Evidence Based Medicine in Geriatrics: Statins for Primary Cardiovascular Disease Prevention in Older Adults

Individual preferences

Risks

Benefits

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• VA CSR&D CDA-2
• NIA National and BostonPepper Center
• NIA R03AG060169 – GEMSSTAR award
• “The average 70-something is not bedridden. ... If the pandemic doesn’t change life expectancy, half the U.S. population will live past 80 years of age.”

- Dr. Louise Aronson, NEJM 2020
The US Demographic is changing: those >85 are the fastest growing segment of the population.

Baby Boomers are just now turning 75!
(born 1946-1964)

The changing U.S. demographic is in part due to gains in average life years, but also in the influx of baby boomers (Blue) born between 1946 and 1964.

Global burden of IHD: 1980-2010

A

Deaths

Year

80+ years
75-79 years
70-74 years
65-69 years
60-64 years
55-59 years
50-54 years
45-49 years
40-44 years
35-39 years
30-34 years
25-29 years
20-24 years
15-19 years
10-14 years
5-9 years
1-4 years
2-364 days

Patient 1: Mr. J

- 82M, independent, hiker
- HL, HTN, glaucoma, family history of CVD
- Former smoker, glass of wine with dinner
- **Medications**: Amlodipine 5mg, Rosuvastatin 20mg, Latanoprost drops
- **Total Cholesterol**: 180 mg/dL
- **LDL-C**: 70 mg/dL
- **HDL-C**: 60 mg/dL
- **Triglycerides**: 95 mg/dL
Patient 2: Ms. G

- 80F, independent, uses cane for stability
- HTN, HL, DM, anxiety, arthritis, h/o colon cancer
- Former smoker, no alcohol
- **Medications**: Metformin 1000mg, Losartan 50mg, Sertraline 50mg, Acetaminophen 1000mg
- **Total Cholesterol**: 240 mg/dL
- **LDL-C**: 189 mg/dL
- **HDL-C**: 55 mg/dL
- **Triglycerides**: 199 mg/dL
Patient 3: Mrs. Y

- 81F, wheelchair for distances
- Assistance with bathing, dressing
- AF, HTN, HL, mild dementia, CKD, osteoporosis, malnutrition, urinary incontinence
- Never smoker, no alcohol
- **Medications**: Donepezil 10mg, Lisinopril 5mg, Pravastatin 20mg, Oxybutinin 10mg, Warfarin 5mg, Vitamin B12, Alendronate 70mg/wk
- **Total Cholesterol**: 220 mg/dL
- **LDL-C**: 130 mg/dL
- **HDL-C**: 40 mg/dL
- **Triglycerides**: 150 mg/dL
How can we individualize care?
2018 AHA ACC Cholesterol Guidelines

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- **Age 20-39 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age 40-75 y**
  - and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)
  - without diabetes mellitus
  - 10-year ASCVD risk percent begins risk discussion

- **Diabetes mellitus and age 40-75 y**
  - Moderate-intensity statin (Class I)

- **Diabetes mellitus and age 40-75 y**
  - Risk assessment to consider high-intensity statin (Class IIa)

- **Age >75 y**
  - Clinical assessment, Risk discussion

---

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>1. In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable.</td>
</tr>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>2. In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy.</td>
</tr>
</tbody>
</table>

Grundy JACC 2018
Table 1 Differences in guideline indications for statins for primary prevention based on age and risk across the age spectrum [8, 14–19]

