


Trends in low-density lipoprotein-cholesterol blood values between 2012 and 2017 suggest sluggish adoption of the recent 2013 treatment guidelines

H. Robert Superko¹  | Paul T. Williams² | Michael Dansinger^{3,4} | Ernst Schaefer^{3,4}

¹Cholesterol, Genetics, and Heart Disease Institute, Carmel, California

²Children's Hospital of Oakland, Oakland, California

³Boston Heart Diagnostics, Framingham, Massachusetts

⁴Department of Internal Medicine, Tuft's University, Medford, Massachusetts

Correspondence

H. Robert Superko, MD, Department of Internal Medicine, 24953 Outlook Lane, Carmel, California 93923.

Email: rsuperko@alumni.ucsd.edu

Background: Over a 14-year period, age-adjusted high total cholesterol (≥ 240 mg/dL) in the United States declined from 18.3% in 1999 to 2000 to 11.0% in 2013 to 2014, coinciding with the 2001 National Cholesterol Education Program Adult Treatment Panel (ATP)-III guidelines that endorsed low-density lipoprotein (LDL)-cholesterol blood value goals. Statin treatment recommendations were revised by the American College of Cardiology and the American Heart Association (ACC/AHA) in November 2013 to a "risk-based prescription" approach that did not utilize blood cholesterol values. This increased dosage and expanded the statin-eligible population by an estimated 12.8 million US adults. These changes should further lower total and LDL cholesterol concentrations nationally.

Methods: We examined data from 507 752 patients nationally aged ≥ 16 years whose fasting bloods were sent to Boston Heart Diagnostics for direct LDL-cholesterol measurements. Between 2012 and 2017, age-adjusted concentrations were examined by analysis of covariance and LDL-cholesterol ≥ 160 mg/dL by logistic regression.

Results: Contrary to expectations, age-adjusted mean LDL-cholesterol concentrations (\pm SE, mg/dL) increased significantly ($P < 10^{-16}$) in men (2012:113.8 \pm 0.3; 2013:115.3 \pm 0.2; 2014:114.7 \pm 0.2; 2015:116.0 \pm 0.2; 2016:117.6 \pm 0.2; and 2017:117.1 \pm 0.2 mg/dL) and women (2012:119.5 \pm 0.3; 2013:120.7 \pm 0.2; 2014:119.8 \pm 0.02; 2015:120.8 \pm 0.2; 2016:122.7 \pm 0.1; and 2017:123.8 \pm 0.2 mg/dL). The percentage with LDL-cholesterol ≥ 160 mg/dL also increased significantly ($P < 10^{-9}$) in men and women. Similar results were obtained for ages 40 to 75 years olds (corresponding to ACC/AHA guidelines).

Conclusion: These results provide additional evidence that declining blood LDL-cholesterol levels observed following the ATP-III recommendations, did not further decline (actually increased) following the 2013 ACC/AHA recommendations.

KEYWORDS

cholesterol, guidelines, heart disease prevention, low density lipoprotein cholesterol

1 | INTRODUCTION

In 2001, the National Cholesterol Education Program Adult Treatment Panel (ATP)-III guidelines provided a comprehensive guide to lipid management, namely, the use of drug therapy in persons with coronary heart disease (CHD) or CHD risk equivalents (10 year risk $> 20\%$) to obtain a low-density lipoprotein (LDL)-cholesterol goal < 100 mg/dL (2.59 mmol/L), considered optimal for primary prevention and < 70

mg/dL (1.81 mmol/L) for secondary prevention.¹ In patients with two or more risk factors and moderate 10-year CHD risk (10%-20%) the proposed goal was < 130 mg/dL, and for those with a $< 10\%$ risk or zero or one risk factor the proposed goal was < 160 mg/dL). In 2004, the guidelines were updated to recommend treatment an option for achieving LDL-cholesterol < 70 mg/dL in very high-risk patients as defined by the Framingham 10-year CHD risk equation for fatal CHD and nonfatal myocardial infarction.² These recommendations likely

contributed strongly to the increase in use of antihyperlipidemic agents in the United States from 6.5% in 1999 to 2002 to 14.3% in 2011 to 2014.³ This increase coincided with a decline in the percent of the US adult population with total cholesterol ≥ 240 mg/dL of 18.3% in 1999 to 2000 to 11.0% by 2013 to 2014,⁴ and a decline in the age adjusted death rate due to heart disease from 257.6 to 167.0 per 100 000 population between 2000 and 2014.⁴ Data from nearly 105 million adults show that mean LDL-cholesterol levels declined from 120 mg/dL in 2001 to 105 mg/dL in 2008, plateauing thereafter through 2011.⁵

In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) changed statin recommendations from a "titration to cholesterol goal" to a "risk benefit"-based approach with reduced emphasis on individual blood LDL-cholesterol values as a goal of treatment.⁶ The recommendations were based exclusively on evidence of statin benefit from randomized controlled trials. Specifically, statin treatment was recommended for adult patients with: (a) atherosclerotic cardiovascular disease (ASCVD); (b) LDL-cholesterol ≥ 190 mg/dL, (c) diabetes between the ages of 40 and 75 years and LDL-cholesterol between 70 and 189 mg/dL; and (d) 7.5% or greater 10-year ASCVD risk and LDL-cholesterol between 70 and 189.⁶ Low-intensity statin therapy (expected LDL-cholesterol lowering <30%) was only recommended for patients who did not tolerate higher intensity statin therapy. Moderate intensity statins (expected LDL-C lowering of 30% to 50%) was generally recommended for primary prevention in subjects with LDL-cholesterol <190 mg/dL. High intensity statins (expected LDL-C lowering $\geq 50\%$) was recommended for patients aged 75 and younger with ASCVD or LDL-cholesterol ≥ 190 mg/dL without safety concerns, and could be considered for individuals with or without diabetes who had a 10-year ASCVD risk $\geq 7.5\%$. Additional factors that may suggest statin therapy include family history of premature ASCVD, lifetime ASCVD risk, an abnormal coronary artery calcium (CAC) or ankle-brachial index (ABI) score, or elevated high-sensitivity C-reactive protein concentrations.⁶ New to the 2013 ACC/AHA guidelines is the concept of shared decision making between the physician and patient.

