MUCH ADO ABOUT STATINS

PRIMARY PREVENTION IN THE ELDERLY

Project ECHO
University of Hawaii JABSOM
Department of Geriatric Medicine
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CHOLESTEROL,

A FANCY WORD FOR FLAVOR.
OBJECTIVE

- To understand current guidelines and principles regarding statin use in primary prevention in the elderly.
YOU GET A STATIN, YOU GET A STATIN!
EVERYBODY GETS A STATIN!!!!
Big Mac with Mc Statins please.

Mc Statins: There's still some hope left.
CASES

• 90 year old Japanese lady with HTN and ESRD, no previous dx of coronary artery disease. Has progressive weakness due to uremia with creatinine = 5. Lives alone and able to ambulate without a walker. She stated that she does not want to ever undergo HD.

• 66 year old gentleman from Uzbekistan with DM, atrial fibrillation. Has been doing lifestyle modification aggressively. LDL 100. His father died of MI at age 67.

• 78 year old Hawaiian gentleman. No HTN, LDL 200. Vegan and lifelong triathlete. Just ran the Hapalua Half Marathon last weekend and was asymptomatic.
CARDIOVASCULAR DISEASE BURDEN IN THE ELDERLY

• The proportion and number of elderly people aged ≥65 years are increasing fast worldwide.

  • At age 65, life expectancy is currently estimated to be >20 years for women and >17 years for men in most high-income countries.

• The prevalence of coronary heart disease in the United States will increase by as much as 43% (about 5 million more) by the year 2030, with an estimated cost of about $70 billion more.
Five major North American and European guidelines on statin use in primary prevention have been published since 2013:

- American College of Cardiology/American Heart Association (ACC/AHA) - 2013
- National Institute for Health and Care Excellence-United Kingdom (NICE-UK) - 2016
- Canadian Cardiovascular Society (CCS) - 2016
- U.S. Preventive Services Task Force (USPSTF) - 2016
- European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) - 2016
CURRENT GUIDELINES

Commonalities:
- all are randomized control trials (RCTs)
- share the same basic concept of allocating statin therapy to those assumed to be at highest risk
  - well-defined high-risk condition (i.e., DM)
  - a high estimated 10-year risk for a first atherosclerotic CVD event using guideline specific risk scores
CURRENT GUIDELINES

Where they differ:

- age ranges studied
- risk scoring and risk threshold for therapy
- LDL cutoffs and treatment target goals
ACC/AHA RECOMMENDATIONS (2013)

• Individuals with clinical ASCVD

• Individuals with primary elevations of LDL ≥ 190 mg/dL

• Individuals 40 to 75 years of age with diabetes and an LDL 70 to 189 mg/dL without clinical ASCVD

• Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL 70 to 189 mg/dL and a 10-year ASCVD risk of 7.5% or higher.
ACC/AHA RISK CALCULATION

Pooled Cohort Equation (PCE)

• Gender, Age, Race, Total Cholesterol, HDL cholesterol, systolic BP, +/- antihypertensive use, +/-1 DM, smoking history

• http://clincalc.com/cardiology/ascvd/pooledcohort.aspx
NICE-UK RECOMMENDATIONS (2014/2016)

• **Atorvastatin 20 mg** for the primary prevention of CVD to people who have a **10% or greater risk** of developing CVD within the next 10 years.

• Patients with **type 1 or type 2 diabetes** should be offered **Atorvastatin 20 mg** for primary prevention of CVD.

• Patients with **established CVD** may need to be offered **Atorvastatin 80 mg**.

• Provider should discuss the benefits of changes to lifestyle with patients before initiating treatment with statins.
NICE-UK RISK CALCULATION

QRISK2

- Age, gender, ethnicity, smoking status, +/- DM, CKD 4 or 5, +/- atrial fibrillation, +/- antihypertensive use, +/- RA, cholesterol/HDL ratio, systolic BP, BMI

- https://qrisk.org/2017/

- There is now a QRISK 3 that includes other factors such as steroid use, mental illness and antipsychotic use, erectile dysfunction and family history
• Statin therapy for **high-risk conditions**: clinical atherosclerosis, AAA, most DM, CKD with age > 50, LDL ≥ 5.0 mmol/L (90 mg/dl)

• **Primary prevention**:
  
