# Statins after 80 years old

## Pros/Cons symposium

## 13th EUGMS Congress
## Nice 20-22 Sept 2017

Athanasios Benetos

**Conflict of interest:**

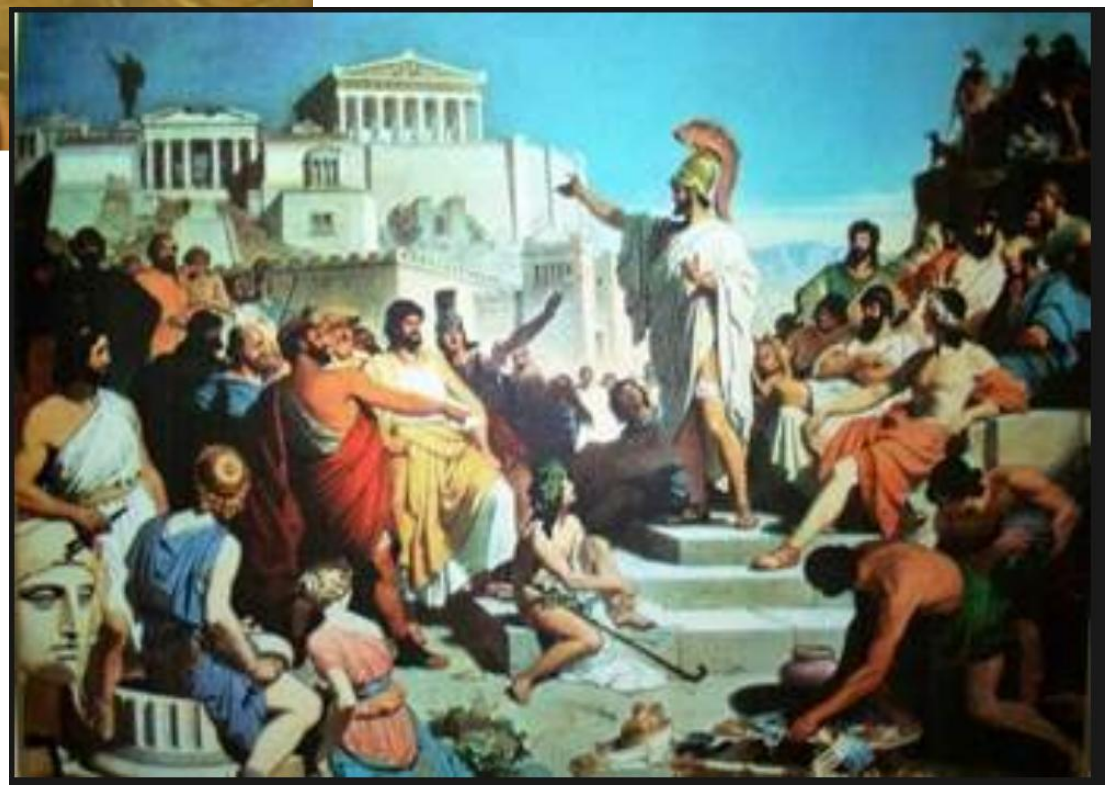
None

The Statinissean War

# Two fearless fighters

Athanasios
the Athenian

Timotheus
the Spartian



**Let’s try to**

**Think…**

# Which are …:

- cholesterol-related risks
- benefits of statins
  - Primary prevention
  - Secondaty prevention
- statin-related side effects

…in people >80 years?