The new guideline substantially increased the number of US adults to whom moderate- or intense-statin therapy was indicated. Approximately 33 million people have a high 10-year ASCVD risk that would qualify them for a high-intensity statin therapy, and an additional 13 million people have a moderate risk for which statins could be considered.^{6,7} Based on the National Health and Nutrition Examination Survey (NHANES) data from 2005 to 2010, an additional 12.8 million people over the previous recommendation would be eligible for statin therapy, with the increase seen mostly among older adults without cardiovascular disease.⁸ Thus, almost one-half (56 million) of all people in the United States between the ages of 40 and 75 years without cardiovascular disease became eligible for therapy.⁸ It is estimated that as many as 475 000 future cardiovascular events could be prevented if statins were assigned to all those who exceeded the $\geq 7.5\%$ cutoff in 10-year ASCVD risk in the 40 to 75 years range.⁸

Several reports on statin prescriptions (behavioral change^{3,9-11}) and total or LDL-cholesterol (physiological responses to the behavioral change^{3,4}) trends proximal to the ACC/AHA guideline release suggest the recommendations have had less impact than anticipated. Although

improved LDL-cholesterol levels are no longer the clinical goal following the "treat to ASCVD risk" from the "treat to LDL-cholesterol target" paradigm change, the substantial expansion of the eligible population and shift to moderate- and high-intensity statin therapy should have reduced LDL-cholesterol concentrations nationally. This should be especially true for newly eligible patients who were heretofore untargeted in the ATP-III treatment guidelines. However, an important limitation of these and earlier analyses of LDL trends that could affect their sensitivity to change include: (a) uncertainty on whether blood was collected in the fasting state,^{5,12} and (b) use of the Friedewald equation to estimate LDL-cholesterol, which is subject to inaccuracy in the presence of high triglycerides and other conditions. In addition, previously reported trends in statin prescriptions¹¹ and LDL levels include only a year or two of post-guideline data which could miss delayed acceptance.

We therefore analyzed direct measurements of LDL-cholesterol levels from 507 752 fasting patients obtained nationally in a large anonymized clinical laboratory data set between 2012 and 2017, to test whether LDL-cholesterol dropped following the 2013 recommendation for wider, more intense statin therapy.

2 | METHODS

The analyses of this report were performed in a large anonymized clinical laboratory (Boston Heart Diagnostics, Framingham, Massachusetts). Due to the anonymized nature of the data analysis, no individual informed consent was required. Initial first visit fasting blood samples from 507 752 patients were measured for LDL-cholesterol between January 1, 2012 and October 31, 2017 from 50 states and the District of Columbia. The observations were confirmed using the first and second follow-up patient samples for analysis. This population sample reflects patients likely assessed for CVD risk and may not reflect the general population.

Age, gender, height, and weight were obtained from the sample submission form. Total cholesterol and LDL-cholesterol were run at the time of collection in a College of American Pathologist (CAP) and Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory (Boston Heart Diagnostics, Framingham, Massachusetts). Enzymatic colorimetric analyses were used for the measurement of total cholesterol and triglycerides¹³ and direct measurement of LDL-cholesterol,¹⁴ and immunoturbidimetric analyses for apo B concentrations. Indirect LDL-cholesterol was obtained from the Friedewald equation: total cholesterol -triglycerides/5 for triglycerides ≤ 400 mg/dL and direct LDL-cholesterol for triglycerides >400 .¹⁵

2.1 | Statistical analyses

Statistical analyses were performed using JMP version 13.2 (SAS Institute, Cary, North Carolina). Mean concentrations and percentages by categories are presented with their SE (\pm SE). The effects of time since January 1, 2012 as a continuous variable (fraction of years) were determined by regression analysis with or without adjustment for age. Analysis of covariance was used to estimate the average age-adjusted total and LDL-cholesterol concentrations by year with or without

adjustment. Logistic regression analyses was used to estimate trends for the percent of the sample having borderline to high (≥ 200 mg/dL) and high total cholesterol (≥ 240 mg/dL), and borderline to very-high (≥ 130 mg/dL), high to very-high (≥ 160 mg/dL), and very-high LDL-cholesterol (≥ 190 mg/dL) with and without adjustment for age. Results are presented for patients' first (denoted as baseline), second (1st follow-up), and third cholesterol samples (2nd follow-up).

3 | RESULTS

Table 1 displays the sample characteristics. The proportion of males and average age decreased over time, suggesting a declining prevalence of higher risk individuals in later years. Table 1 shows that the significant decrease in baseline age was primarily because of its decline between 2012 and 2015.

Figure 1 shows that when adjusted for age, baseline fasting total cholesterol concentrations increased between 2012 and 2017 in women (slope \pm SE: 0.32 ± 0.06 mg/dL annually, $P = 3.8 \times 10^{-8}$) but not in men (-0.06 ± 0.06 , $P = 0.32$). However, logistic regression showed small annual increases in the age-adjusted odds of high total cholesterol between 2012 and 2017 in both sexes (women: 1.8%, $P = 5.7 \times 10^{-7}$; men: 1.4%, $P = 0.003$).

Average fasting LDL-cholesterol concentrations increased significantly from 2012 through 2017 (Table 1). Men's and women's baseline LDL-cholesterol concentration increased annually by an average of 1.13 ± 0.06 and 0.97 ± 0.05 mg/dL, respectively. This was confirmed by average LDL-cholesterol increases of 1.63 ± 0.10 and 2.05 ± 0.10 mg/dL per year on the men's and women's first follow-up visit, respectively, and by 1.14 ± 0.16 and 2.53 ± 0.16 mg/dL per year, respectively, on their second follow-up ($P < 10^{-9}$). Adjustment for age had little effect on these trends: 0.84 ± 0.06 mg/dL per year in men and 1.03 ± 0.05 mg/dL in women at baseline, 1.34 ± 0.10 mg/dL per year in men and 1.87 ± 0.10 mg/dL in women at the 1st follow-up, and 1.04 ± 0.16 mg/dL per year in men and 2.35 ± 0.16 mg/dL in women at the 2nd follow-up (all $P \leq 10^{-10}$). Figure 2 shows that LDL-cholesterol concentrations increased between 2012 and 2017 for men and women 40 and 75 years old (the age range specifically targeted by the ACC/AHA recommendations, males: 1.24 ± 0.06 mg/dL average increase per year $P < 10^{-16}$; females: 1.41 ± 0.06 mg/dL average increase per year, $P < 10^{-16}$), and men and women 60 and 75 years old (ie, the age group most directly affected by expanding eligibility by ASCVD risk, males: 1.24 ± 0.09 mg/dL average increase per year $P < 10^{-16}$; females: 1.97 ± 0.09 mg/dL average increase per year, $P < 10^{-16}$).

In addition, Table 1 shows that the proportion of the sample with LDL-cholesterol ≥ 130 (borderline to very high), ≥ 160 (high to very high), and ≥ 190 mg/dL (very high LDL-cholesterol) also increased significantly between 2012 and 2017 at baseline and during follow-up. In men, each year after 2012 increased the age-adjusted odds for borderline to very-high LDL-cholesterol by 4.6% (95% confidence interval [CI]: 4.0%-5.3%, $P < 10^{-16}$), for high to very-high LDL-cholesterol by 5.9% (95% CI: 5.1%-6.9%, $P < 10^{-16}$), and for very-high LDL by 9.2% (95% CI: 7.6%-10.8%, $P < 10^{-16}$). The corresponding values for

women were 4.7% (95% CI: 4.1%-5.3%, $P < 10^{-16}$), 4.8% (95% CI: 4.1%-5.6%, $P < 10^{-16}$), and 5.4% (95% CI: 4.1%-6.6%, all $P < 10^{-16}$).

