ORIGINAL RESEARCH

Impact of the New ACC/AHA Guidelines on the Treatment of High Blood Cholesterol in a Managed Care Setting

Josephine N. Tran, PharmD, MS; Toros Caglar, PhD; Karen M. Stockl, PharmD; Heidi C. Lew, PharmD; Brian K. Solow, MD; Paul S. Chan, MD, MSc

Stakeholder Perspective, page 442

Am Health Drug Benefits. 2014;7(8):430-443
www.AHDBonline.com

Received August 14, 2014
Accepted in final form October 6, 2014

Disclosures are at end of text

BACKGROUND: In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) together issued new guidelines for the treatment of patients with high cholesterol, providing a new paradigm for the management of cholesterol in the primary and secondary prevention of coronary artery disease.

OBJECTIVE: To examine the impact of the 2013 ACC/AHA cholesterol treatment guidelines on pharmacy utilization of cholesterol-lowering drugs in a real-world managed care setting.

METHODS: Pharmacy claims from OptumRx, a national pharmacy benefit management provider, for the period between January 1, 2013, and December 31, 2013 (baseline period), were used to identify candidates for cholesterol-lowering therapy and to estimate the number of potential patients who will be starting or intensifying statin therapy based on the updated cholesterol treatment guidelines. Potential candidates for cholesterol-lowering treatments included patients with diabetes or hypertension aged 40 to 75 years who were not already receiving a cholesterol-lowering medication, as well as patients receiving cholesterol-lowering therapies during the baseline period. The baseline cholesterol-lowering medication market share was used to project changes in pharmacy utilization over the next 3 years.

RESULTS: Based on the 2013 ACC/AHA cholesterol treatment guidelines, there will be a 25% increase in the proportion of the overall population that is treated with statins over the next 3 years, increasing from 3,909,407 (27.7%) patients to 4,892,668 (34.7%) patients. The largest proportion of the increase in statin utilization is projected to be for primary prevention in patients aged 40 to 75 years who were not receiving any cholesterol-lowering treatment at baseline. These projected changes will increase the overall number of statin prescriptions by 25% and will decrease the number of nonstatin cholesterol-lowering medication prescriptions by 68% during the next 3 years.

CONCLUSION: The new 2013 ACC/AHA cholesterol treatment guidelines are projected to have a significant impact on the utilization of cholesterol-lowering drugs by increasing the overall proportion of the population receiving statin therapy and by decreasing the utilization of nonstatin cholesterol-lowering medications.

In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released together new clinical guidelines for the treatment of patients with high blood cholesterol.[1] The 2013 guidelines provide a new paradigm for cholesterol management in the primary and secondary prevention of coronary artery disease (CAD); these recommendations are based on clinical evidence from randomized controlled trials of cholesterol-lowering therapies rather than on expert consensus as in previous guidelines.[2,3] Before the 2013 guidelines, the Adult Treatment Panel (ATP) III report of the National Cholesterol Education Program was the main clinical guideline for the primary and secondary prevention of CAD.[4]

The ATP III recommends statin therapy in patients with established cardiovascular (CV) disease or diabetes whose low-density lipoprotein cholesterol (LDL-C) levels are ≥100 mg/dL, or in patients with a combination of elevated LDL-C levels and a 10-year risk for CAD based on the Framingham risk calculator.[4] The primary focus of the ATP III guideline was on a treat-to-target strategy, in which lipid-modifying medications were titrated to achieve specific LDL-C levels.

Dr Tran is Senior Research Consultant, Clinical Programs and Outcomes Research, OptumRx, Irvine, CA; Dr Caglar is Senior Research Consultant, Clinical Programs and Outcomes Research, OptumRx; Dr Stockl is Senior Director, Clinical Programs and Outcomes Research, OptumRx; Dr Lew is Vice President, Clinical Programs, OptumRx; Dr Solow is Chief Medical Officer, Clinical, OptumRx; Dr Chan is Associate Professor, Division of Cardiology, University of Missouri-Kansas City.

Based on clinical trials that have shown that LDL-C–lowering therapy reduces the risk for CAD, the ATP III guideline used LDL-C as the target of cholesterol-lowering therapy.[4] This recommendation diverges from current clinical evidence, because there are no major randomized clinical trials that have tested the benefits of treating patients to LDL-C targets.

