STATIN THERAPY IN THE ELDERLY: THERE ARE MILES TO GO BEFORE WE SLEEP

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DISCLOSURES

Speakers Bureau: Amarin, AstraZeneca, GSK, Genzyme, Kowa, Merck
Consultant: Amgen, AstraZeneca, Kowa, Merck, Novartis, Regeneron-Sanofi
Advancing age is a risk factor for the development of CHD, and approximately 85% of persons who die of CHD are age 65 yrs or older. (1,2)

Older patients are much more likely to have established CAD and other forms of atherosclerotic disease given the presence of multiple comorbidities such as diabetes, hypertension, dyslipidemia, sedentary lifestyle, obesity.

Data on older patients from prospective randomized trials are much more limited than for younger people in both primary and secondary prevention settings.

(1) American Heart Association 2014 Heart and Stroke Statistical Update.
CARDIOVASCULAR DISEASE AND THE ELDERLY

- Despite a plethora of data demonstrating the benefits of treating hyperlipidemia, there is a long-standing trend toward underdiagnosing and undertreating dyslipidemia in the elderly. (1)
- Only 40-60% of patients over 65 are prescribed a statin after an acute MI. (2)
- Treatment recommendations should be individualized and take into account multiple factors including cardiovascular risk, life expectancy, frailty, comorbid conditions, cognitive capacity, and potential for drug-drug interactions.

Relation Between Proportional Reduction in Incidence of Major CVD Events & Mean Absolute LDL-C Reduction at Year 1*

0% 10% 20% 30% 40% 50% 60%

Proportional Reduction in CHD Event Rate

0 20 40 60 80

Reduction in LDL-C level (mg/dL)

1 mmol/L reduction in LDL-C results in 20% reduction in CVD risk at 1 yr

n= >90,000
>45,000 on statin  >45,000 on placebo

*Meta-analysis of 14 statin trials (CTT collaborators)

CONCLUSIONS The reductions of LDL-C, non-HDL-C, and apoB levels achieved with statin therapy displayed large interindividual variation. Among trial participants treated with high-dose statin therapy, >40% did not reach an LDL-C target <70 mg/dl. Patients who achieve very low LDL-C levels have a lower risk for major cardiovascular events than do those achieving moderately low levels. (J Am Coll Cardiol 2014;64:485-94) © 2014 by the American College of Cardiology Foundation.

When LDL-C is reduced to 50 mg/dL or lower, the risk for CV events is reduced by more than half.

# Early Onset of Atherosclerosis: Coronary Atherosclerosis in Male Trauma Victims

<table>
<thead>
<tr>
<th>Study Group</th>
<th>N</th>
<th>Mean Age (yr)</th>
<th>Atherosclerosis Incidence (%)</th>
<th>Cross-Sectional Area Narrowing (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enos et al(^1) (Korean War)</td>
<td>300</td>
<td>22.1</td>
<td>77.3</td>
<td>—</td>
</tr>
<tr>
<td>Virmani et al(^2) (Korean War)</td>
<td>94</td>
<td>20.5</td>
<td>56.0</td>
<td>19.0</td>
</tr>
<tr>
<td>McNamara et al(^3) (Vietnam War)</td>
<td>105</td>
<td>22.1</td>
<td>45.0</td>
<td>—</td>
</tr>
<tr>
<td>Joseph et al(^4) (University of Louisville)</td>
<td>95</td>
<td>25.6</td>
<td>75.8</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Ruptured plaque with hemorrhage and thrombus in lumen

Occlusive thrombus with several layers

Inflamed plaque (Di Sciascio, Am Heart J, 1994)
Expected % decrease in IHD events based on decrease in LDL-C and age based on 10 largest cohort studies

<table>
<thead>
<tr>
<th>LDL-C ↓ mmol/L</th>
<th>0.6</th>
<th>1.4</th>
<th>2.2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>50 yrs</strong></td>
<td>39%</td>
<td>68%</td>
<td>84%</td>
</tr>
<tr>
<td><strong>60 yrs</strong></td>
<td>27%</td>
<td>52%</td>
<td>68%</td>
</tr>
<tr>
<td><strong>70 yr</strong></td>
<td>20%</td>
<td>41%</td>
<td>56%</td>
</tr>
</tbody>
</table>

ASCVD Statin Benefit Groups

Heart healthy lifestyle habits are the foundation of ASCVD prevention in individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 yr in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

Adults age >21 y and a candidate for statin therapy

Clinical ASCVD

Yes

Age ≤75 y
High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

Age ≤75 y OR if not candidate for high-intensity statin
Moderate-intensity statin