Table 2 shows that the lack of an LDL-decrease was also observed for calculated LDL, that is, showing no change or increased annually in men and women at baseline (regression slope \pm SE, men: 0.09 ± 0.06 , women: 0.09 ± 0.05 mg/dL per year), and first (men: 0.55 ± 0.10 , women: 0.94 ± 0.10 mg/dL per year) and second follow-up measurements (men: 0.30 ± 0.16 , women: 1.38 ± 0.16 mg/dL per year) when adjusted for age. Age-adjusted Non-HDL-cholesterol also showed no change or a slight increase over times. Despite the significant decreases in plasma triglyceride concentrations between 2012 and 2017, age-adjusted apoB concentrations increased significantly over time for baseline (men: 0.81 ± 0.04 , women: 0.88 ± 0.04 mg/dL per year) and first (men: 1.07 ± 0.07 , women: 1.35 ± 0.07 mg/dL per year), and second follow-up measurements (men: 0.76 ± 0.12 , women: 1.60 ± 0.12 mg/dL per year).

Table 3 examines LDL-cholesterol concentration in 636 604 total patients without regard to fasting status, corresponding to the analyses by Kaufmann et al.⁵ Again, age-adjusted mean LDL-C concentrations increased significantly ($P < 10^{-16}$) in men and women, and the percentage with LDL-cholesterol ≥ 160 mg/dL also increased significantly ($P < 10^{-7}$) in men and women. Similar results were obtained for ages 40 to 75 years old (corresponding to ACC/AHA guidelines).

4 | DISCUSSION

Our analyses in 507 752 patient fasting blood samples failed to demonstrate any significant reduction in LDL-cholesterol levels nationally with respect to overall mean LDL-cholesterol or the percentage of the patient population classified as borderline, high or very high LDL-cholesterol by ATP-III guidelines. We were also unable to demonstrate LDL-cholesterol reductions in the 45 to 74-year-old patient group specifically targeted by the 2013 ACC/AHA recommendations, nor in the 60 to 75 year old age bracket for whom the new recommendations would likely have the greatest impact. This was further confirmed in the patients' first and second follow-up samples. These results are inconsistent with our expectation that expanded statin eligibility and higher recommended doses should further decrease LDL-cholesterol. It is unlikely that the potential to reduce LDL-cholesterol levels nationally had already been achieved by 2012 given the inclusion of heretofore untargeted patients, and clear evidence that higher statin doses further decrease LDL-cholesterol. LDL-cholesterol reduction with moderate and intense statin therapy has been reported to be 10.4% with 40 mg/d pravastatin (moderate therapy) and 41.5% with 80 mg/d atorvastatin (intensive therapy).¹⁶ Moreover, only 8.8 million of the 33 million Americans meeting new eligibility meeting new guidelines for primary prevention of ASCVD are estimated to take statins.¹⁷

Using a national sample of the U.S. population, Pencina et al. estimated that the new guidelines would qualify an additional 12.8 million adults (11.1%) between 40 to 75 years old for statin therapy.⁸ Maddox et al reported that 32.4% of statin-eligible cardiology patients had not received statins, of whom 12.6% had LDL-cholesterol

TABLE 1 Fasting low-density lipoprotein (LDL) cholesterol concentrations (mg/dL) by year

	2012	2013	2014	2015	2016	2017	Trend (P)
Baseline Sample							
Female (N)	15 970	35 716	47 294	61 504	78 936	41 620	—
Male (N)	16 370	32 631	38 933	48 313	60 957	29 508	—
Male (%)	50.6	47.7	45.2	44.0	43.6	41.5	—
Age (years)							
Female	59.3 ± 0.1	57.3 ± 0.1	55.6 ± 0.1	54.5 ± 0.1	54.3 ± 0.1	54.4 ± 0.1	<10 ⁻¹⁶
Male	58.3 ± 0.1	56.4 ± 0.1	55.5 ± 0.1	55.4 ± 0.1	55.1 ± 0.1	55.5 ± 0.1	<10 ⁻¹⁶
Mean LDL-cholesterol (mg/dL)							
Female	119.8 ± 0.3	120.8 ± 0.2	119.8 ± 0.2	120.8 ± 0.2	122.7 ± 0.1	123.7 ± 0.2	<10 ⁻¹⁶
Male	112.1 ± 0.3	114.8 ± 0.2	114.9 ± 0.2	116.2 ± 0.2	118.0 ± 0.2	117.3 ± 0.2	<10 ⁻¹⁶
Age-adjusted LDL-cholesterol (mg/dL)							
Female	119.5 ± 0.3	120.7 ± 0.2	119.8 ± 0.2	120.8 ± 0.2	122.7 ± 0.1	123.8 ± 0.2	<10 ⁻¹⁶
Male	113.8 ± 0.3	115.3 ± 0.2	114.7 ± 0.2	116.0 ± 0.2	117.6 ± 0.2	117.1 ± 0.2	<10 ⁻¹⁶
Borderline to very-high LDL (%)							
Female	36.2 ± 0.4	37.5 ± 0.3	36.7 ± 0.2	37.3 ± 0.2	39.0 ± 0.2	40.6 ± 0.2	<10 ⁻¹⁶
Male	30.3 ± 0.4	32.7 ± 0.3	33.2 ± 0.2	34.5 ± 0.2	36.7 ± 0.2	35.7 ± 0.3	<10 ⁻¹⁶
High to very-high LDL (%)							
Female	14.9 ± 0.3	15.4 ± 0.2	14.6 ± 0.2	14.8 ± 0.1	16.2 ± 0.1	16.9 ± 0.2	5.5 × 10 ⁻¹⁰
Male	11.5 ± 0.2	12.6 ± 0.2	12.5 ± 0.2	13.4 ± 0.2	14.9 ± 0.1	14.8 ± 0.2	<10 ⁻¹⁶
Very-high LDL (%)							
Female	5.2 ± 0.2	5.2 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	5.5 ± 0.1	5.6 ± 0.1	1.3 × 10 ⁻¹¹
Male	3.2 ± 0.1	3.5 ± 0.1	3.5 ± 0.1	4.0 ± 0.1	4.6 ± 0.1	4.8 ± 0.1	<10 ⁻¹⁶
1st follow-up sample (N)							
Female (N)	3437	6418	12 423	15 937	21 783	15 798	
Male (N)	3552	6454	11 633	13 064	18 747	13 283	
Male (%)	50.8	50.1	48.4	45.0	46.3	45.7	
Age (years)							
Female	64.1 ± 0.2	61.2 ± 0.2	60.1 ± 0.1	59.0 ± 0.1	58.6 ± 0.1	58.9 ± 0.1	<10 ⁻¹⁶
Male	62.3 ± 0.2	60.1 ± 0.2	58.9 ± 0.1	58.7 ± 0.1	58.9 ± 0.1	59.0 ± 0.1	<10 ⁻¹⁶
Mean LDL-cholesterol (mg/dL)							
Female	107 ± 0.6	110.6 ± 0.5	110.5 ± 0.3	114.4 ± 0.3	116.3 ± 0.3	116.4 ± 0.3	<10 ⁻¹⁶
Male	97.8 ± 0.6	101.7 ± 0.4	103.1 ± 0.3	105.5 ± 0.3	105.6 ± 0.3	107.3 ± 0.3	<10 ⁻¹⁶
Age-adjusted LDL-cholesterol (mg/dL)							
Female	108.1 ± 0.7	111 ± 0.5	110.6 ± 0.3	114.3 ± 0.3	116.1 ± 0.3	116.3 ± 0.3	<10 ⁻¹⁶
Male	100.1 ± 0.6	102.4 ± 0.5	102.9 ± 0.3	105.2 ± 0.3	105.4 ± 0.3	107.2 ± 0.3	<10 ⁻¹⁶
Borderline to very-high LDL (%)							
Female	23.5 ± 0.7	27.9 ± 0.6	27.7 ± 0.4	31.5 ± 0.4	33.5 ± 0.3	33.8 ± 0.4	<10 ⁻¹⁶
Male	16.9 ± 0.6	20.3 ± 0.5	22.1 ± 0.4	24.6 ± 0.4	25.6 ± 0.3	27.3 ± 0.4	<10 ⁻¹⁶
High to very-high LDL (%)							
Female	9.3 ± 0.5	10.5 ± 0.4	10.7 ± 0.3	12.0 ± 0.3	13.1 ± 0.2	13.0 ± 0.3	<10 ⁻¹⁶
Male	5.6 ± 0.4	6.8 ± 0.3	7.0 ± 0.2	8.6 ± 0.2	9.5 ± 0.2	10.0 ± 0.3	<10 ⁻¹⁶
Very-high LDL (%)							
Female	3.2 ± 0.3	3.3 ± 0.2	3.2 ± 0.2	3.5 ± 0.1	4.3 ± 0.1	4.1 ± 0.2	2.2 × 10 ⁻⁹
Male	1.5 ± 0.2	1.7 ± 0.2	2.0 ± 0.1	2.2 ± 0.1	2.6 ± 0.1	2.9 ± 0.1	1.6 × 10 ⁻¹⁴
2nd follow-up sample (N)							
Female (N)	966	1951	4424	7135	9035	8470	—
Male (N)	990	2045	4375	6151	7808	7575	—
Male (%)	50.6	51.2	49.7	46.3	46.4	47.2	—
Age (years)							
Female	65.0 ± 0.4	63.8 ± 0.3	61.9 ± 0.2	62.0 ± 0.2	61.0 ± 0.1	61.4 ± 0.1	<10 ⁻¹⁶
Male	63.4 ± 0.4	62.5 ± 0.3	60.3 ± 0.2	60.9 ± 0.2	61.2 ± 0.1	61.3 ± 0.2	0.008