The 2013 ACC/AHA clinical guidelines no longer recommend the treat-to-target strategy for the management of cholesterol levels in patients with CAD, and instead recommend the use of fixed-dose, high-intensity and fixed-dose, moderate-intensity statin therapies to treat high-risk populations. These high-risk groups include patients with clinical atherosclerotic CV disease (ASCVD), patients with primary LDL-C elevations of ≥190 mg/dL, patients with diabetes who are aged 40 to 75 years, or patients aged 40 to 75 years without diabetes or ASCVD but with LDL-C levels between 70 mg/dL and 189 mg/dL whose estimated 10-year ASCVD risk is ≥7.5% based on a new risk calculator.[1]

Overall, with a focus on treating high-risk groups with cholesterol-lowering therapies that have been shown in randomized clinical trials to reduce the risk for ASCVD, the 2013 ACC/AHA guidelines recommend the use of statins for ASCVD risk reduction. The guidelines no longer recommend the use of nonstatin cholesterol-lowering therapies for ASCVD risk reduction, and they expand statin therapy for the primary prevention of ASCVD in patients with lower LDL-C levels who are at an increased risk for ASCVD.

Recently, Pencina and colleagues projected that the 2013 guidelines would increase the number of US adults who would be eligible for statin therapy, with the greatest increase expected to be in adults aged 60 to 75 years.[5] However, the potential impact of the 2013 cholesterol treatment guidelines on the pharmacy utilization of statin and nonstatin cholesterol-lowering medications in a managed care organization remains unknown. In this present study, therefore, we sought to estimate the impact of the 2013 guidelines on the pharmacy utilization of cholesterol-lowering medications in various risk groups in a managed care setting.

KEY POINTS

- In late 2013, the American College of Cardiology and the American Heart Association released new guidelines for the treatment of high blood cholesterol, presenting a paradigm change in primary and secondary prevention of heart disease.
- In this new analysis, pharmacy claims data were used to calculate the potential impact of the new guidelines on the use of different classes of cholesterol-lowering medications.
- Based on the 2013 recommendations, this analysis projects that nearly 25% more patients will potentially be starting statin therapy during the next 3 years.
- Most patients are expected to start or switch to a high-dose statin, with the greatest percentage change to be seen in commercial and Medicaid patient populations.
- A 25% increase in overall statin prescriptions and a 68% decrease in nonstatin cholesterol-lowering drug prescriptions are predicted under the new guidelines.
- Overall, the guidelines are projected to have a significant impact on cholesterol-lowering drugs by increasing statin use and decreasing the use of nonstatin cholesterol-lowering medications.

Methods

Study Population

OptumRx is a large pharmacy benefit management company serving more than 30 million people nationwide through a network of more than 66,000 community pharmacies and mail service facilities. Approximately 60% of the OptumRx population consists of commercial patients, 30% are Medicare beneficiaries, and approximately 10% are Medicaid patients. In this study, we used pharmacy claims from OptumRx for the baseline period between January 1, 2013, and December 31, 2013 to determine the number of potential patients who may be starting or switching to statin therapy based on the 2013 cholesterol treatment guidelines. The potential patients in this study included all continuously eligible patients with either pharmacy claims for any cholesterol medication (regardless of age), and patients aged 40 to 75 years who were not receiving any cholesterol treatment medications but who had pharmacy claims for medications for diabetes or hypertension.

We assumed that this first group of patients, who were already receiving cholesterol-lowering treatment, represents either secondary prevention in patients with established CAD or secondary prevention in patients with hypercholesterolemia, according to the 2013 cholesterol treatment guidelines. The latter setting represents patients with established diabetes or patients being treated for primary prevention of ASCVD.

Cholesterol values were not available to assess the risk for patients receiving treatment for the primary prevention of ASCVD. Thus, hypertension medications were used as a proxy to estimate the 10-year CV risk, because this information could be obtained via pharmacy claims, and systolic blood pressure is a major component of the risk calculator.

Diabetes medications that were used based on pharmacy claims and, therefore, did not distinguish between type 1 and type 2 diabetes. These diabetes medications included biguanides, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors. Medications for the treatment of hypertension included beta-blockers, calcium channel blockers, direct renin inhibitors, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors.