# High cholesterol-related risks in the very old

# Total cholesterol and mortality
## (The Framingham Study)

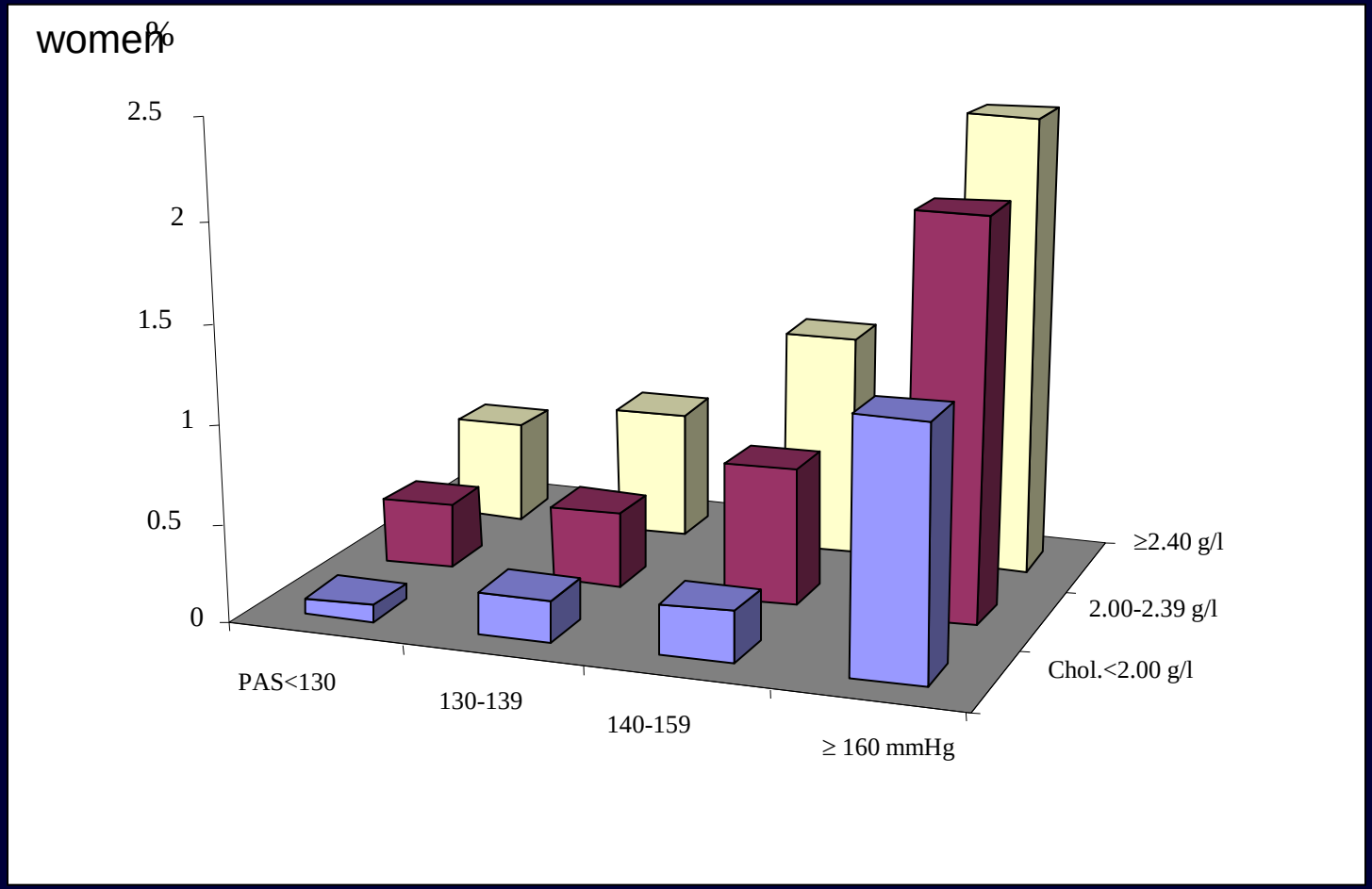
| age | relationship |
|---|---|
| <40 | ++ |
| 50-70 | 0 |
| >80 | - |