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Age Cut Points for Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≤ 64 years old</strong> &amp; <strong>65 years old</strong> &amp; <strong>75 years old</strong> &amp; <strong>85 years old</strong></td>
<td></td>
</tr>
<tr>
<td>ESC/EAS(^a) 2016</td>
<td>5-10% 10-yr risk per SCORE with LDL-C of ≥ 155(^b)</td>
</tr>
<tr>
<td>CCS(^c) 2016</td>
<td>10-19% 10-yr risk per modified FRS-CVD with LDL-C ≥ 135(^b) and one risk factor</td>
</tr>
<tr>
<td>USPSTF 2016</td>
<td>≥ 10% 10-yr risk per PCE with LDL-C ≤ 190 and one or more risk factor</td>
</tr>
<tr>
<td>AHA/ACC(^d) 2018</td>
<td>≥ 7.5% 10-yr risk per PCE with LDL-C 70-189(^b)</td>
</tr>
<tr>
<td>ACC/AHA(^e) 2019</td>
<td>≥ 7.5% 10-yr risk per PCE with LDL-C 70-189(^b)</td>
</tr>
<tr>
<td>NICE-UK(^f) 2014</td>
<td>≥ 10% 10-yr risk per QRISK2 up to age 84</td>
</tr>
<tr>
<td>VA/DoD 2014</td>
<td>Consider moderate intensity statin for 6-12% 10-yr risk per FRE or PCE regardless of age (no age cut point)</td>
</tr>
</tbody>
</table>

**Legend**
- **Recommendation**
  - Strong or Class I
  - Weak or Class IIa
  - Class II b
  - No recommendation
Estimated Remaining Life Years at Each Age

<table>
<thead>
<tr>
<th>Current Age (Yrs)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>18.79</td>
<td>21.39</td>
</tr>
<tr>
<td>70</td>
<td>15.2</td>
<td>17.41</td>
</tr>
<tr>
<td>75</td>
<td>11.9</td>
<td>13.72</td>
</tr>
<tr>
<td>80</td>
<td>8.97</td>
<td>10.39</td>
</tr>
<tr>
<td>85</td>
<td>6.57</td>
<td>7.55</td>
</tr>
<tr>
<td>90</td>
<td>4.23</td>
<td>5.34</td>
</tr>
<tr>
<td>95</td>
<td>3.4</td>
<td>3.73</td>
</tr>
<tr>
<td>100+</td>
<td>2.5</td>
<td>2.65</td>
</tr>
</tbody>
</table>

http://census.gov
Assessment of frailty can re-set life expectancy estimates, independent of age

<table>
<thead>
<tr>
<th>Frailty Score</th>
<th>2002</th>
<th>2002</th>
<th>2002</th>
<th>Mediant Survival Time (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Men</td>
<td>Women</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>75-84</td>
<td>≥85</td>
<td>65-74</td>
</tr>
<tr>
<td>≤0.1</td>
<td>13.0</td>
<td>10.4</td>
<td>6.4</td>
<td>19.2</td>
</tr>
<tr>
<td>&gt;0.1 - ≤0.2</td>
<td>12.4</td>
<td>8.7</td>
<td>5.7</td>
<td>15.1</td>
</tr>
<tr>
<td>&gt;0.2 - ≤0.3</td>
<td>9.5</td>
<td>7.0</td>
<td>4.8</td>
<td>12.0</td>
</tr>
<tr>
<td>&gt;0.3 - ≤0.4</td>
<td>6.8</td>
<td>5.4</td>
<td>3.8</td>
<td>8.5</td>
</tr>
<tr>
<td>&gt;0.4</td>
<td>4.6</td>
<td>3.8</td>
<td>2.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Overall</td>
<td>12.9</td>
<td>8.0</td>
<td>4.9</td>
<td>15.6</td>
</tr>
</tbody>
</table>

