PERSPECTIVE

Statinopause

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Statins are the cornerstone of lipid-lowering therapy for cardiovascular disease prevention. The 2013 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines represent a fundamental shift in how statins will be prescribed. The new guidelines recommend statins for nearly all older patients up to age 75 years, including healthy adults with low normal lipid levels and no atherosclerotic cardiovascular disease (ASCVD) risk factors other than age. Under the 2013 guidelines, age becomes a main determinant for initiating statin therapy for primary prevention among older adults. Specifically, according to the new guidelines, white males aged 63–75, white females aged 71–75, African American males aged 66–75, and African American females aged 70–75 with optimal risk factors would be recommended for statin treatment for primary prevention. Based on the new guidelines, one could term these older adults as having "statin deficiency," a condition warranting statin treatment. We call this putative condition of age-related statin deficiency "statinopause." After careful examination of the trial evidence, we find very little support for the new recommendations for primary prevention. The lack of evidence underscores the need for clinical trials to determine the risks and benefits of statin therapy for primary prevention among older adults.

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INTRODUCTION

The 2013 American College of Cardiology (ACC) and American Heart Association (AHA) lipid-lowering guidelines represent a major shift in the clinical practice of lipid management.[1] The new guidelines abandon the Adult Treatment Panel III (ATP III) guidelines[2] of treating patients to target low-density lipoprotein (LDL) levels. Instead, the new guidelines focus on patients' risk for atherosclerotic cardiovascular disease (ASCVD), defined as coronary heart disease (CHD), stroke, and peripheral arterial disease.[1]

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The new guidelines identify four groups of patients who are at high risk of ASCVD and may therefore benefit from statin therapy. These groups are: 1) patients with clinical ASCVD, 2) patients with LDL levels greater than 190 mg/dl, 3) patients with diabetes aged 40–75 years with LDL levels greater than 70 mg/dL, or 4) patients with an LDL over 70 mg/dl and a 10-year calculated ASCVD risk of 7.5 % or greater. The new guidelines also recommend considering statin therapy for patients aged 40–75 with a 10-year risk between 5 % and 7.5 %. New pooled cohort equations and a calculator[1] were developed to estimate the 10-year risk for ASCVD. The guidelines acknowledge a lack of data for primary prevention in patients over age 75, but the authors suggest that the pooled cohort equations could be used to help inform the treatment decision to age 79.

Many in the medical community have been very critical of the new guidelines for several reasons: 1) the algorithms used to calculate ASCVD risk are flawed,[3] 2) the 10-year risk calculator that would greatly, and unnecessarily, expand the pool of people subjected to statin therapy and its concomitant deleterious side-effects,[4] and 3) the potential bias related to the financial ties between drug manufacturers and the panel that promulgated the guidelines.[5] While the guidelines have been analyzed and critiqued from many angles, little has been written from the perspective of geriatric providers.

The geriatric population is the patient group most affected by the new guidelines. Using the 10-year ASCVD risk calculator with its stated optimal values for total cholesterol of 170 mg/dL, high-density lipoprotein (HDL) of 50 mg/dL, and systolic blood pressure of 110 mmHg, as well as the patient not taking medications for hypertension, not a diabetic, and not a smoker, all white males aged between 63 and 79, all white females aged between 71 and 79, all African American males aged between 66 and 79, and all African American females aged between 70 and 79 would be determined to be statin candidates for primary prevention. Age seems to be the major deciding factor for statin therapy in patients without any other risk factors. If the new guidelines are followed for primary prevention (an ASCVD risk of $\geq$ 7.5 %), essentially everyone in the population will at some time in their life be on a statin. The only segment of the population that would be excluded is people with an LDL less than 70 mg/dl. We see this as analogous to "menopause" for females. Just as menopause is largely driven by age and is inevitable, under the new lipid guidelines, every individual reaching a certain age becomes "statin deficient." Thus, we call this putative age-determined condition "statinopause."