RA Kronmal et al. Arch Int Med 1993

# No positive association between total cholesterol and mortality after the age of 65

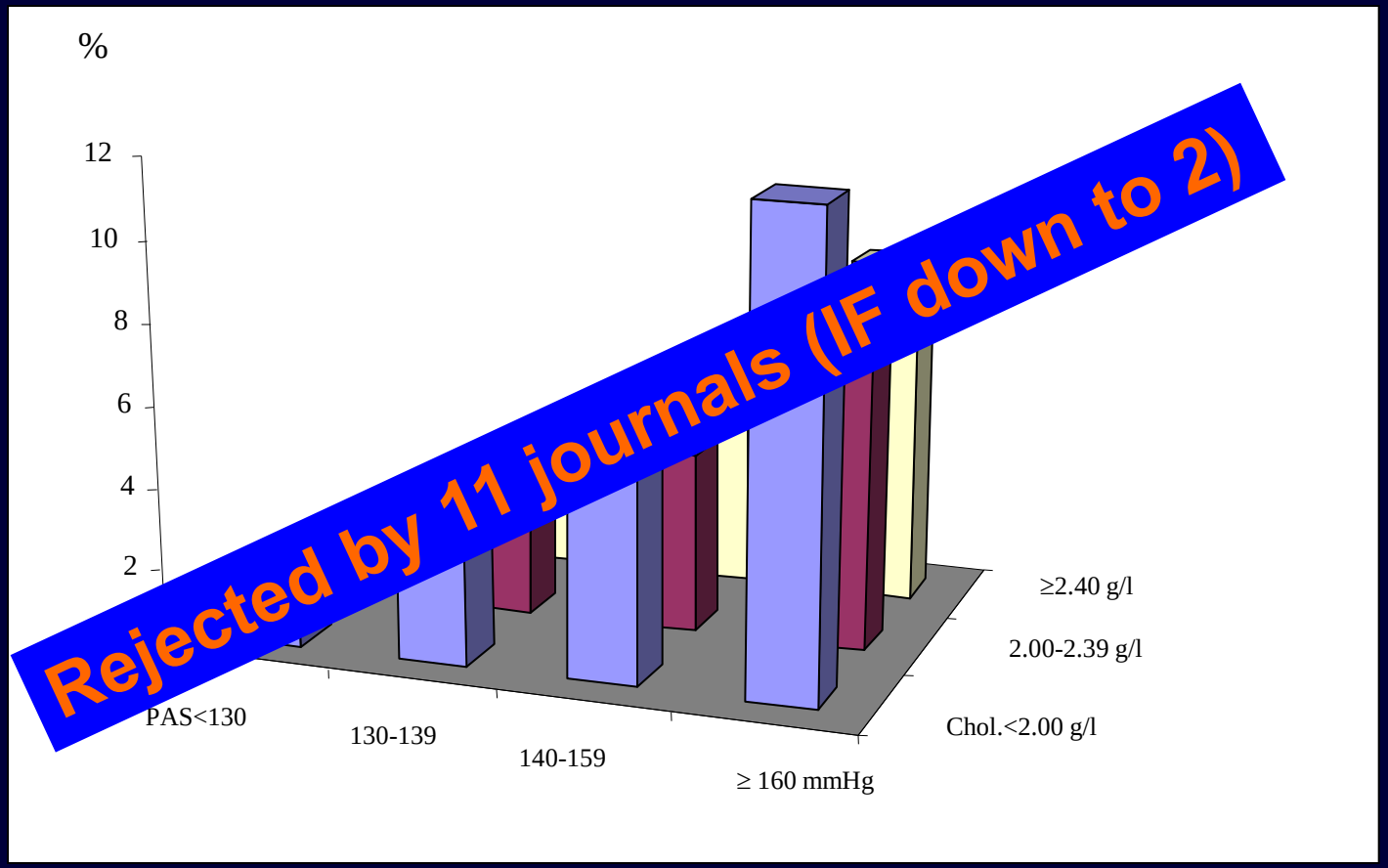
- Krumholz HM, et al. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. JAMA. 1994
- Weverling Rijnsburger AW et al, The Rotterdam Study: Lancet, 1997
- Scats IJ et al; Honolulu Heart Program. Lancet 2001
- Brescianin S et al; Italian Longitudinal Study on Aging. J Am Geriatr Soc. 2003
- Schupf N et al; Northern Manhattan Study J Am Geriatr Soc. 2005
- Melton PE et al; Mennonite community J Hum Biol. 2006
- Spada RS et al ; Sicilian study Arch Gerontol Geriatr. 2007

# CVD mortality rates according to SBP and Total Cholesterol in >108,000 men <55 years




F. Thomas et al, *Eur Heart J*, 2002

# CVD mortality rates according to SBP and Total Cholesterol in15,884 men ≥ 55 ans




F. Thomas et al

# Beneficial effects of statins in older adults?

# JUPITER
# in the “older group”
# >70; mean 74 years

- Rosuvastatin therapy had significant:
- - **beneficial effects for CVD morbidity and mortality** (HR: 0.61 [95% CI, 0.46–0.82]),
- …**but rates of all-cause death did not differ significantly between the statin group and the placebo** group.