LDL-C ≥190 mg/dL

No

High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

Diabetes Type 1 or 2 Age 40-75 y

Yes

Estimated 10-y ASCVD risk ≥7.5%
High-intensity statin

No

Moderate-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy

High
Daily dose lowers LDL-C by approx ≥50%

Moderate
Daily dose lowers LDL-C by approx 30% to 50%

Initiation of Statin Therapy ASCVD

Clinical ASCVD

Not currently on statin therapy

- Fasting lipid panel
- ALT
- CK (if indicated)
- Consider evaluation for other secondary causes or conditions that may influence statin safety

Aged ≤75 y
without contraindications, conditions or drug-drug interactions influencing statin safety, or a history of statin intolerance

Initiate high-intensity statin therapy
Counsel on healthy lifestyle habits

Aged >75 y
with conditions, or drug-drug interactions influencing statin safety, or a history of statin intolerance

Initiate moderate-intensity statin therapy
Counsel on healthy lifestyle habits

Monitor statin therapy

Evaluate and Treat Laboratory Abnormalities

1. Triglycerides ≥500 mg/dL
2. LDL-C ≥190 mg/dL
   - Secondary causes
     - If primary, screen family for FH
3. Unexplained ALT >3X ULN

CK = creatine kinase.
Change in Statin Intensity Pre- and Post-Hospitalization for Acute Coronary Syndrome

ELIGIBILITY: MRC/BHF Heart Protection Study

- Increased risk of CHD death due to prior disease:
  - Myocardial infarction or other coronary heart disease;
  - Occlusive disease of non-coronary arteries; or
  - Diabetes mellitus or treated hypertension

- Age 40-80 years

- Total cholesterol $\geq 3.5$ mmol/l ($\geq 135$mg/dl)

- Statin or vitamins not considered clearly indicated or contraindicated by patient’s own doctors
# AGE & SEX at BASELINE

<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>9839</td>
<td>48%</td>
</tr>
<tr>
<td>65-69</td>
<td>4891</td>
<td>24%</td>
</tr>
<tr>
<td>70-74</td>
<td>4543</td>
<td>22%</td>
</tr>
<tr>
<td>&gt;74</td>
<td>1263</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15,454</td>
<td>75%</td>
</tr>
<tr>
<td>Female</td>
<td>5082</td>
<td>25%</td>
</tr>
</tbody>
</table>
### SIMVASTATIN: MAJOR VASCULAR EVENT by AGE & SEX

<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>SIMVASTATIN (10269)</th>
<th>PLACEBO (10267)</th>
<th>Rate ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65</td>
<td>831 (16.9%)</td>
<td>1091 (22.1%)</td>
<td>STATIN better</td>
</tr>
<tr>
<td>65 - 69</td>
<td>512 (20.9%)</td>
<td>665 (27.2%)</td>
<td>PLACEBO better</td>
</tr>
<tr>
<td>70 - 74</td>
<td>548 (23.8%)</td>
<td>620 (27.7%)</td>
<td></td>
</tr>
<tr>
<td>≥ 75</td>
<td>142 (23.1%)</td>
<td>209 (32.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1666 (21.6%)</td>
<td>2135 (27.6%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>367 (14.4%)</td>
<td>450 (17.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>24% SE 3 reduction</td>
</tr>
</tbody>
</table>

(2P<0.00001)
Pravastatin in Elderly Individuals at Risk of Vascular Disease

Presented at Late Breaking Clinical Trials

AHA 2002
PROSPER

5,804 high-risk elderly patients

- Age 70–82 years
- Pre-existing vascular disease (coronary, cerebral, or peripheral)
- High-risk for vascular disease (smoking, hypertension, or diabetes)
- Total cholesterol 4.0–9.0 mmol/L
- Triglyceride < 6.0 mmol/L

Pravastatin
40 mg per day
n = 2,891

Placebo
n = 2,913

Endpoints:
- Primary – composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke

Average follow-up = 3.2 years

Lancet 2002; 360: 1623–30
PROSPER: CLINICAL EVENTS*

CV Death / MI / Stroke
P = 0.014

CV Death / MI
P = 0.006

CV Death
P = 0.043

Stroke
P = 0.047

Pravastatin
Placebo

* Mean follow-up = 3.2 years

Lancet 2002; 360: 1623–30
The PROSPER trial was the first major study to show a benefit with a lipid-lowering agent specifically in high-risk elderly patients.