Under the new guidelines, age 75 is the upper limit for "statinopause," but only for initiating therapy. No indications are given to discontinue statin therapy at age 75 if therapy has already commenced at a younger age. Because many people are started on statin therapy before age 75, under the new guidelines, they may continue taking statins indefinitely. Therefore, the upper limit of age 75 has little significance. As a result, the new guidelines impact statin use among even the oldest patients, although there are very few studies for patients older than 85 and no clear benefit for this age group.[7,8]

A recent study by Pencina et al.[9] compared the impact of the ATP-III guidelines with the new guidelines for treatment of cholesterol using the National Health and Nutrition Examination Surveys (NHANES) from 2005–2010. Pencina et al. found that the new guidelines potentially increase the net number of new statin prescriptions by 12.8 million, including 10.4 million for primary prevention. The majority of new users would be older adults. Therefore, Pencina et al. conclude that the new ACC/AHA guidelines would significantly increase statin use in older adults between the ages of 60–75 years.

EXAMPLE FROM GERIATRIC CLINICAL PRACTICE

A 74-year-old Hispanic woman with hypertension, gastroesophageal reflux disease, and vitamin B12 deficiency presented to our clinic for routine follow-up. She presented with no symptoms. She had no family history of premature coronary heart disease. Her medications included lisinopril 10 mg daily, vitamin B12 1000 mcg daily, vitamin D 1000 units daily, and omeprazole 20 mg daily. Her blood pressure was 131/57, heart rate 69, and body mass index (BMI) 24. She had a normal complete blood count, metabolic panel, thyroid-stimulating hormone level, and a hemoglobin A1C of 5.7. Her lipid profile was HDL 64 mg/dl, total cholesterol (TC) 174 mg/dl, triglyceride (TG) 153 mg/dl, and LDL 80 mg/dl. Statin therapy for primary cardiovascular prevention was considered. The patient's Framingham 10-year cardiovascular disease (CVD) risk was calculated to be 6 %.[10] Based on the ATP III LDL targets,[2] the patient's risk factors (age and antihypertensive medication) and a 6 % 10-year CVD risk, a statin would not be recommended. However, based on the new ASCVD calculator, this patient has a 10-year ACSVD risk of 19.5 % and would be recommended for the initiation of statin therapy with no guidelines as to when to end statin treatment.

REVIEW OF THE EVIDENCE

Careful examination of the studies used as the basis for the new ACC/AHA guidelines shows that a broad strokes application of the guidelines is not justified. The principal primary prevention trials used to derive the ASCVD risk scoring and 7.5 % risk level for primary prevention were three randomized control studies (AFCAPS/TexCAPS, MEGA and JUPITER) and two meta-analyses [Cholesterol Treatment Trialists' (CTT) 2012 and Cochrane 2011 and 2013, with the Cochrane 2013 review including results of four clinical trials not included in the 2011 review].[11–16] The applicability of the guidelines should be limited to the inclusion criteria of the patient populations enrolled in the trials. Extrapolating the data to patients with different risk factors is not evidence-based and would be difficult to defend.

Upon closer examination, these trials are not applicable to our patient, and therefore neither are either the 2013 AHA/ACC pooled cohort equations, or the guideline to treat adults without clinical ASCVD or diabetes, but with a 10-year ASCVD risk≥7.5 %. Our patient would also not meet the lipid criteria for the AFCAPS/TexCAPS and MEGA trials, and the JUPITER trial enrolled only patients with a CRP≥ 2 mg/L. A review of all the randomized control trials in both the CTT 2012 and Cochrane 2013 shows that our patient would not have met the entry criteria for any of the trials, including three major, primary prevention trials: ASCOT-LLA, WOSCOPS and CARDS. The ASCOT-LLA patients had hypertension and three cardiovascular risk factors, WOSCOPS enrolled men aged 45–64 with cholesterol >272 mg/dl and CARDS examined statins in diabetics.[17–19] Tables 1 and 2 review the inclusion criteria for the each trial in CTT 2012 and Cochrane 2011/2013, and highlight how our patient would not have been included in any of the studies.