TABLE 1 (Continued)

	2012	2013	2014	2015	2016	2017	Trend (P)
Mean LDL-cholesterol (mg/dL)							
Female	104.1 ± 1.2	103.4 ± 0.8	106.8 ± 0.6	108.6 ± 0.4	113.4 ± 0.4	112.9 ± 0.4	<10 ⁻¹⁶
Male	94.3 ± 1.0	95.4 ± 0.7	98.6 ± 0.5	99.4 ± 0.5	101.7 ± 0.4	99.7 ± 0.4	1.5 × 10 ⁻¹²
Age-adjusted mean LDL-cholesterol (mg/dL)							
Female	105.1 ± 1.2	104.0 ± 0.9	106.8 ± 0.6	108.7 ± 0.5	113.2 ± 0.4	112.8 ± 0.4	<10 ⁻¹⁶
Male	95.9 ± 1.1	96.4 ± 0.8	98.0 ± 0.5	99.2 ± 0.5	101.7 ± 0.4	99.7 ± 0.4	1.5 × 10 ⁻¹²
Borderline to very-high LDL (%)							
Female	21.2 ± 1.3	20.4 ± 0.9	23.8 ± 0.6	26.4 ± 0.5	31.5 ± 0.5	30.8 ± 0.5	<10 ⁻¹⁶
Male	13.2 ± 1.1	15.0 ± 0.8	18.7 ± 0.6	19.5 ± 0.5	22.1 ± 0.5	21.4 ± 0.5	<10 ⁻¹⁶
High to very-high LDL (%)							
Female	8.2 ± 0.9	7.9 ± 0.6	9.1 ± 0.4	9.6 ± 0.3	11.7 ± 0.3	11.9 ± 0.4	<10 ⁻¹⁶
Male	4.5 ± 0.7	4.5 ± 0.5	5.7 ± 0.3	7.1 ± 0.3	8.3 ± 0.3	8.3 ± 0.3	<10 ⁻¹⁶
Very-high LDL (%)							
Female	2.3 ± 0.5	2.5 ± 0.4	3.3 ± 0.3	3.0 ± 0.2	3.6 ± 0.2	4.0 ± 0.2	4.3 × 10 ⁻⁷
Male	0.7 ± 0.3	1.3 ± 0.3	1.3 ± 0.2	2.2 ± 0.2	2.4 ± 0.2	2.2 ± 0.2	2.5 × 10 ⁻⁶

Except for sample size, values are unadjusted and age-adjusted mean ± SE for age and LDL cholesterol concentrations, and percentage ± SE for borderline to very-high (≥120 mg/dL), high to very-high (≥160 mg/dL) and very high-LDL-cholesterol (≥190 mg/dL).

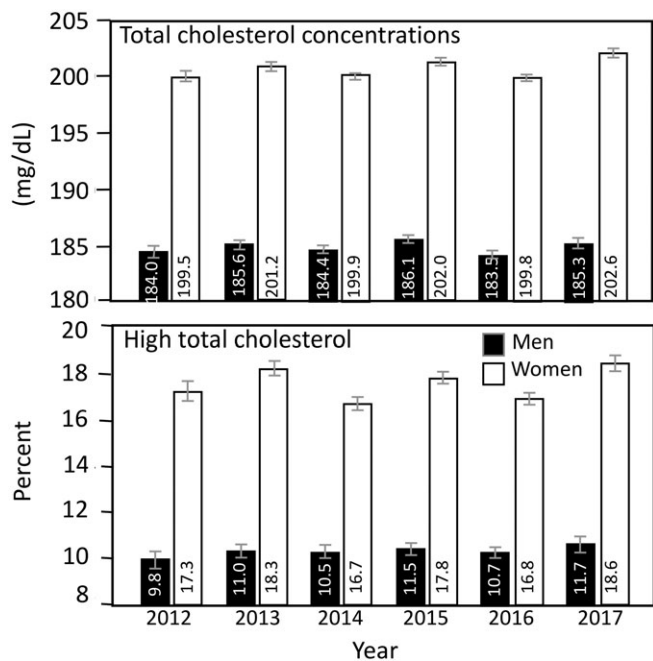


FIGURE 1 Analysis of covariance of the mean total cholesterol concentrations and the percent of subjects with high total cholesterol concentrations at baseline adjusted for age. Brackets represent 95% confidence intervals. Logistic regression analyses estimated that the odds of subjects with high total cholesterol increased by an average of per year in men and per year in women. All subjects were aged 16 years and older