Cholesterol-Lowering Therapy

For all patients eligible for cholesterol-lowering therapy in the study cohort, we identified whether they had any pharmacy claims for treatment during the study period. Claims information was obtained for several classes of cholesterol-lowering therapies, including statins, bile acid–binding resins, cholesterol absorption inhibitors, fibrates, niacin, and omega-3 fatty acids.

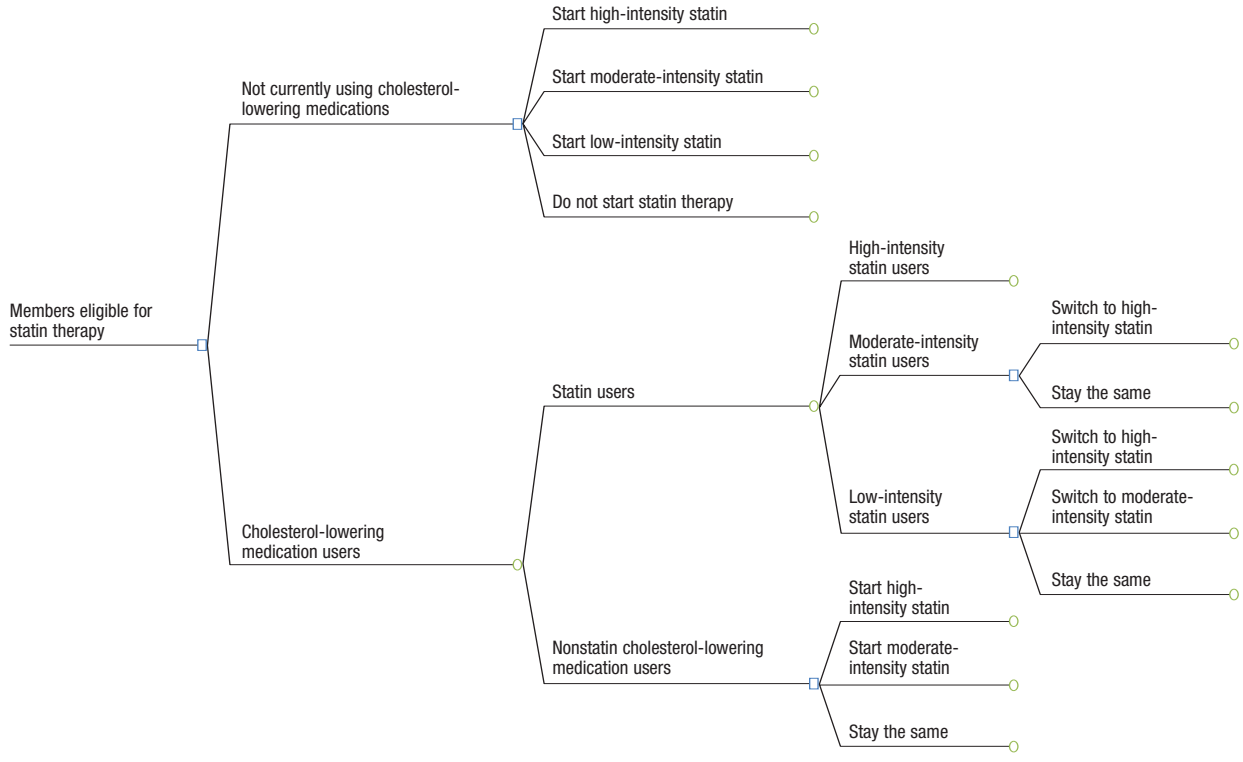
For patients receiving statin therapy, the average daily dose for each statin over the time period was used to determine the statin intensity that each patient was taking, and patients were categorized based on their treatment intensity (ie, low, moderate, high), using the definitions in the 2013 ACC/AHA cholesterol treatment guidelines (**Table 1**).[1]

Table 1 Statin Intensity Classifications

High-intensity statin therapy (daily dose lowers LDL-C on average by approximately ≥50%)	Moderate-intensity statin therapy (daily dose lowers LDL-C on average by approximately 30% to <50%)	Low-intensity statin therapy (daily dose lowers LDL-C on average by <30%)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg twice daily	
	Pitavastatin 2-4 mg	

LDL-C indicates low-density lipoprotein cholesterol.
Reprinted with permission from Stone NJ, et al. *J Am Coll Cardiol.* 2014;63(25 pt B):2889-2934.