Assessing the benefits of statins specifically among the geriatric population is difficult because older patients have historically been excluded from major clinical trials, including lipid trials. PROSPER[20] and HPS[21] are the only two large randomized control trials specifically designed to assess statins in older adults (ages 70–82 in PROSPER and 70–80 in HPS). However, these trials were for secondary prevention or high-risk primary prevention. While subgroup analysis of the trials SSSS (4S),[22] LIPID[23] and CARE[24] did demonstrate the efficacy of statins in older populations, these trials enrolled only patients with known coronary artery disease. The only primary prevention trial with a sub-analysis of older patients (age 70 and older) was the JUPITER trial,[25] which targeted individuals with a CRP≥2 mg/L.

"STATINOPAUSE" AND THE GERIATRIC PERSPECTIVE

The risk of potential harm to many patients, particularly the geriatric population, and high resource commitment due to the new guidelines should not be ignored. Statins are known to cause myopathy and have been associated with diabetes,[26] liver dysfunction and cataracts.[27] In addition, there are always concerns for clinicians when adding more medications to an older adult's medication regimen, particularly for those with multiple chronic conditions. Adding a statin can increase the

Table 1. Review of the Inclusion Criteria for Trials in CTT 2012

Study	Patients	Lipid parameters	ASCVD risk factors	Comparison‡
MEGA*	7,832 patients: male and females, ages 40–70	Total Cholesterol 220–270 mg/dL	Hypercholesterolemia	Age cutoff and elevated total cholesterol level
ASCOT-LLA	10,305 patients: male and females, ages 40–79	Total Cholesterol ≤250 mg/dL	Hypertension and three cardiovascular risk factors (DM, PAD, CVA, smoker or low HDL)	Cardiovascular risk factors
AFCAPS/ TexCAPS 1998*	6,605 patients: males ages 45–73, females post-menopausal 55–73	TC 180–264 mg/dL; LDL 130–190 mg/dL; HDL≤45 mg/dL for males and≤47 mg/dL for females	Hypercholesterolemia	Hypercholesterolemia and or low HDL
ASPEN 2006*	2,410 patients: male and females, ages 40–75	LDL≤140 mg/dl if documented MI. If no documented MI, LDL≤160 mg/dl, TG≤600 mg/dl	Type II Diabetes	Secondary prevention in subgroup of patients and DM
CARDS 2004/2008*	2,838 patients: male and females, ages 40–75	LDL≤160 mg/dl, TG≤600 mg/dl	Type II Diabetes and one of the following: SBP≥ 140 mmHg or DBP≥90 mmHg, Retinopathy Micro/macro albuminuria, Smoker	Diabetes and cardiovascular risk factors
