, and response to Rx
- Beware the influence of secondary prevention insights influencing primary prevention
  - Earlier, longer Rx might not require a very low LDL-C

Would earlier more intensive statin Rx leave less residual risk? Survival curves diverge with increasing duration of Rx in RCT's.

Would the relative risk reduction with (intensive) statin Rx initiated at younger age and carried over >10 years be greater than that observable in 5 year RCT's?

When life time risk is substantial is it sensible to defer statin until the 10 year risk is substantial?



Beltowski, J Adverse Effects of Statins – Mechanisms and Consequences. Current Drug Safety 2009;4:209

Statins are not vitamins…

- Pharmacology: Inhibit HMG-CoA _ Mevalonate
  - Impair formation of non-steroid isoprenoids: impair protein prenylation, dolichol synthesis (protein glycosylation), side chain of Coenzyme Q, selenoprotein synthesis
  - Potency (inhibition of HMG-CoA Reductase)
  - Lipophilicity determines extrahepatic HMG-CoA Reductase inhibition
  - Drug metabolism determines drug levels 3A4: simva, lova, atorva (vs 2C9 Fluva, and Urine Prava and Rosuva)

Statins are not vitamins…

- Muscle injury (asymptomatic, symptomatic, CK elevation (< 10 ULN, 10-50, > 50) (myopathy, myalgia, rhabdo)
  - Risk: hard to assess because of "noise" with nonspecific Sx and other causes CK elevation
  - Drug (potency, lipophilicity), dose, and concomitant Rx determine risk
    - Cyclosporine, Azole antifungals, Macrolide Ab, Gemfibrozil, HIV Protease Inhibitors, Amiodarone, Diltiazem and Verapamil, Niacin
    - Patient factors: neuromuscular disease, genes for hepatic statin uptake
  - Baycol (cerivastatin) substantial risk of rhabdo: potent, lipophilic
- Clinically important muscle injury is uncommon and largely avoidable

Statins are not vitamins…

- Less certain, less common, more conjectural
  - Pregnancy (Category X, risk uncertain)
  - Peripheral neuropathy
  - Cognition and memory loss
  - Cancer: nothing obvious in RCT's (qualified)
  - Autoimmune disease induction
  - Acute Liver failure (risk on statin similar to risk in general population) is extremely rare: Atorvastatin .03-.14 per million Rx

But they do appear very safe!

- In RCT's (in the short run - 5 years), in middle age (men)
- Late f/u from RCT's (4S, WOSCOPS) is weak reassurance
- Muscle Injury is the most important obvious clinical issue (less obvious in RCT's)
- How low would risk have to be over the long run to justify Rx in a young individual (at low short term CVD Risk) over many, many years?

How to focus Rx

- Risk stratification approaches (Google):
  - NCEP ATP III
  - Framingham 10 year risk
  - European SCORE
  - Reynolds Risk Score
- hsCRP and other novel risk factors (non-HDL-C, apoB, Lp-PLA2, and many more
- Coronary Calcium Screening

Challenges in Focusing Rx

- Important difference between 10 yr risk and life-time risk (at what LDL-C level and age is statin warranted in the absence of other CHD risk?)
  - HeFH with LDL >> 200 at young age
  - 55yo post menopausal female whose only CHD risk factor is LDL 190
- What 10 year risk is so low that Rx can and should be safely deferred? 1%, 5%, 10%?
- Risk stratification is less important if Rx is easy, inexpensive, and safe…generic statin Rx is close!

Coronary Calcium Score

- Single most effective tool for stratifying risk (No calcium = virtually no short term risk; graded relation between calcium score and risk) with important qualifications:
  - Most of the data in middle aged (less information on young < 40-45 and old > 65-70)
  - Slippery slope toward additional testing, repeat testing, and angiography/PCI CAC > 400 scores)
  - No (compelling) RCT evidence to demonstrate improved outcomes
  - Labeling and its psychic consequences
  - Cost effectiveness when risk is likely to be so low or so high that prevention management obvious

Gov Rick Perry signs the Texas Heart Attack Prevention Bill (Act HB 1290) 6/2009:

Insurers must cover the cost of CAC scans and carotid ultrasonography for men ages 45-76 and women ages 55-76, all diabetics of any age, and those deemed to be at intermediate Framingham risk