Figure 1 Flow Diagram to Determine Who Will Be Starting or Switching Statin Therapies



Note: See Table 1 for statin dosing intensity information.

Estimating the Impact of the New Cholesterol Guidelines on Treatment

A projection model was constructed using Microsoft Excel 2010 to estimate the changing proportion of patients receiving statins and nonstatin cholesterol-lowering treatments, and to estimate the number of patients receiving statin therapy during the baseline period who would have received an intensified statin dosing (**Figure 1**).

Table 2 provides a summary of the model inputs and the assumptions used in the model. We assumed that all patients receiving statin therapy at baseline who were already using this for primary or secondary prevention (eg, patients with previous myocardial infarction or coronary revascularization) would continue to receive therapy. For patients aged 40 to 75 years who were not receiving cholesterol-lowering medications, we assumed that all patients with diabetes would initiate a statin treatment, based on the 2013 guidelines.

We also assumed, based on expert opinion, that 60% of patients with hypertension would meet the primary prevention criteria for a ≥7.5% 10-year risk for CV events and would be initiated on statin therapy. Systolic blood pressure is a big part of the risk calculator; however, because we are using medications for hypertension as a proxy, some patients receiving these medications may have their hypertension controlled with treatment.

Our model also estimates that 33% of patients who were receiving only nonstatin cholesterol-lowering medications at baseline would switch to a statin treatment based on the 2013 guidelines. Although nonstatin cholesterol-lowering medications are no longer recommended for ASCVD risk reduction, some patients receiving these nonstatin cholesterol-lowering medications were presumed to be intolerant of statin therapy.[6-8]

Finally, for patients receiving a statin and a concomitant nonstatin cholesterol-lowering medication, we projected that 100% of patients would have their nonstatin cholesterol-lowering medications discontinued, because these are no longer recommended for ASCVD risk reduction. Studies have shown declining persistence to therapy, or the duration of time from initiation to discontinuation of therapy, over time for new therapies[9-11]; therefore, our model projects that approximately 66% of patients, whom we assumed would start receiving statin therapy, would continue to use treatment at the end of the 3-year projection period.

To estimate the number of patients receiving a statin at baseline who would have intensification of statin

Table 2 Summary of Model Inputs and Assumptions

Model inputs	• Pharmacy claims from a national PBM provider between November 1, 2012, and October 31, 2013, were used to project the number of potential patients who will be starting or switching statin therapies • Potential statin users include: – Continuously eligible patients with diabetes or hypertension aged 40-75 years who are not receiving any cholesterol medications – Continuously eligible patients receiving lower-intensity statins or other nonstatin cholesterol-lowering therapies • Baseline cholesterol drugs market share was used to project pharmacy utilization for potential patients who will be starting or switching therapies • Expert opinion was used when information was not available in the medical literature
Assumptions	• Patients receiving a statin at baseline will not be taken off statin therapy • Patients receiving a statin and a nonstatin cholesterol-lowering medication will have the nonstatin agent removed • Patients who were not receiving any cholesterol-lowering medications, were aged 40-75 years, and have diabetes or hypertension will start statin therapy; approximately 60% of members receiving hypertension medication and all members receiving diabetes medications will start receiving a statin[a] • Approximately 33% of patients receiving nonstatin cholesterol-lowering medications will be switching to statin therapy[a] • Approximately 50% of patients receiving low-intensity statin therapies will switch to a moderate-intensity or high-intensity statin therapy[a] • Approximately 25% of patients receiving a moderate-intensity statin will switch to a high-intensity statin[a] • Patients are assumed to use the same current market share for various statin medications • Approximately 66% of patients newly starting statin therapy are projected to continue therapy over time[b]

[a]Estimates based on expert specialist opinion.
[b]Estimate based on ranges between 40% and 73% found in the literature.[9-11]
PBM indicates pharmacy benefit management.

dosing—because the 2013 cholesterol guidelines recommend moderate- to high-dose statin therapy for all 4 treatment groups—we calculated the proportion of patients at baseline who were receiving statins at low-, moderate-, and high-intensity potencies, as outlined in Table 1. Based on expert opinion, we assumed that 50% of patients receiving a low-intensity statin would be switched to a moderate- or high-intensity statin, and 25% of patients receiving a moderate-intensity statin would be switched to a high-intensity statin based on the 2013 guideline recommendations for specific groups. We based these assumptions on the fact that not all patients can tolerate higher-intensity statin treatment[6-8]; these latter patients would continue to receive their baseline statin strength.