  • not for low risk individuals with modified FRS-CVD score < 10%
  
  • statin therapy for high risk modified FRS-CVD score ≥ 20%
  
  • statin therapy for **intermediate risk** 10%-19% with LDL ≥ 3.5 mmol/L (63 mg/dl)
  
  • statin therapy for **intermediate risk**, LDL < 3.5 mmol/L but with apoB ≥ 1.2 g/L, or non-HDL ≥ 4.3 mmol/L (77 mg/dl), or men > 50 years and women > 60 years with ≥ 1 CV risk factor
FRS-CVD (Modified Framingham Risk Scoring for CVD)

- Age, gender, HDL, total cholesterol, systolic blood pressure, smoking status, +/- DM

USPSTF RECOMMENDATIONS (2016)

Similar to ACC/AHA in both scoring method, recommendations and goals except risk threshold to treat was ≥ 10% in the PCE.
ESC/EAS RECOMMENDATIONS (2016)

- Statin therapy for SCORE risk threshold $5\%$ (high risk) to $\geq 10\%$ (very high risk)
- LDL $\geq 155$ mg/dl for high risk and $\geq 100$ for very high risk
- Treatment target of LDL $< 100$ for high risk and LDL $< 70$ for very high risk
SCORE (Systematic Coronary Risk Evaluation)

- Age, gender, smoking status, cholesterol status, country of origin

### Table 1: Eligibility for Primary Prevention With Statins (Class I or Strong Indication)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>High estimated 10-yr risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age range, yrs</td>
<td>40–75</td>
<td>30–84</td>
<td>30–75*</td>
<td>40–75</td>
<td>40–65†</td>
</tr>
<tr>
<td>Risk model</td>
<td>PCE</td>
<td>QRISK2</td>
<td>Modified FRS-CVD</td>
<td>PCE</td>
<td>SCORE</td>
</tr>
<tr>
<td>Predicted endpoints</td>
<td>Nonfatal MI, CHD death, stroke</td>
<td>CHD, stroke, TIA (fatal and nonfatal)</td>
<td>MI, angina, CHD death, heart failure, stroke, TIA, PAD</td>
<td>Similar to ACC/AHA</td>
<td>Fatal ASCVD</td>
</tr>
<tr>
<td>Risk threshold for therapy</td>
<td>≥7.5%</td>
<td>≥10%</td>
<td>10%–19% (intermediate), ≥20% (high risk)</td>
<td>≥10%</td>
<td>5% to &lt;10% (high risk), ≥10% (very high risk)</td>
</tr>
<tr>
<td>Risk factor requirements</td>
<td>No</td>
<td>No</td>
<td>Yes if 10%–19% risk*, No if ≥20% risk</td>
<td>≥1†</td>
<td>No</td>
</tr>
<tr>
<td>LDL-C before treatment, mg/dl</td>
<td>70–189</td>
<td>No</td>
<td>≥135 if 10%–19% risk*, No if ≥20% risk</td>
<td>≤190</td>
<td>≥155 if high risk</td>
</tr>
<tr>
<td>LDL-C treatment target, mg/dl</td>
<td>No</td>
<td>High intensity: &gt;40%↓§</td>
<td>&lt;77/≥50%↓*</td>
<td>No</td>
<td>&lt;100/≥50%↓ if high risk</td>
</tr>
<tr>
<td><strong>High-risk clinical condition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH and/or high cholesterol, mg/dl</td>
<td>LDL-C ≥190</td>
<td>No§</td>
<td>LDL-C ≥190</td>
<td>No§</td>
<td>FH or TC &gt;310</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40–75 yrs of age</td>
<td>High-risk type 1§</td>
<td>≥40 yrs of age*</td>
<td>No‡</td>
<td>&gt;40 yrs of age</td>
</tr>
<tr>
<td>CKD (eGFR), ml/min/1.73 m²</td>
<td>No</td>
<td>&lt;60§</td>
<td>&lt;60†</td>
<td>No</td>
<td>30–59 = high risk</td>
</tr>
</tbody>
</table>
For apparently healthy individuals, all 5 statin guidelines provide strong Class I recommendations for initiating statin therapy in those at high risk.