Glynn RJ, et al. Rosuvastatin for primary prevention in older …
Ann Intern Med. 2010; 152(8):488–496.

# HOPE 3
# in the “older group”
# > 65; mean 71 years)

- **Statin reduced the risk for the composite outcome of death from cardiovascular causes and nonfatal myocardial infarction or stroke: HR: 0.75 [95% CI, 0.61–0.93]).**

Yusuf S et al. HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016; 374(21):2021–2031.

# PROSPER Study
# aged 70-82 years (mean 75 years)

- Pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals.
- No effect on total mortality
- No effect on strokes
- Slight though statistically significant increase in cancers

Shepherd J et al Lancet. 2002 Nov 23;360(9346):1623-30.

# Etude PROSPER

## Incidence of primary end point, according to subgroup

| | Placebo | | Pravastatin | | Hazard ratio (95% CI) | p* |
|---|---|---|---|---|---|---|
| | Total number | Number with event (%) | Total number | Number with event (%) | | |
| Previous vascular disease† | | | | | | |
| No | 1654 | 200 (12·1) | 1585 | 181 (11·4) | 0·94 (0·77–1·15) | 0·19 |
| Yes | 1259 | 273 (21·7) | 1306 | 227 (17·4) | 0·78 (0·66–0·93) | |
| Sex | | | | | | |
| Female | 1505 | 194 (12·9) | 1495 | 186 (12·4) | 0·96 (0·79–1·18) | 0·13 |
| Male | 1408 | 279 (19·8) | 1396 | 222 (15·9) | 0·77 (0·65–0·92) | |
| LDL cholesterol (mmol/L) | | | | | | |
| <3·41 | 978 | 158 (16·2) | 972 | 137 (14·1) | 0·88 (0·80–1·10) | 0·69 |
| 3·41–4·11 | 1000 | 173 (17·3) | 956 | 153 (16·0) | 0·88 (0·70–1·10) | |
| >4·11 | 935 | 142 (15·2) | 963 | 118 (12·3) | 0·77 (0·60–0·98) | |
| HDL cholesterol (mmol/L) | | | | | | |
| <1·11 | 1035 | 200 (19·3) | 1016 | 132 (13·0) | 0·64 (0·52–0·80) | 0·0069 |
| 1·11–1·37 | 925 | 162 (17·5) | 926 | 155 (16·7) | 0·93 (0·75–1·16) | |
| >1·37 | 953 | 111 (11·6) | 949 | 121 (12·8) | 1·09 (0·84–1·41) | |
| Current smoker | | | | | | |
| No | 2108 | 348 (16·5) | 2138 | 293 (13·7) | 0·81 (0·69–0·95) | 0·30 |
| Yes | 805 | 125 (15·5) | 753 | 115 (15·3) | 0·96 (0·74–1·24) | |
| History of hypertension | | | | | | |
| No | 1120 | 190 (17·0) | 1092 | 162 (14·8) | 0·85 (0·69–1·05) | 0·91 |
| Yes | 1793 | 283 (15·8) | 1799 | 246 (13·7) | 0·84 (0·71–1·00) | |
| History of diabetes | | | | | | |
| No | 2593 | 414 (16·0) | 2588 | 338 (13·1) | 0·79 (0·69–0·91) | 0·015 |
| Yes | 320 | 59 (18·4) | 303 | 70 (23·1) | 1·27 (0·90–1·80) | |

*p for interaction values for heterogeneity of treatment across subgroups. †Any of stable angina or intermittent claudication, or stroke, transient ischaemic attack, myocardial infarction, arterial surgery, or amputation for vascular disease more than 6 months before study entry.

Shepherd J et al Lancet. 2002 Nov 23;360(9346):1623-30.