In addition, we assessed the impact of the 2013 guidelines on medication treatment patterns among commercial, Medicare, and Medicaid health plans. We assumed that the cholesterol medication market share for commercial, Medicare, and Medicaid plans remained the same over the 3-year period of our projections—that is, the percentage of each cholesterol medication use relative to each other would be the same over time for each plan. The cholesterol medication market share was used to determine which statin medications the patients are projected to be using. For example, the patients who are expected to start high-intensity statins would be divided among the high-intensity statins based on the proportions of the various high-dose statins.

Assumptions and expert opinions were used in the model where the information in the medical literature

Table 3 Baseline Cholesterol-Lowering Medication Utilization

Patients receiving cholesterol-lowering medications		Patients in a commercial plan, N (%) (N = 4,402,866)	Patients in a Medicaid plan, N (%) (N = 2,173,914)	Patients in a Medicare plan, N (%) (N = 7,537,720)	Total population, N (%) (N = 14,114,500)
Statin users, by dosing intensity[a]	Low-intensity statin	54,503 (13.20)	18,684 (21.90)	497,458 (14.60)	570,645 (14.60)
	Moderate-intensity statin	287,968 (69.80)	59,556 (69.70)	2,377,955 (69.70)	2,725,480 (69.70)
	High-intensity statin	70,329 (17.00)	7196 (8.40)	535,758 (15.70)	613,283 (15.70)
	Total	412,800 (9.380)	85,436 (3.93)	3,411,171 (45.25)	3,909,407 (27.70)
Statin and nonstatin cholesterol-lowering medication users[b]	Total	45,327 (1.030)	10,159 (0.47)	364,656 (4.84)	420,142 (2.98)
Nonstatin cholesterol-lowering medication users	Bile acid–binding resins	10,285 (12.39)	1629 (9.06)	92,151 (15.89)	104,065 (15.29)
	Cholesterol absorption inhibitors	13,800 (16.62)	1573 (8.74)	141,624 (24.43)	156,997 (23.06)
	Fibrates	42,835 (51.59)	12,430 (69.09)	279,033 (48.13)	334,298 (49.10)
	Niacin	10,300 (12.41)	2120 (11.78)	64,621 (11.15)	77,041 (11.32)
	Omega-3 fatty acids	15,204 (18.31)	1899 (10.56)	62,893 (10.85)	79,996 (11.75)
	Total	83,024 (1.89)	17,990 (0.83)	579,786 (7.69)	680,800 (4.82)
All cholesterol-lowering medication users[c]	Total	450,497 (10.23)	93,267 (4.29)	3,626,301 (48.11)	4,170,065 (29.54)
Patients aged 40-75 years not receiving cholesterol-lowering medications					
With diabetes		48,796 (3.00)	15,211 (5.10)	213,098 (8.70)	277,105 (6.40)
With hypertension claims but no diabetes		230,743 (14.40)	41,289 (13.90)	761,533 (31.20)	1,033,565 (23.80)
Overall total		1,605,973 (36.48)	297,051 (13.66)	2,442,821 (32.41)	4,345,845 (30.79)

[a]See Table 1 for statin dosing intensity definitions.
[b]These patients are receiving a statin and a nonstatin cholesterol-lowering medication, and these counts are not mutually exclusive of the patients counted under the statin and the nonstatin cholesterol-lowering medication user groups.
[c]Unique members who are receiving any cholesterol-lowering medications.

was limited or where exact measures were not known at the time. A univariate sensitivity analysis was conducted to examine the uncertainties in the model. The measures we examined included (1) the percentage of patients receiving a statin and a concomitant nonstatin cholesterol-lowering medication who were projected to have the nonstatin cholesterol-lowering medications discontinued, (2) the percentage of patients who were not taking a cholesterol medication but who would be starting a statin therapy, and (3) the percentage of patients who would be intensifying their statin therapy.