What is the evidence for statins to date?
### Older Adult Subgroups in Primary Prevention Statin Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Older Subgroup</th>
<th>Statin</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUPITER</td>
<td>≥70 yrs</td>
<td>Rosuva</td>
<td>39% ↓ risk</td>
</tr>
<tr>
<td></td>
<td>N=5696</td>
<td>20mg</td>
<td></td>
</tr>
<tr>
<td>HOPE 3</td>
<td>≥70 yrs</td>
<td>Rosuva</td>
<td>25% ↓ risk</td>
</tr>
<tr>
<td></td>
<td>N=3086</td>
<td>10mg</td>
<td></td>
</tr>
<tr>
<td>ALLHAT-LLT</td>
<td>≥75 yrs</td>
<td>Prava</td>
<td>34% ↑ risk</td>
</tr>
<tr>
<td></td>
<td>N=375</td>
<td>40mg</td>
<td></td>
</tr>
<tr>
<td>PROSPER</td>
<td>70–82 yrs</td>
<td>Prava</td>
<td>6% ↓ risk</td>
</tr>
<tr>
<td></td>
<td>N=5804</td>
<td>40mg</td>
<td></td>
</tr>
</tbody>
</table>

Statin better than Placebo.

39% ↓ risk,
25% ↓ risk,
34% ↑ risk,
6% ↓ risk.
Meta-analysis of 28 trials major statin trials: 186,854 participants, only 8% were ≥75 years

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Participants without vascular disease</th>
<th>Events per Annum</th>
<th>Statin or more intensive</th>
<th>Control or less intensive</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤55 years</td>
<td>290 (0.8)</td>
<td>408 (1.2)</td>
<td>0.68 (0.56–0.83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;55 to ≤60 years</td>
<td>350 (1.0)</td>
<td>415 (1.2)</td>
<td>0.81 (0.67–0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 to ≤65 years</td>
<td>416 (1.1)</td>
<td>545 (1.5)</td>
<td>0.73 (0.61–0.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 to ≤70 years</td>
<td>374 (1.2)</td>
<td>581 (1.8)</td>
<td>0.61 (0.51–0.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;70 to ≤75 years</td>
<td>400 (2.1)</td>
<td>462 (2.4)</td>
<td>0.84 (0.70–1.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>295 (2.7)</td>
<td>308 (2.8)</td>
<td>0.92 (0.73–1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2125 (1.3)</td>
<td>2719 (1.6)</td>
<td>0.75 (0.71–0.80)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trend test $\chi^2 = 3.85$ (p = 0.05)

**Age >75 (N=6,449)**

HR 0.92 (0.73 – 1.16)

Safety and Benefit of Discontinuing Statin Therapy in the Setting of Advanced, Life-Limiting Illness
A Randomized Clinical Trial
Statin discontinuation at end of life: Improvement in measures of QOL, no difference in mortality

<table>
<thead>
<tr>
<th>Domain Measure</th>
<th>Estimate (95% CI)</th>
<th>Favors Discontinuation</th>
<th>Favors Continuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.18 (-0.28 to 0.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>-0.08 (-0.43 to 0.26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td>0.39 (-0.02 to 0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-being</td>
<td>0.32 (0.00 to 0.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support</td>
<td>0.53 (0.16 to 0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.26 (0.02 to 0.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard items</td>
<td>-2.19 (-5.01 to 0.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin items</td>
<td>-0.23 (-1.39 to 0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All items</td>
<td>-2.45 (-5.02 to 1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKPS scale score</td>
<td>-0.80 (-4.11 to 2.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total medications</td>
<td>-0.67 (-1.29 to -0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>-0.25 (-0.77 to 0.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRN ≥1/2 d</td>
<td>-0.19 (-0.46 to 0.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRN &lt;1/2 d</td>
<td>-0.11 (-0.32 to 0.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommend care</td>
<td>0.08 (-0.05 to 0.20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kutner JS et al. JAMA IM. 2015.
Limited trial data has led to observational data
Study design considerations in pharmacoepidemiology

Confounding by indication, healthy user bias
→ Propensity score methods  
(mimic balance in clinical trials)

Prevalent user bias
→ New user design

Immortal time bias
→ Appropriately account for time not on treatment

Seeger JD et al Med Care 2007.  
Retrospective cohort study in Spain

- 46,864 adults aged 75 ands older without ASCVD
  → stratified by diabetes status at baseline
- New user design, propensity score adjustment
- Exclusion: “to avoid frailty bias, people with cancer, dementia, or paralysis, and those receiving dialysis, living in residential care, or with an organ transplant.”
- Co-primary outcome: time to ASCVD event, mortality