<100 mg/dL, from a retrospective analysis of 1 174 545 of the National Cardiovascular Data Registry Practice Innovation and Clinical Excellence (NCDR PINNACLE) registry between 2008 and 2012.¹⁸ Thirty-six percent of diabetics and 37% of patients with an estimated ASCVD risk of ≥7.5% were untreated.¹⁹ Patients with LDL-cholesterol previously characterized as normal (70 to 100 mg/dL) would now be considered for pharmacotherapy, and many have risk >7.5% on the basis of age alone, including nearly all African-American men over the

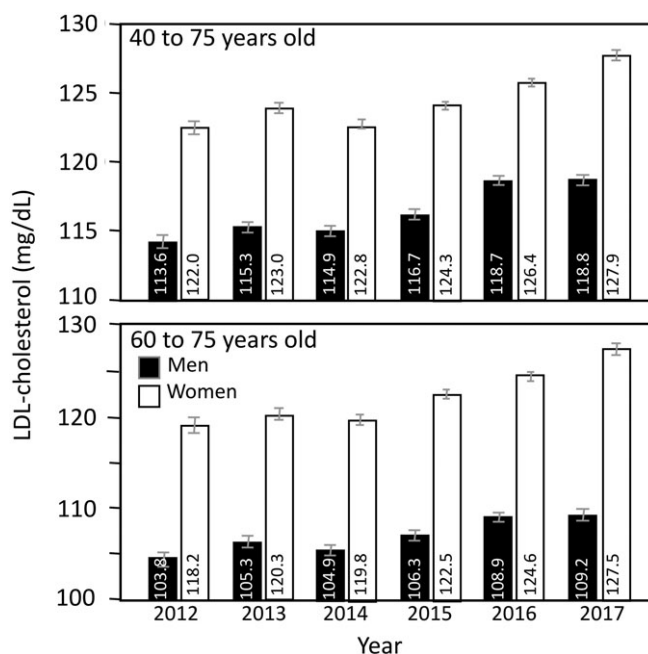


FIGURE 2 Mean low-density lipoprotein cholesterol concentrations in adults 40 to 75 (the age range targeted by the ACC/AHA guidelines) and adults 60 to 74 years (the age range expected to be particularly impacted by the treat for risk approach of the ACC/AHA guidelines) at baseline adjusted for age

age of 63. Because age is such an important determinant of CVD risk, under the new guidelines statins would be indicated for approximately 77% of adults between 60 and 75 years of age.²⁰

Our results are consistent with other reports showing little change in statin therapy following the guideline release. Nationally, prevalence of high cholesterol increased non-significantly from 11.0% in 2013-2014 to 12.4% in 2015-2016,⁴ and heart disease deaths increased from 167.0 per 100 000 population in 2014 to 168.5 in 2015.³ Okerson et al... reported that LDL-cholesterol levels have remained unchanged in 90 287 ASCVD patients who were

TABLE 2 BMI, and fasting concentrations of total cholesterol, triglycerides, calculated low-density lipoprotein (LDL) cholesterol concentrations, non-HDL-cholesterol, and apo B concentrations by year