JUPITER 2008*	17,802 patients: males ages ≥50, females ages≥ 60	LDL <130 mg/dL	NONE	hsCRP ≥ 2 mg/L criteria for study
KAPS 1995*	2682 patients: males ages 44–65	LDL≥than 154 mg/dl	NONE	High LDL and age cutoff
WOSCOPS	6,595 patients: males ages 45–64	Total cholesterol >272 mg/dL	Hypercholesterolemia	Hypercholesterolemia and age cutoff
GISSI-HF	4,631 patients: male and females, ages 18 and older	No specifications	Heart Failure	Secondary prevention
ALERT	2,100 patients: male and females, ages 30–75	TC 154–348 mg/dl if no history of MI TC 154–270 mg/dl with history of MI	Renal transplant	Renal transplant on immunosuppressant elevated TC and history of MI in subgroup of patients
ALLHAT-LLA	10,3554 patients: male and females, age 55 and older	LDL 120–189 mg/dl – without CAD LDL 100–129 mg/dl with CAD	14 % of patients with CAD and 35 % with Type II diabetes	CAD and DM in subgroup of patients
Post-CABG	1,351 patients: male and females, (92 % male) ages 21–74	LDL 130-175 mg/dl TC≤200 mg/dl	CAD with CABG	Secondary prevention
GISSI-P*	4,271 patients: male and females, no defined age limits	Initial enrollment TC≥200 mg/dl then changed to <250 mg/dl	Myocardial Infarction	Secondary prevention
LIPID	9,014 patients: male and female, ages 31–75	TC 155–271 mg/dl TG<445 mg/dl	Acute MI or recent documented unstable angina	Secondary prevention
PROSPER	5.804 patients: male and females, ages 70–82	TC 154–348 mg/dl TG<531 mg/dl	Pre-existing vascular disease or high risk for vascular disease	Secondary prevention or high-risk primary prevention
CORONA	5,011 patients: male and females, age 60 and older	No specifications	Heart failure NYHA class II-IV secondary to ischemic heart disease	Secondary prevention
CARE	4,159 patients: male and females, ages 21–75	LDL 115–174 mg/dl TC <240 mg/dl	Myocardial infarction	Secondary prevention
ALLIANCE	2,442 patients: male and females, ages 18 and older	LDL 110–200 mg/dl for those on lipid lowering medication and 130–250 mg/dl for those not on med	Known CAD (MI, PCI or CABG or Unstable angina)	Secondary prevention
LIPS	1,677 patients: male and females, ages 18–80	TC 135–270 mg/dl TG<400 mg/dl	Underwent PCI	Secondary prevention
AURORA	2,776 patients: male and females, ages 50–80	No specifications	ESRD on hemodialysis	High-risk primary prevention
SSSS (4S)	4,444 patients: male and females, ages 35–70	TC – 212–309 mg/dl	MI or angina pectoris	Secondary prevention and hypercholesterolemia
4D	1,255 patients: male and females, ages 18–80	LDL 80–190 mg/dl TG<1000 mg/dl	ESRD on dialysis and DM	High-risk primary prevention