Well represented in other high-quality prevention statin trials.
PRIMARY PREVENTION IN THE ELDERLY (66-75 YEARS)

• For apparently healthy individuals 66-75 years of age, 4 out of the 5 guidelines continue to provide Class I or strong risk-based recommendations for primary prevention.

• ESC/EAS guideline no longer has recommendations because SCORE is not applicable beyond age 65.

• ESC/EAS instead has a caveat recommends consideration of statins for its with HTN, smoking, DM and hyperlipidemia
PRIMARY PREVENTION IN THE ELDERLY (66-75 YEARS)

- ACC/AHA, CCS, USPTF provide the same risk-based indications for statin therapy up to age 75.
- NICE-UK provides the same recommendations up to age 84.
PRIMARY PREVENTION IN THE ELDERLY (66-75 YEARS)

• Clinical trial evidence supports the use of statin therapy for primary prevention of nonfatal ASCVD in elderly individuals 66 to 75 years of age.

• Other supporting primary prevention trials:
  
  • MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese)
  
  • CARDS (Collaborative Atorvastatin Diabetes Study)
  
  • JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin)
  
  • HOPE-3 (Heart Outcomes Prevention Evaluation 3)
PRIMAR Y PREVENTION IN THE ELDERLY (66-75 YEARS)

- 2 meta-analyses and 8 more RCTs found that primary prevention of statins were **highly effective in reducing the risk of MI and stroke**, but not all-cause mortality or cardiovascular death.

- **Rosuvastatin** - JUPITER and HOPE-3 showed reduced risk of nonfatal MI, nonfatal stroke or cardiovascular death substantially by 49% in ages 65-70 and by 26% in age ≥ 70.
PRIMARY PREVENTION IN THE VERY ELDERLY (>75 YEARS OF AGE)

- For apparently healthy very elderly individuals, only 1 (NICE-UK) of the 5 guidelines continues to provide strong risk-based recommendations for initiating primary prevention with statins.

- QRISK2 goes up to 84 years of age

- QRISK2 puts everyone ≥ 75 years above the 10% risk threshold

- Provides specific recommendation of Atorvastatin 20 mg ≥ 85 years of age.
**PRIMARY PREVENTION IN THE VERY ELDERLY (>75 YEARS OF AGE)**

- This population is at high risk for ASCVD by virtue of age alone, but evidence of efficacy for primary prevention with statins is sparse in this age group as only few have been included in RCTs.

- Efficacy of statin therapy in secondary prevention in this population is well documented.

- PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease).
PRIMARY PREVENTION IN THE VERY ELDERLY (>75 YEARS OF AGE)

• Extrapolation of data from those <75 years to those ≥75 years should be done cautiously considering the following:
  • comorbidity
  • polypharmacy
  • potential side effects
  • limited life expectancy
### Central Illustration: Age-Dependent Implementation of Guidelines in Clinical Practice

<table>
<thead>
<tr>
<th>Sex: Male</th>
<th>SBP: 135 mm Hg</th>
<th>HDL cholesterol: 37 mg/dL</th>
<th>Race: White</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>Total cholesterol: 232 mg/dL</td>
<td>Diabetes: No</td>
<td>No antihypertensives</td>
</tr>
<tr>
<td></td>
<td>Age 56</td>
<td>Age 66</td>
<td>Age 76</td>
</tr>
<tr>
<td>PCE:</td>
<td>18%</td>
<td>26%</td>
<td>34%</td>
</tr>
<tr>
<td>QRISK2:</td>
<td>17%</td>
<td>28%</td>
<td>43%</td>
</tr>
<tr>
<td>Framingham:</td>
<td>31%</td>
<td>49%</td>
<td>NA</td>
</tr>
<tr>
<td>SCORE:</td>
<td>4%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

#### Guideline Recommendation

<table>
<thead>
<tr>
<th>ACC/AHA</th>
<th>NICE</th>
<th>CCS</th>
<th>USPSTF</th>
<th>ESC/EAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>✔️ Class I</td>
<td>✔️ Strong</td>
<td>✔️ Strong</td>
<td>✔️ Level B</td>
<td>✗</td>
</tr>
<tr>
<td>✔️ Class I</td>
<td>✔️ Strong</td>
<td>✔️ Strong</td>
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<td>✗</td>
</tr>
<tr>
<td>✔️ Class Ib</td>
<td>✔️ Strong</td>
<td>✔️ Strong</td>
<td>✔️ Level B</td>
<td>✗</td>
</tr>
</tbody>
</table>