- The primary endpoint of CV Death / MI / stroke was reduced significantly in the pravastatin arm.
- All components of the endpoint showed a benefit with pravastatin.
- The major safety concern was the increased rate of any cancer in the pravastatin arm, which was not confirmed in a meta-analysis.
Bayesian Forest Plot for All-Cause Mortality

Statin therapy reduced the incidence of all-cause mortality by 22% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 28.
Bayesian Forest Plot for Coronary Heart Disease Mortality

Statin therapy reduced the incidence of coronary heart disease mortality by 30% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 34.
Bayesian Forest Plot for Nonfatal Myocardial Infarction

Statin therapy reduced the incidence of nonfatal myocardial infarction by 26% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 38.
Bayesian Forest Plot for Revascularization

Statin therapy reduced the need for revascularization (percutaneous coronary intervention or aortocoronary bypass surgery) by 30% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 24.
Statins for Secondary Prevention in Elderly Patients: A Hierarchical Bayesian Meta-Analysis


Bayesian Forest Plot for Stroke

Statin therapy reduced the incidence of stroke by 25% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 58.
Figure Legend:

RRs of Myocardial Infarction and Stroke
Gray squares represent relative risks (RRs) in trials. The 95% confidence intervals (CIs) for individual trials are denoted by lines and those for the pooled RRs by open diamonds. Meta-analysis is performed by fixed effects model. AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; JUPITER = Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk.
**Figure Legend:**

**RRs of All-Cause Death and Cardiovascular Death**

Gray squares represent RRs in trials. The 95% CIs for individual trials are denoted by lines and those for the pooled RRs by open diamonds. Meta-analysis is performed by fixed effects model. Abbreviations as in Figure 2.
EFFICACY OF STATIN THERAPY IN DIABETIC AND NONDIABETIC OLDER PERSONS

- 5152 men and women from the Age, Gene/Environment Susceptibility-Reykjavik Study, mean age 77 years, range of 66-96 years.
- Main outcome measure: Cardiovascular and all cause mortalities and the RR of dying according to statin use and history of coronary heart disease (CHD) in persons with type 2 diabetes and those without diabetes with a median follow-up time of 5.3 years,
- Statin use was associated with a 50% (95% CI 8% to 72%) lower cardiovascular mortality and 53% (29% to 68%) lower all-cause mortalities in persons with diabetes.
- For those without diabetes, statin use was associated with a 16% lower cardiovascular and 30% lower all-cause mortalities. Persons with diabetes using statins had a comparable risk of cardiovascular and all-cause mortality to that of the general population without diabetes.
- The effect was independent of the level of glycemic control.
- These data suggest that in the general population of older people with diabetes, statin medication markedly reduces the excess cardiovascular and all-cause mortality risk, irrespective of the presence or absence of coronary heart disease or glucose-lowering medication.

(A) Cardiovascular disease (CVD) mortality and (B) all-cause mortality per 1000 person years for subjects without type 2 diabetes (not T2D) and with type 2 diabetes (T2D) according to statin use and prevalent coronary heart disease (CHD).

### A. Cardiovascular Disease Mortality

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Deaths</th>
<th>N</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>not T2D</td>
<td>359</td>
<td>4513</td>
<td>6.9</td>
</tr>
<tr>
<td>not T2D with chd not on statins</td>
<td>33</td>
<td>156</td>
<td>11.9</td>
</tr>
<tr>
<td>not T2D with chd on statins</td>
<td>48</td>
<td>491</td>
<td>9.0</td>
</tr>
<tr>
<td>not T2D without chd not on statins</td>
<td>255</td>
<td>3438</td>
<td>6.7</td>
</tr>
<tr>
<td>not T2D without chd on statins</td>
<td>23</td>
<td>428</td>
<td>5.7</td>
</tr>
<tr>
<td>T2D</td>
<td>87</td>
<td>639</td>
<td>10.3</td>
</tr>
<tr>
<td>T2D with chd not on statins</td>
<td>18</td>
<td>50</td>
<td>24.6</td>
</tr>
<tr>
<td>T2D with chd on statins</td>
<td>12</td>
<td>99</td>
<td>11.3</td>
</tr>
<tr>
<td>T2D without chd not on statins</td>
<td>51</td>
<td>366</td>
<td>10.1</td>
</tr>
<tr>
<td>T2D without chd on statins</td>
<td>6</td>
<td>124</td>
<td>5.2</td>
</tr>
</tbody>
</table>

