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/cholestrol/index.htm)
• USPHE Task force 2006: (www.ahrq.gov/CLINIC/usphstfs/usph stfschol.htm)
• European 2007
• Canadian Cardiovascular Society 2008
• ACC/AHA Secondary Prevention 2008
• 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 2006
• Coronary Screening: Expert Opinion: JACC 2010
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?

Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)

New Exercise Goal: 60 Minutes a Day
Can the polypill save the world from heart disease? Lancet 2009; 373:1313

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 intensity 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio</th>
<th>Confidence Interval</th>
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<tbody>
<tr>
<td>All cause mortality</td>
<td>.88</td>
<td>.81-.96</td>
</tr>
<tr>
<td>Major coronary events</td>
<td>.70</td>
<td>.61-.81</td>
</tr>
<tr>
<td>Major cerebrovascular events</td>
<td>.81</td>
<td>.71-.93</td>
</tr>
<tr>
<td>Cancer</td>
<td>.97</td>
<td>.89-1.05</td>
</tr>
<tr>
<td>Major coronary events men</td>
<td>.72</td>
<td>.61-.86</td>
</tr>
<tr>
<td>Major coronary events women</td>
<td>.79</td>
<td>.56-1.13</td>
</tr>
<tr>
<td>Major coronary events age &lt; 65</td>
<td>.62</td>
<td>.42-.87</td>
</tr>
<tr>
<td>Major coronary events age &gt; 65</td>
<td>.86</td>
<td>.67-1.09</td>
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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?

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, Gemifbrozil, 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 lifetime 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 pm (niacin?) to achieve low LDL-C and hsCRP and favorable HDL-C, non-HDL-C
**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

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**Primary Prevention Issue**

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