ASCVD, Atherosclerotic cardiovascular disease; CVA, Cerebrovascular accident; CABG, Coronary artery bypass graft surgery; CAD, Coronary artery disease; DM, Diabetes; DBP, Diastolic blood pressure; ESRD, End stage renal disease; HDL, High-density lipoprotein; CRP, High-sensitivity C-reactive protein; LDL, Low-Density lipoprotein; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; PAD, Peripheral arterial disease; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglycerides

[*] Trial also included in the Cochrane 2011/2013 review

[‡] Comparison to case presentation patient highlighting how she would not have met the inclusion criteria for the trials

Table 2. Review of the Inclusion Criteria for Trials in Cochrane 2011/2013

Study	Patients	Lipid parameters	ASCVD risk factors	Comparison‡
BONE 2007	626 postmenopausal females	LDL 130–190 mg/dl	NONE	Only assessed effects of Atorvastatin on bone mineral density
CAIUS 1996	205 patients: male and females, ages 45–65	LDL 150–250 mg/dl	Carotid artery lesion	Hypercholesterolemia and age cutoff
CELL A/CELL B 1996	681 patients: male and females, ages 30–59	TC ≥ 250 mg/dl on three occasions	Two cardiovascular risk factors: HTN smoker, obesity, history or family history of CAD	Hypercholesterolemia; age cutoff; CAD risk factors
CERDIA 2004	250 patients male and females, ages 30–80	No specifications	Type II Diabetes	Diabetes
DEROSA 2003	99 patients: male and females, ages 40 and older	TC≥240 mg/dl	Obese BMI≥30 kg/m^2; hypercholesterolemia	High-risk primary prevention
HYRIM 2004/2007	177 patients: males ages 40–74	TC<300 mg/dl	Obese BMI 25–35 kg/m^2; sedentary lifestyle; male	High-risk primary prevention
METEOR 2010	984 patients: males ages 45–70, females ages 55–70	LDL 120–190 mg/dl with only age as risk factor LDL 120–160 mg/dl with ≥ 2 CAD risk factors TG <500 mg/dl	At least one maximum carotid artery intimal media thickness > 1.2 mm	Age cutoff Increased risk primary prevention; mild hypercholesterolemia
MRC/BHF Heart Protection	20,536 patients: male and females, ages 40–80	TC at least 135 mg/dl no upper limit	At least one of: 1) coronary disease; 2) occlusive disease of non-coronary arteries; 3) DM (type 1 or 2); or 4) Treated HTN if also male and≥65 years of age.	High-risk primary or secondary prevention.
PHYLLIS 2004	508 patients: males and post-menopausal females, ages 45–70	LDL 160–200 mg/dl	HTN; hypercholesterolemia; carotid atherosclerosis	Higher risk primary prevention and age cutoff
PREVEND IT 2004	1439 patients: male and females, ages 28–75	TC<309 mg/dl with no history of MI and < 193 mg/dl with history of MI	Micro albuminuria > 10 mg/L	Micro albuminuria (average age was 51 years)

ASCVD atherosclerotic cardiovascular disease, BMI body mass index, CAD coronary artery disease, DM diabetes, HTN hypertension, LDL low-density lipoprotein, MI myocardial infarction, TC total cholesterol, TG triglycerides
‡Comparison to case presentation patient highlighting how she would not have met the inclusion criteria for the trials

risk for adverse drug events, potential drug–drug interactions, and can complicate medication adherence. Further, statins have been associated with cognitive changes,[8,28] as well as confusion and memory loss,[8,29] which can complicate the care of the older adult.

Unfortunately, the exclusion of older adults, such as our patient, in clinical trials is common.[30] A review of 109 randomized control trials published in 2007 found that nearly 20 % excluded patients above a specified age, and that nearly half of the remaining trials excluded individuals using criteria that could overly impact older adults.[31] This underrepresentation even includes clinical research on diseases that disproportionally affect older adults, such as cardiovascular disease[32] and cancer.[33] In addition, the evidence base for the clinical care of older adults with multiple chronic diseases is limited.[34] Adults with multiple comorbidities are often excluded from randomized control trials, and if included, studies address multiple chronic diseases in limited ways.[34,35] The absence of evidence among this population highlights the difficulty for providers and patients to fully understand and estimate the risks and benefits of medications, especially for primary prevention and for patients with multiple chronic conditions. There is a paucity of evidence to guide clinicians on primary cardiovascular prevention for older adults.

Some projections estimate that under the new guidelines, an additional 46 million Americans would be considered as "statin deficient." Worldwide, this figure would exceed 1 billion.[4] This increase would greatly strain an already tight health-care budget. All agree that when statin therapy is clearly indicated, its benefits far outweigh its risks. In such cases, the cost of therapy is negligible in comparison to the more costly events (stroke, myocardial infarction) it can prevent. However, when the indication is not clear, absence of evidence should preclude its use until there is strong evidence to recommend it.

The new guidelines have highlighted the necessity of conducting a statin trial for patients with normal LDL levels, and minimal ASCVD risk factors other than age. The new guidelines, if implemented, would mean that almost everybody reaching "statinopause" should be on statin therapy. As Tables 1 and 2 highlight, the evidence is simply insufficient to support statin therapy for everyone. Until a study in older adults with minimal ASCVD risk factors is completed, we believe physicians should discuss with their patients the unclear evidence for statin therapy and the risks associated with the medication. Additional research is needed for all segments of the geriatric population, from the otherwise healthy older adult in "statinopause" to the very old and those with multiple chronic conditions. Until future studies are done, the decision

to treat should be individualized after carefully weighing the benefits and risks and engaging in a shared physician–patient decision-making discussion.

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