Results

Table 3 shows the baseline cholesterol utilization patterns in the commercial, Medicaid, and Medicare populations. During the baseline period, we identified 14,114,500 continuously eligible patients in the national pharmacy benefit organization. Of these, 4,170,065 (29.5%) patients were already receiving a cholesterol-lowering medication, whereas 4,345,845 (30.8%) patients aged 40 to 75 years were not receiving any cholesterol-lowering medications.

Of the patients not receiving cholesterol-lowering medications at baseline, 277,105 patients had pharmacy claims for diabetes mellitus and 1,033,565 patients had pharmacy claims for hypertension medications. A total of 3,909,407 (27.7%) patients were receiving statin therapy for cholesterol management at baseline, with the majority of them in the Medicare population (45.25%), followed by the commercial (9.38%) and Medicaid (3.93%) populations.

Table 4 Projected Cholesterol-Lowering Medications Utilization

Patients receiving cholesterol-lowering medications		Patients in a commercial plan, N (%) (N = 4,402,866)	Patients in a Medicaid plan, N (%) (N = 2,173,914)	Patients in a Medicare plan, N (%) (N = 7,537,720)	Total population, N (%) (N = 14,114,500)
Statin users, by dosing intensity[a]	Low-intensity statin	27,252 (4.4)	9342 (7.3)	248,729 (6.0)	285,323 (5.8)
	Moderate-intensity statin	392,928 (64.2)	90,642 (70.8)	2,566,826 (61.8)	3,050,396 (62.3)
	High-intensity statin	192,302 (31.4)	28,021 (21.9)	1,336,627 (32.2)	1,556,950 (31.8)
	Total	612,482 (13.91)	128,005 (5.89)	4,152,182 (55.09)	4,892,668 (34.66)
Statin and nonstatin cholesterol-lowering medication users[b]	Total	0 (0)	0 (0)	0 (0)	0 (0)
Nonstatin cholesterol-lowering medication users	Bile acid–binding resins	5667 (22.4)	1000 (19.1)	48,163 (33.4)	54,831 (31.4)
	Cholesterol absorption inhibitors	4801 (19.0)	378 (7.2)	41,549 (28.8)	46,728 (26.8)
	Fibrates	13,270 (52.5)	4204 (80.1)	77,550 (53.8)	95,024 (54.4)
	Niacin	3901 (15.4)	790 (15.1)	21,231 (14.7)	25,922 (14.8)
	Omega-3 fatty acids	7018 (27.8)	535 (10.2)	16,180 (11.2)	23,733 (13.6)
	Total	25,257 (0.57)	5247 (0.24)	144,137 (1.91)	174,641 (1.24)
All cholesterol-lowering medication users[c]	Total	637,739 (14.48)	133,252 (6.13)	4,296,319 (57.00)	5,067,309 (35.90)
Patients aged 40-75 years not receiving cholesterol-lowering medications					
With diabetes claims		0 (0)	0 (0)	0 (0)	0 (0)
With hypertension claims, but no diabetes medication claim		92,297 (6.51)	16,516 (6.42)	304,613 (17.18)	413,426 (11.99)
Overall total		1,418,731 (32.22)	257,067 (11.83)	1,772,803 (23.52)	3,448,601 (24.43)

[a]See Table 1 for statin dosing intensity definitions.
[b]These patients are receiving a statin and a nonstatin cholesterol-lowering medication, and these counts are not mutually exclusive of the patients counted under the statin and the nonstatin cholesterol-lowering medication user groups.
[c]Unique members who are receiving any cholesterol-lowering medications.

A total of 23,180,535 statin prescriptions were processed across the populations over the 1-year study period. The majority of statin users were receiving moderate-intensity statins (69.7%), followed by high-intensity statins (15.7%), and low-intensity statins (14.6%). A total of 4.8% of the overall population was receiving a nonstatin cholesterol-lowering medication for the management of cholesterol, with 61.7% of these patients concomitantly receiving a statin. The remaining 38.3% of patients were receiving nonstatin cholesterol-lowering medications only and would qualify for statin therapy. Among patients receiving a nonstatin cholesterol-lowering medication, 13.8% of patients were taking bile acid–binding resins, 20.9% were using cholesterol absorption inhibitors, 44.4% were using fibrates, 10.2% were taking niacin, and 10.6% used omega-3 fatty acids.