Older adults with diabetes may benefit from statins for ASCVD and mortality prevention

Mean age 81
>60% women

Retrospective cohort study in France

• French national health insurance claims database, 2012-14
• 120,173 adults without ASCVD, ≥75 with a statin medication possession ratio (MPR) at least 80% in each of the previous 2 years
• Propensity score weights
• Nursing home patients excluded
• Primary outcome: time to hospitalization for an ASCVD event
Statin discontinuation after age 75 was significantly associated with an increased risk of an ASCVD event.

60% women

Results were unchanged when considering statin intensity or frailty.“

Retrospective cohort study in the US

JAMA | Original Investigation

Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older

Ariela R. Orkaby, MD, MPH; Jane A. Driver, MD, MPH; Yuki-Lam Ho, MPH; Bing Lu, MD, PhD; Lauren Costa, MPH; Jacqueline Honerlaw, RN, MPH; Ashley Galloway, MPH; Jason L. Vassy, MD, MPH; Daniel E. Forman, MD; J. Michael Gaziano, MD, MPH; David R. Gagnon, MD, PhD; Peter W. F. Wilson, MD; Kelly Cho, PhD; Luc Djousse, MD, ScD
Retrospective cohort study in US Veterans

- US Veterans ≥75 with regular use of VA healthcare, 2002-2012
- No exclusion for cancer, dementia or paralysis
- Aging specific variables:
  - Arthritis, dementia, polypharmacy (≥5 medication classes), gait abnormality)
- New user design, Propensity score overlap weighting
- Co-primary outcome: All-cause and ASCVD mortality

Results: 326,981 Veterans included with 57,178 (17.5%) new statin users

- Mean age 81±4 years (range, 75-107)
- 91% White
- 97% Men
  --> In total 8,737 women
- 4% Hispanic/Latinx
- Followed for an average 7 years
- 53,727 (94%) had at least one follow up prescription

Most common statins:
- Simvastatin: 84.8%
- Lovastatin: 11.0%
- Pravastatin: 2.5%
- Fluvastatin: 1.2%
- Atorvastatin and Rosuvastatin: 0.5%

Among US veterans ≥75 without ASCVD, statin therapy was significantly associated with a lower risk of mortality.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Weighted rate/1000 person-years</th>
<th>Weighted incidence rate difference/1000 person-years (95% CI)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin user (N = 57 178)</td>
<td>Statin nonuser (N = 269 803)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>78.7</td>
<td>98.2</td>
<td>-19.45 (-20.38 to -18.52)</td>
<td>0.75 (0.74 to 0.76)</td>
</tr>
<tr>
<td>All CV death</td>
<td>22.6</td>
<td>25.7</td>
<td>-3.09 (-3.63 to -2.55)</td>
<td>0.80 (0.78 to 0.81)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCVD composite</td>
<td>66.3</td>
<td>70.4</td>
<td>-4.05 (-5.09 to -3.02)</td>
<td>0.92 (0.91 to 0.94)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13.2</td>
<td>12.6</td>
<td>0.56 (0.13 to 0.98)</td>
<td>0.99 (0.97 to 1.03)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>18.4</td>
<td>18.2</td>
<td>0.25 (-0.26 to 0.76)</td>
<td>0.98 (0.96 to 1.01)</td>
</tr>
<tr>
<td>CABG surgery/PCI</td>
<td>35.2</td>
<td>39.2</td>
<td>-3.38 (-4.12 to -2.64)</td>
<td>0.89 (0.88 to 0.91)</td>
</tr>
</tbody>
</table>
Results were unchanged when stratified by sex, race, age, diabetes, dementia and arthritis.
Retrospective cohort study in England and Wales