### B. All-Cause Mortality

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Deaths</th>
<th>N</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>not T2D</td>
<td>874</td>
<td>4513</td>
<td>21.5</td>
</tr>
<tr>
<td>not T2D with chd not on statins</td>
<td>58</td>
<td>156</td>
<td>29.0</td>
</tr>
<tr>
<td>not T2D with chd on statins</td>
<td>93</td>
<td>491</td>
<td>19.2</td>
</tr>
<tr>
<td>not T2D without chd not on statins</td>
<td>666</td>
<td>3438</td>
<td>22.9</td>
</tr>
<tr>
<td>not T2D without chd on statins</td>
<td>57</td>
<td>428</td>
<td>16.0</td>
</tr>
<tr>
<td>T2D</td>
<td>178</td>
<td>639</td>
<td>29.1</td>
</tr>
<tr>
<td>T2D with chd not on statins</td>
<td>31</td>
<td>50</td>
<td>63.3</td>
</tr>
<tr>
<td>T2D with chd on statins</td>
<td>27</td>
<td>99</td>
<td>27.8</td>
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<tr>
<td>T2D without chd not on statins</td>
<td>105</td>
<td>366</td>
<td>29.5</td>
</tr>
<tr>
<td>T2D without chd on statins</td>
<td>15</td>
<td>124</td>
<td>14.5</td>
</tr>
</tbody>
</table>

Elin Olafsdottir et al. BMJ Open 2011;1:e000132
EFFICACY OF STATIN THERAPY IN OLDER PERSONS IN AUSTRALIA

- Community-dwelling men participating in the Concord Health and Ageing in Men Project, Sydney, Australia. Men aged ≥70 years (n=1665).
- Data collected during baseline assessments and follow-up (maximum of 6.79 years) were obtained.
- At baseline, 43% of participants reported taking statins. Over 6.79 years of follow-up, 132 (7.9%) participants were institutionalized and 358 (21.5%) participants had died.
- In the adjusted models, baseline statin use was not statistically associated with increased risk of institutionalization (HR=1.60; 95% CI 0.98 to 2.63) or death (HR=0.88;95% CI 0.66 to 1.18).
- There was no significant association between duration and dose of statins used with either outcome.

Kaplan-Meier survival curves for the time until institutionalisation (log-rank test, p<0.0001) and death (log-rank test, p<0.0001) by reported statin exposure and frailty.

EFFICACY OF STATIN THERAPY IN PERSONS UP TO AGE 90

- A representative sample (born 1920–1921) from the Jerusalem Longitudinal Cohort Study (1990–2010) was assessed at ages 70, 78, and 85 for fasting serum TC, low-density (LDL), and high-density lipoprotein (LDL); triglycerides; statin usage; social, functional, and medical domains; and all-cause mortality data (1990–2010).
- Survival was significantly increased among subjects treated with statins versus no statins at ages 78 to 85 (74.7% vs 64.3%, log rank P = .07) and 85 to 90 (76.2% vs 67.4%, P = .01).
- After adjustment, TC was not associated with mortality from 70 to 78, 78 to 85, or 85 to 90.
- Among older people, cholesterol levels were unrelated to mortality between the ages of 70 and 90. The protective effect of statins observed among the very old appears to be independent of TC.

- J.M. Jacobs et al. / JAMDA 14 (2013) 883e888
Jerusalem Longitudinal Cohort Study

Age 78-85
Log-rank $P = .07$

Age 85-90
Log-rank $P = .01$
Cognitive Impairment and Dementia Development in the Heart Protection Study

HPS included men and women 40-80 years of age with non-fasting TC > 135 mg/dL and medical history of cerebrovascular disease, coronary disease, other occlusive arterial disease, diabetes mellitus or treated hypertension. Subjects were randomly assigned to statin or placebo for about 5 years and seen in the clinic at 4, 8, and 12 months and then every 6 months. Cognitive impairment and dementia were assessed at the final follow-up using the modified Telephone Interview for Cognitive Status (TICS-m); 89% of subjects were assessed in the clinic and 11% by telephone. A score below 22 out of 39 was indicative of some cognitive impairment; N = 20,536

Pravastatin and cognitive function in the elderly (PROSPER)

- 5,804 patients, mean age 75.4 y

*J Neurol.* 2010 Jan;257(1):85-90
CONCLUSIONS

- There appears to be consistent benefit of statin therapy in the elderly.
- There is little to no evidence discernible from clinical trials using other classes of lipid lowering agents, though data will be forthcoming from the IMPROVE-IT trial for ezetimibe use.
- Benefit from statins is demonstrated in subgroup analyses of individual prospective randomized clinical trials, meta-analyses, and prospective observational cohorts in multiple nations around the world.
- Clinical judgement should prevail whenever prescribing statin therapy in the very old (>85-90 yrs) and patients who are frail or have significant disability or visceral organ insufficiency, such as hepatic dysfunction or significant chronic kidney disease.