	2012	2013	2014	2015	2016	2017	Trend (P)
Baseline mean BMI (kg/m ²)							
Female	29.89 ± 0.10	29.34 ± 0.07	28.89 ± 0.06	28.60 ± 0.05	28.78 ± 0.04	28.24 ± 0.06	<10 ⁻¹⁶
Male	29.98 ± 0.08	30.12 ± 0.06	29.83 ± 0.05	29.65 ± 0.04	29.70 ± 0.04	29.37 ± 0.06	<10 ⁻¹⁶
Mean age-adjusted BMI (kg/m ²)							
Female	30.01 ± 0.10	29.39 ± 0.07	28.89 ± 0.06	28.57 ± 0.05	28.76 ± 0.04	28.23 ± 0.06	<10 ⁻¹⁶
Male	30.14 ± 0.08	30.14 ± 0.06	29.80 ± 0.05	29.62 ± 0.04	29.68 ± 0.04	29.39 ± 0.06	<10 ⁻¹⁶
Mean total cholesterol (mg/dL)							
Female	200.5 ± 0.4	201.7 ± 0.2	200.0 ± 0.2	201.8 ± 0.2	199.6 ± 0.2	202.4 ± 0.2	0.05
Male	182.2 ± 0.3	185.1 ± 0.2	184.6 ± 0.2	186.3 ± 0.2	183.9 ± 0.2	185.4 ± 0.3	0.0005
Mean age-adjusted total cholesterol (mg/dL)							
Female	199.5 ± 0.3	201.2 ± 0.2	199.9 ± 0.2	202.0 ± 0.2	199.8 ± 0.2	202.6 ± 0.2	<10 ⁻⁷
Male	184.0 ± 0.3	185.6 ± 0.2	184.4 ± 0.2	186.1 ± 0.2	183.5 ± 0.2	185.3 ± 0.3	0.32
Mean triglycerides (mg/dL)							
Female	130.9 ± 0.7	125.4 ± 0.4	122.7 ± 0.4	118.0 ± 0.3	116.5 ± 0.3	116.0 ± 0.4	<10 ⁻¹⁶
Male	143.6 ± 0.8	144.8 ± 0.6	145.4 ± 0.6	141.7 ± 0.5	139.6 ± 0.5	140.7 ± 0.7	<10 ⁻¹²
Mean age-adjusted triglycerides (mg/dL)							
Female	129.0 ± 0.6	124.4 ± 0.4	122.5 ± 0.4	118.3 ± 0.3	116.9 ± 0.3	116.4 ± 0.4	<10 ⁻¹⁶
Male	145.3 ± 0.9	145.2 ± 0.6	145.3 ± 0.6	141.6 ± 0.5	139.2 ± 0.5	140.6 ± 0.7	<10 ⁻¹⁶
Mean LDL-cholesterol calculated (mg/dL)							
Female	114.3 ± 0.3	115.2 ± 0.2	113.5 ± 0.2	115.8 ± 0.2	113.7 ± 0.2	115.3 ± 0.2	0.23
Male	106.5 ± 0.3	108.6 ± 0.2	108.2 ± 0.2	110.2 ± 0.2	108.5 ± 0.2	109.4 ± 0.2	<10 ⁻¹⁰
Mean age-adjusted LDL-cholesterol calculated (mg/dL)							
Female	114.2 ± 0.3	115.1 ± 0.2	113.5 ± 0.2	115.8 ± 0.2	113.7 ± 0.2	115.3 ± 0.2	0.08
Male	108.2 ± 0.3	109.0 ± 0.2	108.0 ± 0.2	110.0 ± 0.2	108.2 ± 0.2	109.3 ± 0.2	0.12
Mean non-HDL-cholesterol (mg/dL)							
Female	138.7 ± 0.6	140.1 ± 0.2	137.9 ± 0.2	139.4 ± 0.2	137.9 ± 0.2	139.7 ± 0.2	0.73
Male	137.2 ± 0.6	136.8 ± 0.2	136.1 ± 0.2	137.8 ± 0.2	136.0 ± 0.2	137.2 ± 0.3	0.62
Mean age-adjusted non-HDL-cholesterol (mg/dL)							
Female	138.3 ± 0.6	139.9 ± 0.2	137.8 ± 0.2	139.5 ± 0.2	138.0 ± 0.2	139.8 ± 0.2	0.32
Male	138.6 ± 0.5	137.4 ± 0.2	136.1 ± 0.2	137.7 ± 0.2	135.7 ± 0.2	137.2 ± 0.3	0.0008
Mean Apo B (mg/dL)							
Female	97.5 ± 0.2	95.3 ± 0.3	98.1 ± 0.1	98.0 ± 0.1	98.8 ± 0.1	99.7 ± 0.1	<10 ⁻¹⁶
Male	95.0 ± 0.2	94.2 ± 0.2	97.8 ± 0.2	97.8 ± 0.1	98.2 ± 0.1	99.1 ± 0.2	<10 ⁻¹⁶
Mean age-adjusted apo B (mg/dL)							
Female	97.0 ± 0.2	95.1 ± 0.2	98.1 ± 0.1	98.1 ± 0.1	98.9 ± 0.1	99.7 ± 0.1	<10 ⁻¹⁶
Male	96.0 ± 0.2	94.4 ± 0.2	97.7 ± 0.2	97.7 ± 0.1	98.0 ± 0.1	99.1 ± 0.2	<10 ⁻¹⁶
1st follow-up mean BMI (kg/m ²)							
Female	29.87 ± 0.18	29.82 ± 0.15	29.27 ± 0.11	28.69 ± 0.10	28.85 ± 0.08	28.56 ± 0.09	<10 ⁻¹⁶
Male	29.99 ± 0.14	30.27 ± 0.12	29.94 ± 0.09	29.72 ± 0.09	29.66 ± 0.07	29.45 ± 0.08	<10 ⁻⁹
Mean age-adjusted BMI (kg/m ²)							
Female	30.22 ± 0.17	29.94 ± 0.15	29.35 ± 0.11	28.59 ± 0.10	28.76 ± 0.08	28.56 ± 0.10	<10 ⁻¹⁶
Male	30.30 ± 0.14	30.31 ± 0.11	29.93 ± 0.09	29.64 ± 0.09	29.60 ± 0.07	29.49 ± 0.08	<10 ⁻¹⁴
Mean total cholesterol (mg/dL)							
Female	187.3 ± 0.7	190.4 ± 0.5	189.6 ± 0.4	195.2 ± 0.3	193.5 ± 0.3	194.9 ± 0.4	<10 ⁻¹⁶
Male	166.4 ± 0.7	170.9 ± 0.5	171.2 ± 0.4	174.8 ± 0.4	170.6 ± 0.3	174.3 ± 0.4	<10 ⁻¹²
Mean age-adjusted total cholesterol (mg/dL)							
Female	187.6 ± 0.7	190.5 ± 0.5	189.6 ± 0.4	195.2 ± 0.3	193.5 ± 0.3	194.8 ± 0.3	<10 ⁻¹⁶
Male	168.7 ± 0.7	171.6 ± 0.5	171.0 ± 0.4	174.4 ± 0.4	170.4 ± 0.3	174.2 ± 0.4	<10 ⁻⁵
Mean triglycerides (mg/dL)							
Female	127.0 ± 1.2	125.4 ± 1.2	123.5 ± 0.7	118.8 ± 0.6	114.7 ± 0.5	114.4 ± 0.6	<10 ⁻¹⁶
Male	135.9 ± 1.8	134.2 ± 1.4	136.1 ± 0.9	136.0 ± 0.9	128.4 ± 0.7	130.8 ± 0.9	<10 ⁻⁸

TABLE 2 (Continued)