• Primary Care database 1990-2000 followed to 2017
• 110,243 adults without ASCVD, ≥60 separated by birth cohorts
• 6-month sliding window ‘landmarking’
• Primary outcome: all cause mortality

Statin use was associated with a lower risk of all-cause mortality in all age groups.
Limitations of observational data

• Residual confounding
• Generalizability: European cohorts, US Veterans, exclusion of nursing home patients
• Varying statins over time (VA study: Simvastatin)
• Side effects, drug-drug interaction, impact on function, cognition
• Patient centered outcomes?
Other important considerations: Statins and Cognitive Impairment

• Existing randomized evidence with statins in later life finds no adverse effect on cognitive function\textsuperscript{1}.

• Clinical \textbf{and subclinical} CVD increase the risk for vascular cognitive impairment and dementia (VCID)\textsuperscript{2}.
  • Statins prevent ischemic stroke, a significant contributor to vascular dementia\textsuperscript{3}.

• Lower BP targets lower risk of MCI/dementia — further linking vascular health and cognition\textsuperscript{4}.

\textsuperscript{1}Prosper Trial J Neurol, 2010. 257(1): p. 85-90
\textsuperscript{3}Heart Protection Study, Lancet, 2002. 360(9326): p. 7-22
\textsuperscript{4}Sprint Mind JAMA. 2019 Feb 12;321(6):553-561
There has been a decline in the incidence of dementia over the last 30-years: in part due to improved CV prevention.

Table 2. Temporal Trends in the Incidence of Dementia.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. of Cases</th>
<th>Total No. of Observation Periods</th>
<th>5-Yr Cumulative Hazard Rate (95% CI)</th>
<th>5-Yr Hazard Ratio (95% CI)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epoch 1 (2.9–4.4)</td>
<td>Epoch 2 (0.59–1.04)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Epoch 2 (2.2–3.5)</td>
<td>Epoch 3 (0.47–0.83)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Epoch 3 (1.8–2.8)</td>
<td>Epoch 4 (0.41–0.77)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epoch 4 (1.5–2.6)</td>
<td>Trend (0.72–0.90)</td>
<td></td>
</tr>
<tr>
<td>Overall dementia</td>
<td>371</td>
<td>9015</td>
<td>3.6</td>
<td>0.78</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.8</td>
<td>0.62</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>2.2</td>
<td>0.56</td>
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<td></td>
<td>2.0</td>
<td>0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>264</td>
<td>9015</td>
<td>2.0</td>
<td>1.00</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>2.0</td>
<td>0.88</td>
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<td></td>
<td>1.7</td>
<td>0.70</td>
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<td></td>
<td>1.4</td>
<td>0.88</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>0.70–1.43 (0.62–1.25)</td>
<td>0.77–1.00</td>
<td></td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>84</td>
<td>9014</td>
<td>0.8</td>
<td>0.89</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.8</td>
<td>0.46</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0.4</td>
<td>0.45</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
<td>(0.51–1.56)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(0.2–0.7)</td>
<td>(0.25–0.86)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.2–0.7)</td>
<td>(0.23–0.87)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.2–0.7)</td>
<td>(0.56–0.90)</td>
<td></td>
</tr>
</tbody>
</table>

* The baseline examination period was between 1977 and 1983 for the first epoch, between 1986 and 1991 for the second epoch, between 1992 and 1998 for the third epoch, and between 2004 and 2008 for the fourth epoch.

† The 5-year cumulative hazard rates (the cumulative incidence of dementia per 100 persons over a period of 5 years) are adjusted for age and sex.

‡ The 5-year hazard ratios (the incidence of dementia during each epoch relative to the incidence during the first epoch) are adjusted for age and sex.