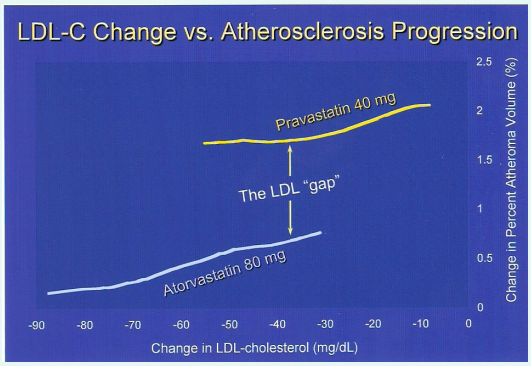
Similar to “enthusiast” SHAPE Task Force 2006 recommendation

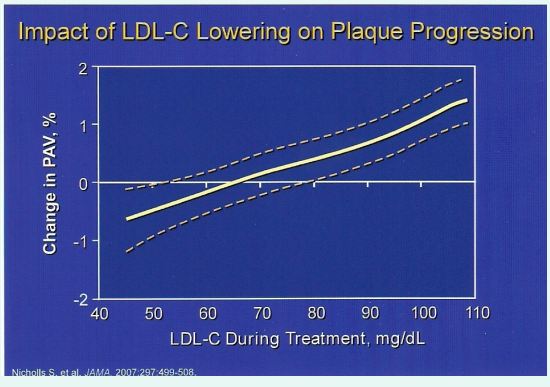
Advantages of Risk Stratification

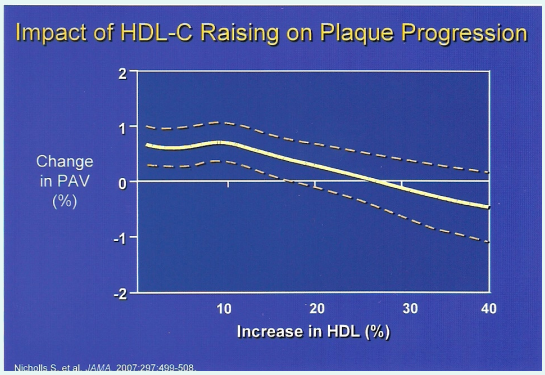
- Time frame for risk stratification parallels RCT and mimics what is feasible.
  - Will patients really take statins for 10-20 years?
- Use to motivate life-style change and engage the patient in risk modification

What's the target of Rx

- Statin at dose proven beneficial in RCT of primary prevention
- Statin at dose proven beneficial in RCT of secondary prevention
- Statin with dose adjusted to achieve
  - LDL-C < 130 or 100 or < 70 and/or
  - hsCRP < 2
- Statin and additional Rx prn (niacin?) to achieve low LDL-C and hsCRP and favorable HDL-C, non-HDL-C







Primary Prevention Issue	Skeptic	Enthusiast
Use of Evidence	V strict	Willing to extrapolate widely
Statin Effectiveness	Only that demonstrated within RCT's	Likely greater with earlier, longer, more intensive Rx
Statin Safety	Uncertain, use caution	Almost certainly safe, like a vitamin
Risk Stratification	Use Framingham or other validated risk model	More Info is better; CAC score in all at any risk
Treat young when 10 yr risk low	No, definitely	Yes, definitely
Target	LDL < 100 (130)	LDL < 70 and hsCRP and nonLDL-C < 100
Combination Rx	Rarely	Low threshold
Who Pays for High Technology	Patient	"Covered Benefit"

Primary Prevention CVD: State of the Art

- Science: atherosclerosis biology, CVD risk stratification, and clinical trials
- Evidence synthesis: Practice Guidelines
- Important Uncertainty:
  - Efficacy of earlier statin Rx (longer, more intensive)
  - Safety of statin Rx given for many years
- Complex clinical milieu of differing patient expectations, direct advertising, treatment skeptics and enthusiasts

CONCLUSIONS

- It is much too easy to treat a risky lifestyle with statin
- Practice guidelines should anchor clinical management
- Individualized treatment recommendations should be contingent upon
  - 10 year risk as well as life-time risk (common sense, risk scores, and focused coronary calcium screening)
  - Uncertainty about the benefit of “early” Rx as well as its risk
  - Patient expectations