	2012	2013	2014	2015	2016	2017	Trend (P)
Mean age-adjusted triglycerides (mg/dL)							
Female	126.3 ± 1.3	125.1 ± 1.0	123.4 ± 0.7	118.9 ± 0.6	114.8 ± 0.5	114.4 ± 0.6	<10 ⁻¹⁶
Male	138.6 ± 1.7	135.0 ± 1.3	135.9 ± 0.9	135.6 ± 0.9	128.1 ± 0.7	130.6 ± 0.9	<10 ⁻¹²
Mean LDL-cholesterol calculated (mg/dL)							
Female	101.7 ± 0.6	105.0 ± 0.5	103.6 ± 0.3	109.4 ± 0.3	107.3 ± 0.3	107.9 ± 0.3	<10 ⁻¹⁶
Male	92.5 ± 0.6	95.9 ± 0.4	96.6 ± 0.3	100.1 ± 0.3	96.5 ± 0.3	99.4 ± 0.3	<10 ⁻¹⁵
Mean age-adjusted LDL-cholesterol calculated (mg/dL)							
Female	102.8 ± 0.7	105.4 ± 0.5	103.8 ± 0.3	109.2 ± 0.3	107.1 ± 0.3	107.7 ± 0.3	<10 ⁻¹⁶
Male	94.8 ± 0.6	96.6 ± 0.4	96.4 ± 0.3	99.7 ± 0.3	96.3 ± 0.3	99.3 ± 0.3	<10 ⁻⁷
Mean non-HDL-cholesterol (mg/dL)							
Female	124.7 ± 1.1	130.0 ± 0.5	128.5 ± 0.4	132.9 ± 0.3	130.9 ± 0.3	131.7 ± 0.3	<10 ⁻¹⁰
Male	117.4 ± 1.1	122.2 ± 0.5	123.2 ± 0.4	126.1 ± 0.4	121.9 ± 0.3	125.4 ± 0.4	0.0002
Mean age-adjusted non-HDL-cholesterol (mg/dL)							
Female	125.9 ± 1.2	130.3 ± 0.5	128.6 ± 0.4	132.9 ± 0.3	130.7 ± 0.3	131.7 ± 0.3	<10 ⁻⁷
Male	120.7 ± 1.2	123.1 ± 0.5	123.1 ± 0.4	125.8 ± 0.4	121.7 ± 0.3	125.3 ± 0.3	0.07
Mean Apo B (mg/dL)							
Female	89.9 ± 0.4	89.4 ± 0.3	93.1 ± 0.3	94.9 ± 0.2	95.5 ± 0.2	95.8 ± 0.2	<10 ⁻¹⁶
Male	86.1 ± 0.4	85.7 ± 0.3	90.5 ± 0.3	91.5 ± 0.2	90.6 ± 0.2	92.7 ± 0.3	<10 ⁻¹⁶
Mean age-adjusted apo B (mg/dL)							
Female	90.3 ± 0.5	89.5 ± 0.4	93.1 ± 0.3	94.8 ± 0.2	95.4 ± 0.2	95.7 ± 0.2	<10 ⁻¹⁶
Male	87.5 ± 0.4	86.0 ± 0.3	90.5 ± 0.3	91.1 ± 0.2	90.4 ± 0.2	92.6 ± 0.2	<10 ⁻¹⁶
2nd follow-up mean BMI (kg/m ²)							
Female	30.37 ± 0.31	29.97 ± 0.25	28.94 ± 0.18	28.71 ± 0.15	28.50 ± 0.13	28.69 ± 0.13	<10 ⁻⁹
Male	30.87 ± 0.27	29.83 ± 0.18	30.40 ± 0.15	29.81 ± 0.13	29.55 ± 0.11	29.62 ± 0.11	<10 ⁻⁷
Mean age-adjusted BMI (kg/m ²)							
Female	30.66 ± 0.30	30.18 ± 0.23	29.05 ± 0.19	28.71 ± 0.15	28.35 ± 0.13	28.67 ± 0.13	<10 ⁻¹⁴
Male	31.05 ± 0.25	29.97 ± 0.18	30.38 ± 0.14	29.78 ± 0.13	29.47 ± 0.11	29.65 ± 0.11	<10 ⁻⁹
Mean total cholesterol (mg/dL)							
Female	183.6 ± 1.4	182.4 ± 1.0	185.0 ± 0.7	189.1 ± 0.5	190.7 ± 0.5	192.2 ± 0.5	<10 ⁻¹⁶
Male	162.0 ± 1.2	164.0 ± 0.9	166.1 ± 0.6	167.6 ± 0.5	166.7 ± 0.5	166.1 ± 0.5	0.008
Mean age-adjusted total cholesterol (mg/dL)							
Female	184.2 ± 1.4	182.8 ± 1.0	185.1 ± 0.7	189.2 ± 0.5	190.6 ± 0.5	192.1 ± 0.5	<10 ⁻¹⁶
Male	163.6 ± 1.3	164.9 ± 0.9	165.5 ± 0.6	167.4 ± 0.5	166.8 ± 0.5	166.1 ± 0.5	0.03
Mean triglycerides (mg/dL)							
Female	130.3 ± 2.3	124.1 ± 1.6	122.2 ± 1.2	119.5 ± 0.9	113.6 ± 0.7	115.7 ± 0.8	<10 ⁻¹⁶
Male	135.9 ± 2.7	135.1 ± 2.2	134.2 ± 1.4	132.5 ± 1.2	126.7 ± 1.1	125.9 ± 1.0	<10 ⁻¹⁰
Mean age-adjusted triglycerides (mg/dL)							
Female	130.1 ± 2.3	124.0 ± 1.6	122.2 ± 1.1	119.5 ± 0.9	113.6 ± 0.8	115.7 ± 0.8	<10 ⁻¹⁶
Male	138.0 ± 2.9	136.4 ± 2.0	133.3 ± 1.4	132.2 ± 1.2	126.7 ± 1.0	126.0 ± 1.1	<10 ⁻¹¹
Mean LDL-cholesterol calculated (mg/dL)							
Female	98.8 ± 1.2	98.2 ± 0.9	100.0 ± 0.6	103.2 ± 0.5	104.1 ± 0.4	104.2 ± 0.4	<10 ⁻¹⁶
Male	88.5 ± 1.0	89.7 ± 0.7	92.0 ± 0.5	93.8 ± 0.5	92.6 ± 0.4	91.9 ± 0.4	0.01
Mean age-adjusted LDL-cholesterol calculated (mg/dL)							
Female	99.8 ± 1.2	98.2 ± 0.8	100.0 ± 0.6	103.2 ± 0.5	104.1 ± 0.4	104.2 ± 0.4	<10 ⁻¹⁶
Male	90.0 ± 1.1	90.5 ± 0.8	91.4 ± 0.5	93.6 ± 0.5	92.6 ± 0.4	91.9 ± 0.4	0.05
Mean non-HDL-cholesterol (mg/dL)							
Female	123.9 ± 2.2	122.4 ± 0.9	124.5 ± 0.6	127.0 ± 0.5	127.6 ± 0.5	128.2 ± 0.5	<10 ⁻¹¹
Male	111.8 ± 2.0	115.9 ± 0.9	118.2 ± 0.6	119.6 ± 0.5	117.4 ± 0.5	117.1 ± 0.5	0.91
Mean age-adjusted non-HDL-cholesterol (mg/dL)							
Female	125.3 ± 2.3	123.0 ± 1.0	124.6 ± 0.6	127.1 ± 0.5	127.4 ± 0.5	128.1 ± 0.5	<10 ⁻⁹
Male	114.6 ± 2.3	117.1 ± 0.9	117.5 ± 0.6	119.4 ± 0.5	117.5 ± 0.5	117.2 ± 0.5	0.73

TABLE 2 (Continued)

	2012	2013	2014	2015	2016	2017	Trend (P)
Mean Apo B (mg/dL)							
Female	88.2 ± 0.8	85.2 ± 0.6	91.4 ± 0.4	91.6 ± 0.3	94.0 ± 0.3	94.0 ± 0.3	<10 ⁻¹⁶
Male	84.0 ± 0.8	82.1 ± 0.5	87.6 ± 0.4	88.1 ± 0.4	88.1 ± 0.3	87.6 ± 0.3	<10 ⁻¹²
Mean age-adjusted Apo B (mg/dL)							
Female	88.7 ± 0.9	85.5 ± 0.6	91.4 ± 0.4	91.6 ± 0.3	93.9 ± 0.3	94.0 ± 0.3	<10 ⁻¹⁶
Male	84.9 ± 0.8	82.7 ± 0.6	87.4 ± 0.4	87.9 ± 0.4	88.0 ± 0.3	87.7 ± 0.3	<10 ⁻¹⁰

TABLE 3 Baseline LDL-cholesterol concentrations by year without regard to fasting status (fasting, nonfasting and unknown fasting status) corresponding to the analyses by Kaufmann et al⁵