JAMA Internal Medicine | Original Investigation

# Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults
## The ALLHAT-LLT Randomized Clinical Trial

Benjamin H. Han, MD, MPH; David Sutin, MD; Jeff D. Williamson, MD; Barry R. Davis, MD, PhD; Linda B. Piller, MD, MPH; Hannah Pervin, PhD; Sara L. Pressel, MS; Caroline S. Blaum, MD; for the ALLHAT Collaborative Research Group

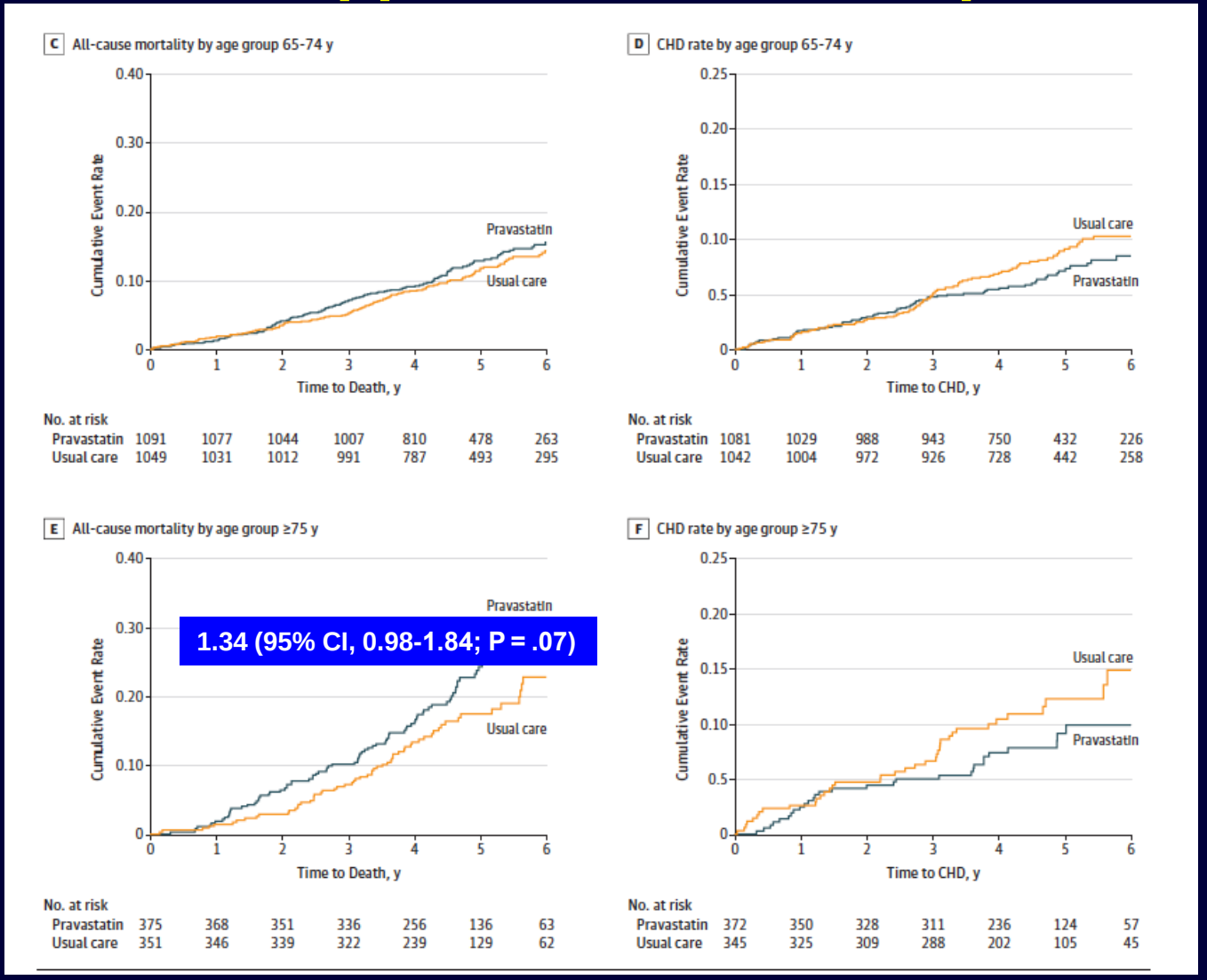
JAMA Intern Med. 2017;177(7):955-965.

# Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial

- To examine statin treatment among adults aged 65 to 74 years and 75 years and older when used for primary prevention in the Lipid-Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT).
- Post hoc secondary data analyses
- participants 65 years and older without evidence of atherosclerotic cardiovascular disease;
- 2867 ambulatory adults with hypertension and without baseline atherosclerotic cardiovascular disease
- The ALLHAT-LLT was conducted from February 1994 to March 2002 at 513 clinical sites.

Han BH et al, ALLHAT Collaborative Research Group *JAMA Intern Med*. 2017;177:955-965.

# Further analysis in 2 age groups: 65-74, upper and >75 lower panel




Han BH et al, ALLHAT Collaborative Research Group JAMA Intern Med. 2017;177:955-965.

## Key Points

**Question** Are statins beneficial when used for primary cardiovascular prevention in older adults?

**Findings** In this post hoc secondary analysis of older adults in the randomized clinical trial Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial (ALLHAT-LLT), there were no significant differences in all-cause mortality or cardiovascular outcomes between pravastatin sodium and usual care for primary prevention for adults 65 years and older.

**Meaning** No benefit was found when a statin was given for primary prevention to older adults. Treatment recommendations should be individualized for this population.

*JAMA Intern Med*. 2017;177(7):955-965.

# Interest for treating with statins the older adults >75 years

**No benefits in primary prevention**

**Some evidence for secondary prevention in patients 70-82**

# What about after 80 years old ?

## Effect of Statin Therapy on Mortality in Older Adults Hospitalized with Coronary Artery Disease: A Propensity-Adjusted Analysis

*Daniel P. Rothschild, MD, Eric Novak, MS, and Michael W. Rich, MD*

J Am Geriatr Soc 64:1475–1479, 2016.

# No difference on mortality between statin users vs. non-users after acute coronary disease in patiients over 80 years old

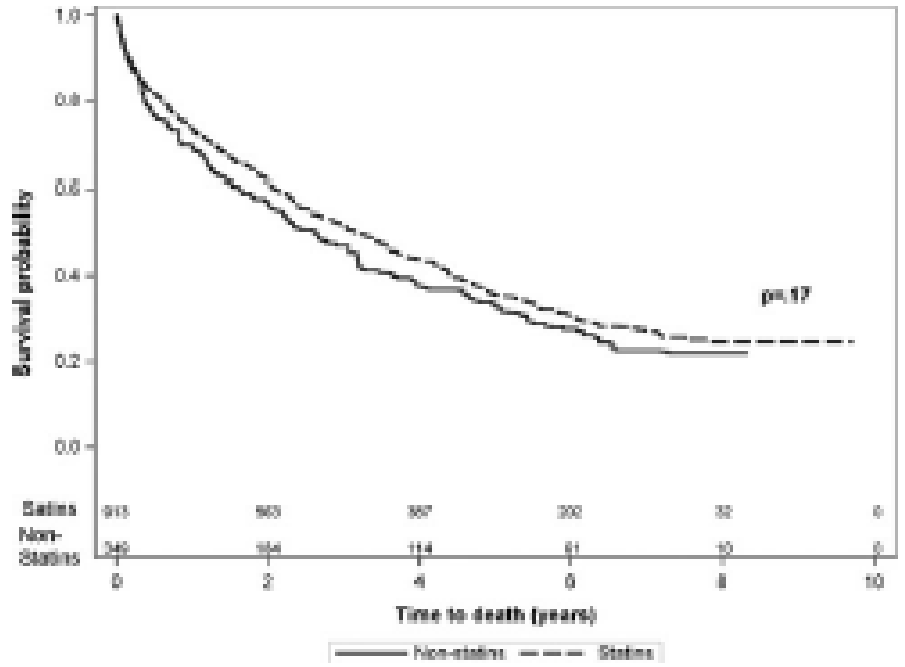



Figure 2. Inverse propensity treatment-weighted survival curves.

J Am Geriatr Soc 64:1475–1479, 2016.