§ We estimated linear trends (the decline per decade in the 5-year incidence of dementia) using the elapsed mean time (in decades) between the first epoch and each consecutive epoch.
Statins and Physical Function

• In randomized trials, participants on statin are only 0.3% more likely to report muscle symptoms compared to those on placebo\(^1\)

• A meta-analysis found no evidence for a negative effect of statins on physical function\(^2\)

• Physical disability results from a diverse set of physiologic and physical contributors\(^3\)

• Statins may preserve physical function by preventing disabling vascular events, reducing inflammation, or improving vascular health\(^4\)

\(^1\) Lancet, 2016. 388(10059): p. 2532-2561
\(^3\)Circulation, 2017. 135(16): p. e894-e918.
Statins, Nocebo, Pre-existing Symptoms

- In practice, 10% stop taking statins because of subjective muscle symptoms
- Muscle symptoms are not higher with statin than placebo in blinded studies
- Asking about muscle symptoms increases reporting 3-fold (for placebo, too)
- Causal associations are flawed
  - Cross over controlled design in statin intolerant patients found that those getting statin first had slightly more symptoms, but 26% of placebo first also reported symptoms.

### Side effects in Randomized Trials
(Statin vs. Placebo)

| Routine asked about muscle symptoms | HPS Trial: 32.9% vs. 33.2% | CORONA Trial: 8.9% vs. 8.3% |
| Did not ask about symptoms          | HOPE-3: 5.8% vs. 4.7%       | 8 other trials: 4.8% vs. 4.4% |

SAMSON trial, N-of-1-trail: 90% of statin related complaints are due to the nocebo effect

You’re Over 75, and You’re Healthy. Why Are You Taking a Statin?

Risks

Benefits

Individual preferences

Elixir Of Life? Elderly Taking Statins Reduces Risk To Death By A Quarter Among Those Over 75 Years Old

Statins, pills that are known to lower cholesterol may reportedly reduce the risk of early death among people over the age of 75 years old.

Jul 8, 2020

For Older People, Reassuring News in the Statin Debate

There is accumulating evidence that the benefits of statins far outweigh possible risks, and nearly all statins on the market are now available as inexpensive generics.

The side effects of statins leave many patients and doctors wary – despite their lifesaving capabilities

... the American College of Cardiology, statins use was not associated with a decline in memory or cognition over a six-year period in an elderly ...

May 4, 2020
Statins Are Effective for...

- Secondary prevention of CV events in those w/CVD
- Primary prevention of CV events up to age 75
- Primary prevention over age 75, particularly in the setting of multiple chronic conditions
- Other common conditions such as MCI/dementia, functional decline, or HFpEF

A healthy 80-year-old has 8-9 additional years of life.
Use of statins for primary and secondary prevention is increasing over time, but still low.

**Older adults (>79 years)—Medical Expenditure Panel (AHRQ, CDC)**

- N=1,722,860
- 16% DM (N=282,932)
- 63% female (N=1,078,333)

**Statin Users**
- 31% on a statin (mostly prevalent use)
- 51% of DM on a statin

**Older Adults (≥75 years) without CVD (PCORnet)**

- N=1,722,860
  - 16% DM (N=282,932)
  - 63% female (N=1,078,333)

**Statin Users**
- 31% on a statin (mostly prevalent use)
- 51% of DM on a statin

Johannsen et al JAMA IM 2015.
Older Populations Are at Risk for...

- ✔ Cognitive impairment and dementia
- ✔ Frailty and mobility limitations
- ✔ Multi-factorial contributions of acute and chronic conditions
- ☐ Treatments to reverse cognitive impairment and disability

Best bet is effective prevention.
We need more data – trials are coming!