	2012	2013	2014	2015	2016	2017	Trend (P)
Age ≥ 16 years sample							
Female	23 645	48 333	61 971	73 110	95 306	49 177	
Male	23 049	43 181	51 161	58 394	73 924	35 353	
Mean age-adjusted LDL-cholesterol (kg/m ²)							
Female	120.3 ± 0.3	121.4 ± 0.2	119.8 ± 0.2	120.8 ± 0.1	122.3 ± 0.1	123.6 ± 0.2	<10 ⁻¹⁶
Male	114.3 ± 0.3	115.9 ± 0.2	114.8 ± 0.2	116.1 ± 0.2	117.5 ± 0.1	117.0 ± 0.2	<10 ⁻¹⁶
High LDL-cholesterol (≥160 mg/dL, %)							
Female	15.2 ± 0.2	15.8 ± 0.2	14.5 ± 0.1	14.7 ± 0.1	16.0 ± 0.1	16.8 ± 0.2	<10 ⁻¹⁶
Male	11.9 ± 0.2	12.9 ± 0.2	12.6 ± 0.1	13.3 ± 0.1	14.6 ± 0.1	14.7 ± 0.2	<10 ⁻¹⁶
Age 45-74 years sample							
Female	5323	10 744	14 699	17 954	23 886	12 605	
Male	4719	9219	11 556	13 333	17 569	8575	
Mean age-adjusted LDL-cholesterol (kg/m ²)							
Female	122.9 ± 0.3	124.1 ± 0.2	122.8 ± 0.2	124.3 ± 0.2	126.0 ± 0.1	127.9 ± 0.2	<10 ⁻¹⁶
Male	114.2 ± 0.3	116.0 ± 0.2	115.1 ± 0.2	116.8 ± 0.2	118.6 ± 0.2	118.8 ± 0.2	<10 ⁻¹⁶
High LDL-cholesterol (≥160 mg/dL, %)							
Female	16.5 ± 0.3	17.3 ± 0.2	16.4 ± 0.2	16.9 ± 0.2	18.4 ± 0.1	19.6 ± 0.2	<10 ⁻¹⁶
Male	12.1 ± 0.2	13.1 ± 0.2	12.8 ± 0.2	13.8 ± 0.2	15.2 ± 0.2	15.5 ± 0.2	<10 ⁻¹⁶

continuously enrolled 6 months before and 7 months after the first ASCVD diagnosis between 2012 and 2014.¹² Tran et al reported little appreciable change in statin use, only a slight increase in prescription intensity, and no changes in patient LDL-cholesterol levels after the guideline release in 610 535 ASCVD and diabetes patients belonging to a US health insurance organization.⁹ Retrospective analysis of 1 100 682 patients in the Veterans Affairs Corporate Data Warehouse found that use of moderate to high-intensity statins increased by less than 1 % following the guideline change and by 2% following formulary change.¹⁰ They concluded that greater accessibility of genetic atorvastatin was more important than the revised guidelines in increasing moderate-to-high-intensity prescriptions. In another study from the Veterans Affairs Health System, Rodriguez et al. reported that high-intensity statin use increased from 28% in 331 927 ASCVD patients before the guidelines release to 35% in 326 759 ASCVD patients after guideline's release.¹¹ Men, younger individuals, and patients in academic and West Coast hospitals were more likely to receive more intensive statin therapy relative to pre-release levels.¹² However, Rosenson et al. reported that statin use following

hospital discharge for myocardial infarction had increased from 33.5% in 2011 to 71% in 2014 for patients with commercial health care and from 24.8% in 2011 to 57.5% in 2014 for Medicare patients.²¹

A number of factors may contribute to the lack of decline in blood LDL-cholesterol values following the 2013 ACC/AHA guidelines. Admittedly, changes in medical practice are generally sluggish—the Institute of Medicine has estimated that the incorporation of new knowledge into clinical practice takes an average of 17 years.²² One year after the ACC/AHA guidelines were published, Virani et al found that health care providers were unaware of the ACC/AHA guidelines, use of the 10-years ASCVD risk estimator to guide statin treatment, and the four major groups likely to benefit from statin use.²³ Most continued to prescribe statins in response to targeted LDL-C levels. Patients and physicians might also be reluctant to prescribe a cholesterol lowering medication in the absence of high cholesterol and concern for statin overtreatment.²⁴ The very success of ATP-III may also discourage change. Resistance to the new guidelines might also arise from the publication of other guidelines that still employ the “treat to target” approach to high cholesterol.^{25,26} An additional factor may be

the inclusion of the "Shared Decision Making (SDM)" concept of the ACA/AHA guidelines that involved inclusion of the patient in the decision to use lipid lowering agents.^{6,27} An analysis of a secondary prevention population in a managed care organization reported that only 37.2% of ASCVD patients were on high-intensity statin therapy.² The decreased emphasis on nonstatin drug therapy in the 2013 ACC/AHA guidelines suggests many high-risk patients should receive statin therapy and nothing else.²⁸

The 2013 guidelines do not negate the clinical significance of lowering LDL-cholesterol to reduce ASCVD risk, rather, none of the randomized controlled clinical trials used to prove the benefits of statin therapy titrated dosing to a specific LDL-cholesterol goal. Lifestyle changes for lowering LDL-cholesterol continue to be a major component of the recommendations. Epidemiological evidence clearly shows very low CHD risk for LDL-cholesterol levels <100 mg/dL vs accelerated risk for high (160-189 mg/dL) and very high LDL-cholesterol (≥ 190 mg/dL).²⁹ Moreover, randomized trials of LDL-cholesterol reduction have demonstrated the lower the LDL-cholesterol achieved, the greater the reduction in cardiovascular events.³⁰ More simply said, there is a clinical benefit to higher dose statin than need to achieve lower LDL-cholesterol levels. As a result of some confusion some investigators have called for reconsideration of the new guidelines.³¹

Caveats and limitations: The strength of our results is the large sample size from throughout the United States using a standard laboratory assay in a single laboratory. A second strength is the inclusion of first and second repeat blood value sample analysis to assess temporal change during follow-up care. However, our results are based on a sample of opportunity rather than a rigorously designed sampling strategy for precisely estimating total and LDL-cholesterol levels throughout the country. Limited data were available for characterizing the population. Boston Heart Diagnostics provides a series of more advanced lipoprotein measurements and one limitation is that the sample may include a higher proportion of patients who did not respond satisfactorily to standard treatment. The database did not contain information on the source of the sample to preserve anonymity. Although most of the samples were provided from general and specialty practice rather than institutions, the exact proportion are not known. In addition, treatment status is unknown for many patients in that it is not known whether a nonresponse to cholesterol medication use means no drugs were used or the question was ignored.

Another limitation is that improvements in LDL-cholesterol could theoretically be missed due to the perceived discouragement for follow-up blood work. For example, 20.8% of received multiple measurement LDL-cholesterol measurements that would now become unnecessary for cholesterol management from retrospective analysis of 1 174 545 of the National Cardiovascular Data Registry Practice Innovation and Clinical Excellence (NCDR PINNACLE) registry between 2008 and 2012.¹⁹ However, Table 2 shows an absence of change over time for the first and second follow-up measurements LDL-cholesterol, this suggest to us that changes in LDL-cholesterol monitoring does not explain the apparent stable or slightly increasing LDL-cholesterol levels since 2012.

5 | CONCLUSIONS

In conclusion, our analyses in 507 752 patients provide preliminary evidence that the expected increase in statin therapy, following the ACC/AHA guidelines, did not occur nationally, and that total and LDL-cholesterol levels actually increased contrary to expectations. One possibility may be sluggish implementation of the new guidelines into clinical practice as well as ambiguity in, or lack of clear evidence for, the management recommendations.¹⁹ Others report that disagreement with the recommendations was the main hindrance to adoption of the 2013 ACC/AHA Guidelines for the Prevention of Primary and Secondary Atherosclerotic Disease.²⁴

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CONFLICTS OF INTEREST

The authors declare no potential conflict of interests.

ORCID

H. Robert Superko  <https://orcid.org/0000-0002-3542-0393>

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