# Risks of statins in the older

Original Investigation

# Statins and Musculoskeletal Conditions, Arthropathies, and Injuries

Ishak Mansi, MD; Christopher R. Frei, PharmD, MSc; Mary Jo Pugh, PhD; Una Makris, MD; Eric M. Mortensen, MD, MSc

**Table 4. Outcomes in Statin Users in Comparison With Similar Nonusers in the Propensity Score–Matched Cohort**

| Outcome[a] | No. (%) | | OR (95% CI) | *P* Value |
|---|---|---|---|---|
| | Statin Users | Nonusers | | |
| Msk1, all musculoskeletal diseases | 6053 (86.9) | 5905 (84.8) | 1.19 (1.08-1.30) | <.001 |
| Msk1a, osteoarthritis/arthropathies | 5127 (73.6) | 5032 (72.2) | 1.07 (0.99-1.16) | .07 |
| Msk1b, dislocation/strain/sprain | 2452 (35.2) | 2265 (32.5) | 1.13 (1.05-1.21) | .001 |
| Msk2, musculoskeletal pain | 5113 (73.4) | 4989 (71.6) | 1.09 (1.02-1.18) | .02 |

JAMA Intern Med. 2013;173(14):1-10

Advancing age has been associated with increased risk of statin-induced muscle disorder across the entire spectrum, as well as with a significantly greater incidence of the more severe forms of this disorder reported among the oldest groups of statin users

Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Circulation. 2002;106:1024–1028

Gaist D, Rodríguez LA, Huerta C, Hallas J, Sindrup SH. Lipid-lowering drugs and risk of myopathy: a population-based follow-up study. Epidemiology. 2001;12:565–569.

# Risks of Statin Therapy in Older Adults

**Gregory Curfman, MD**
**Harvard Medical School, Boston, Massachusetts;**
**Health Care Policy and Law Editor,**
**JAMA Internal Medicine.**

The Medical Expenditure Panel Survey: In USA, statin use for primary prevention in adults older than 79 years increased more than 3-fold, from 8.8% in 1999-2000 to 34.1% in 2011-2012.

JAMA Intern Med. 2017;177(7):966.

# Statins and cognitive function 2012

FDA Drug Safety Communication
Important safety label changes to cholesterol-lowering statin drugs.

On 28 February 2012, the United States Food and Drug Administration (FDA) issued a new warning for the labeling of statin drugs regarding potential **adverse effects on cognition**, based on post-marketing surveillance reports, case reports, controlled trials (RCTs).

# Statins and cognitive function 2013

American College of Cardiology/American Heart Association Cholesterol Guideline safety statement

"for individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy."

Stone NJ, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol Circulation 2013 November 12

# Statins and cognitive function 2014

**American Medical Directors Association (AMDA)**

…recommended that statins not be routinely prescribed in adults aged 70 and older as a part of the American Board of Internal Medicine Choosing Wisely campaign.

This recommendation was based on the lack of association of high cholesterol levels and outcomes in older adults, as well as the potential for an increased risk of statin-related adverse events, including cognitive impairment, falls, neuropathy, and muscle damage.

AMDA. [Accessed April 22, 2014] Five Things Physicians and Patients Should Question. 2013. (http://www.amda.com/tools/choosingwisely.cfm)

# Statins and dementia 2002

- The use of statins is associated with a lower prevalence of dementia and has a positive impact on the progression of cognitive impairment.

Hajjar Iet al. J Gerontol A Biol Sci Med Sci. 2002 57:M414-8.

# Statins and dementia 2005

- **Statin drug use was associated with a slight reduction in cognitive decline in an elderly population. This relationship could not be completely explained by the effect of statins on lowering of serum cholesterol.**

Bernick C, et al; Cardiovascular Health Study Collaborative Research Group. Neurology. 2005;65:1388-94.