**PREVENTABLE Trial:** Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults

Will enroll 20,000 adults ≥75, free of dementia, disability, and CVD - Atorvastatin vs placebo
PREVENTABLE
Pragmatic Goal

• Get the right drug to the right people
  • Clarifying the effectiveness of statins for improving health of older adults w/o CVD
  • Ask if effective vascular prevention reduces risk of other common conditions of aging (MCI or dementia, disability, or HFpEF)

• Identify who should start taking a statin and who should stop
Individualizing care for older adults
"Because of your age, I’m going to recommend doing nothing."
Preventing cardiovascular disease in older adults:
One size does not fit all
Gait speed, the “6th vital sign”, is a quick way to measure frailty anywhere.
Improvement in gait speed by 0.1 m/s can decrease 1 year mortality by 10%.
Gait Speed Assessment

Frailty cut off:
4m in <5 seconds (0.8m/s)

Mobility Assessment in Older Adults

Kirstyn James, M.D., Andrea Wershof Schwartz, M.D., M.P.H.,
and Ariela R. Orkaby, M.D., M.P.H.
Our patients
Patient 1 Mr. J

- 82M, independent, hiker
- HTN, glaucoma, family history of CVD
- Former smoker, glass of wine with dinner
- **Medications**: Amlodipine 5mg, Rosuvastatin 20mg, Latanoprost drops
- **Total Cholesterol**: 180 mg/dL
- **LDL-C**: 70 mg/dL
- **HDL-C**: 60 mg/dL
- **Triglycerides**: 95 mg/dL

4m gait speed: 3.2 sec = 1.25 m/s

Robust/Non-frail
- Maintenance of activity
- Continue statin
Patient 2: Ms. G

- 80F, independent, uses cane for stability
- HTN, HL, DM, anxiety, arthritis, h/o colon cancer
- Former smoker, no alcohol
- **Medications:** Metformin 1000mg, Losartan 50mg, Sertraline 50mg, Acetaminophen 1000mg
- **Total Cholesterol:** 240 mg/dL
- **LDL-C:** 189 mg/dL
- **HDL-C:** 55 mg/dL
- **Triglycerides:** 199 mg/dL

4m gait speed: 5.3 sec = 0.75 m/s

- Encourage activity, PT to improve mobility
- Nutrition review
- Consider adding a statin
Patient 3: Mrs. Y

- 81F, wheelchair for distance
- Assistance with bathing, dressing
- AF, HTN, HL, mild dementia, CKD, osteoporosis, malnutrition, urinary incontinence
- Never smoker, no alcohol
- **Medications:** Donepezil 10mg, Lisinopril 5mg, Pravastatin 20mg, Oxybutinin 10mg, Warfarin 5mg, Vitamin B12, Alendronate 70mg/wk
- **Total Cholesterol:** 220 mg/dL
- **LDL-C:** 130 mg/dL
- **HDL-C:** 40 mg/dL
- **Triglycerides:** 150 mg/dL

4m gait speed: 9.6 sec = 0.42m/s

**Frail**
- Encourage activity, diet may need to be liberalized
- Unlikely to benefit from statin treatment
Bottom Line

• Age is the driving risk factor for CVD, risk calculators are unhelpful
• Everyone benefits from lifestyle improvement
• Consider frailty and function before prescribing
• In those without a life limiting illness:
  • Consider low-intensity, low dose statin trial
    e.g. pravastatin 10mg
    -- Start low, go slow ... but get there!
  • Change in LDL is more important than a target
  • If HDL is low and/or TGs are high consider adding meds
• In those with life limiting disease: deprescribing statins is appropriate
Statins for Primary Prevention in Older Adults

July 27, 2022
Ariela R. Orkaby, MD, MPH
aorkaby@bwh.harvard.edu
J-shaped relationship between cholesterol and mortality – largely driven by end-stage diseases (e.g. cancer, heart failure)

New evidence: Elevated LDL is associated with an increased risk of ASCVD, especially in late life.
For every 39 mg/dL (1.0 mmol/L) increase in LDL, the risk of an MI/ASCVD event rises, with the highest rates in those over age 80.

There is a linear relationship between lower LDL and risk of major vascular events.

Statins, Sub-clinical CVD, and Age: The role of Coronary Artery Calcium for risk stratification