- ✔️: Strong Statin Recommendation
- ✗: Not Recommended for Statin
- - - : Weak Statin Recommendation

Figure 2: Detection Rate in Elderly Individuals >65 Years of Age With a First MI

- All Elderly: n = 777 (100%)
  - ACC/AHA: 41
  - NICE: 31
  - CCS: 38
  - USPSTF: 1

- 66-75 y: n = 331 (43%)
  - ACC/AHA: 92
  - NICE: 69
  - CCS: 88
  - USPSTF: 0

- >75 y: n = 446 (57%)
  - ACC/AHA: 57
  - NICE: 3
  - CCS: 3
  - USPSTF: 0
  - ESC/EAS: 1
NET BENEFIT CONSIDERATIONS

• Statin-Associated Symptoms (SAS)
  • statins are safe and well tolerated in the elderly >65 years with the caveat that limited data exists on the very old
  • Muscle discomfort and pain
    • appear to be unrelated to age and statin therapy
    • “nocebo” effect - muscle symptoms often mistakenly perceived by patients to be statin-related due to being told about possible side effects
NET BENEFIT CONSIDERATIONS

• Myopathies (including Rhabdomyolysis)
  • higher risk with age
  • higher risk with higher doses
• Metabolic Syndrome
  • increased risk in those who are already predisposed to DM
  • new diagnosis of DM will usually require additional drug therapy - polypharmacy may become an issue
NET BENEFIT CONSIDERATIONS

• Cognition, memory loss and dementia
  • current evidence does not support statin might cause these
  • not enough evidence stating that statins prevent these
NET BENEFIT CONSIDERATIONS

- Drug-drug interactions
  - usually in statins metabolized by CYP3A4 (ie. Atorvastatin)

- Adverse effects
  - usually resolve rapidly after discontinuation of treatment.
MORBIDITY VS. MORTALITY BENEFIT

• No longer feasible to concentrate on longevity and all-cause mortality alone.
  • Majority of ASCVD events are non-fatal.
  • Morbidity and treatment costs are rising.
  • Number of patients living longer with chronic diseases are increasing.
Patient preference and goals discussion is crucial based on their values:

- **Longevity** - little data to support primary prevention

- Nonfatal and potentially disabling MI or stroke - reasonable to initiate statin therapy
MORBIDITY VS. MORTALITY BENEFIT

- Attitudes regarding this have been seen to be age-dependent
  - <65 years weigh avoiding death the highest
  - ≥65 years value avoiding MI or stroke
DEPRESCRIBING STATINS

- Reasonable to consider this in the very old though there are no definitive guidelines
  - issues with adherence
  - increased risk for SAS
  - low chance of benefit because of limited life expectancy
- Benefit of statin therapy persists after discontinuation (long-term legacy benefit)
- No evidence of “rebound” adverse effects in primary prevention
FUTURE PERSPECTIVE

• **STAREE** (Statins for Reducing Events in the Elderly) - currently underway, recruiting individuals ≥70 years of age to determine efficacy and safety in the elderly.

• **Improving risk stratification methods** for eligibility for initiating statins (QRISK3).

• **“Derisking”** - personalized treatment by use of negative risk markers (ie. absence of coronary artery calcification.)
BACK TO THE CASES: WHAT WOULD YOU DO?

• 90 year old Japanese lady with HTN and ESRD, no previous dx of coronary artery disease. Has progressive weakness due to uremia with creatinine = 5. Lives alone and able to ambulate without a walker. She stated that she does not want to ever undergo HD.

• 66 year old gentleman from Uzbekistan with DM, atrial fibrillation. Has been doing lifestyle modification aggressively. LDL 100. His father died of MI at age 67.

• 78 year old Hawaiian gentleman. No HTN, LDL 200. Vegan and lifelong triathlete. Just ran the Hapalua Half Marathon last weekend and was asymptomatic.
QUESTIONS?

BUCKET LIST

- Bucket of Fried Chicken
- Bucket of Shrimp
- Bucket of Tartar Sauce
- Bucket of Chili
- Bucket of Popcorn
- Bucket of Cholesterol Medicine