# In people >80 years?

- cholesterol-related risks — NO
- benefits of statins
  - Primary prevention — NO
  - Secondaty prevention — Yes (until 82…)
- statin-related side effects — YES

# Statins, the evidence :
# 3 more years (at least) to wait

The Australian STAREE (Statins in ReducingEvents In the Elderly) trial of atorvastatin calcium vs placebo in individuals older than 70 years is now in progress, and the results are expected in 2020.

http://www.staree.org.au

# The Population Impact and Cost-Effectiveness of Statins for Primary Prevention in Adults 75 and Older in the United States

**Michelle C. Odden, PhD[1], Mark J. Pletcher, MD, MPH[2], Pamela G. Coxson, PhD[3], Divya Thekkethala, B.S.[1], David Guzman, MS[3], David Heller, MD[3], Lee Goldman, MD, MPH[4], and Kirsten Bibbins-Domingo, PhD, MD[2,3]**

[1]School of Biological and Population Health Sciences, Oregon State University, Corvallis, OR

[2]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA

[3]Department of Medicine, University of California, San Francisco, CA

[4]College of Physicians and Surgeons, Columbia University, New York, NY, USA

Unlike previous analyses which showed that a large theoretical adverse effect would be required to counterbalance the cardiovascular benefits in the general population (28), our analysis showed that in older adults even a small adverse effect of statins on functional limitation and mild cognitive impairment could result in net harm. In our simulations, a 10–30% increased risk of these side effects would offset the cardiovascular benefit.

Our results provide strong motivation for further investigations into the incidence of side effects from statins in a diverse group of elders, including those who are frail and have complex comorbidity. Due to the sample size required to identify potential risks in a diverse population, pragmatic trials and improved post-marketing surveillance are the most promising approaches for this goal.

Ann Intern Med. 2015 April 21; 162(8): 533–541.

# Muscular effects of statins in the elderly female: a review

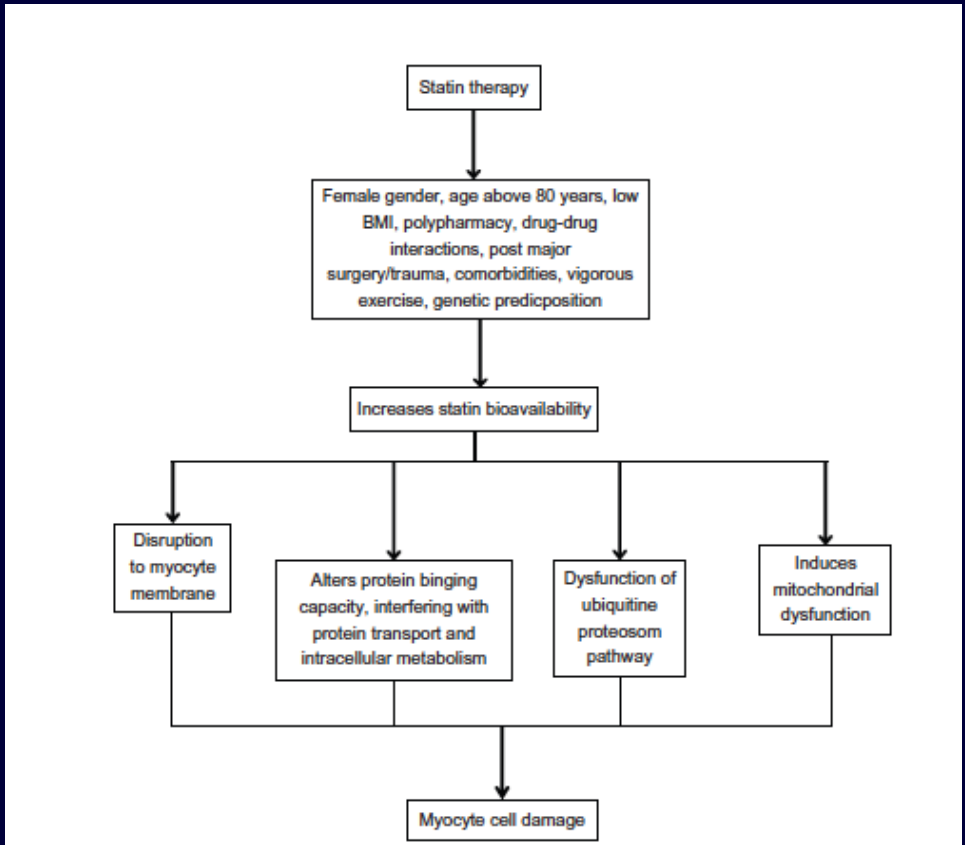



Figure 1 Conceptual diagram illustrating potential pathway by which statins induce myopathy.

Bhardwaj S et al, Clin Interv Aging. 2013;8:47-59.