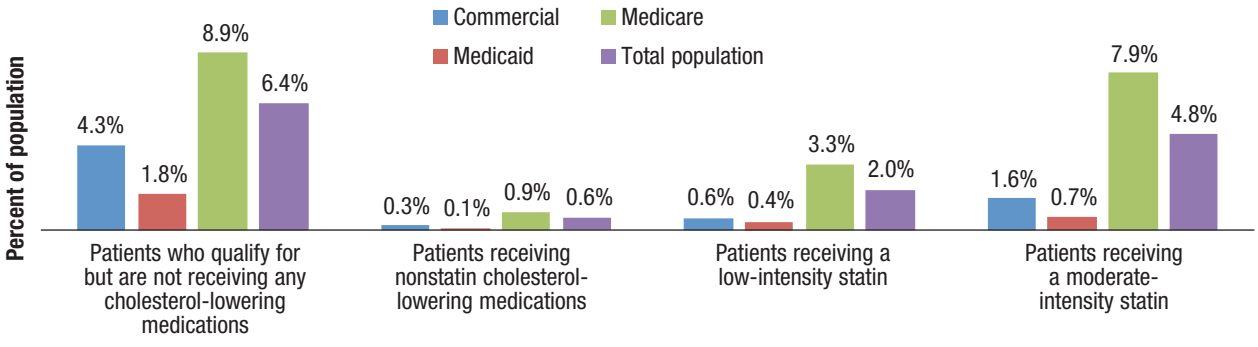
Applying our projections, of the 14,114,500 patients identified, an estimated 4,892,668 (34.66%) patients will receive statin therapy for cholesterol management under the 2013 guidelines, with the majority of statin users being in the Medicare population (55.09%), followed by the commercial (13.91%) and Medicaid (5.89%) populations (**Table 4**).

The largest increase in statin utilization over the next 3 years is estimated to be in the group of patients between the ages of 40 and 75 years who are not receiving any cholesterol medications and who are now starting statin therapy (**Figure 2**). This group accounts for approximately 897,244 (6.4%) patients of the total population, with the largest impact seen in the Medicare population (8.9%), followed by the commercial (4.2%) and Medicaid (1.8%) populations (Figure 2). The remaining 86,017 (0.6%) patients starting a statin medication were previously only receiving a nonstatin cholesterol-lowering medication.

Our analysis also revealed a significant impact on the number of patients who would be switching their type of cholesterol-lowering therapy (Figure 2). It is projected that 285,323 patients who are receiving a low-intensity statin will be intensified to a moderate-intensity or high-intensity statin, whereas 681,370 patients receiving a moderate-intensity statin will switch to a high-intensity statin. For patients receiving a nonstatin cholesterol-lowering medication, with the assumption that 33% of patients will switch to a statin therapy, an estimated 86,017 are projected to start a moderate- or high-intensity statin. In addition, 420,142 patients who were receiving concomitant therapy with a statin and a nonstatin cholesterol-lowering medication are projected to have the nonstatin cholesterol-lowering medication discontinued (Table 4).

The projected impact of the new guidelines is an overall 25% increase in the number of patients who

Figure 2 Projected Percentage of the Population Starting Statin Therapy or Switching to Higher-Intensity Statin Therapy



Population by health plan type	Patients who qualify for but are not receiving any cholesterol-lowering medications, N (%)	Patients receiving nonstatin cholesterol-lowering medications, N (%)	Patients receiving a low-intensity statin, N (%)[a]	Patients receiving a moderate-intensity statin, N (%)[a]
Commercial (N = 4,402,866)	187,242 (4.3)	12,440 (0.3)	27,252 (0.6)	71,992 (1.6)
Medicaid (N = 2,173,914)	39,984 (1.8)	2584 (0.1)	9342 (0.4)	14,889 (0.7)
Medicare (N = 7,537,720)	670,018 (8.9)	70,993 (0.9)	248,729 (3.3)	594,489 (7.9)
Total population (N = 14,114,500)	897,244 (6.4)	86,017 (0.6)	285,323 (2.0)	681,370 (4.8)

[a]See Table 1 for statin dosing intensity information.

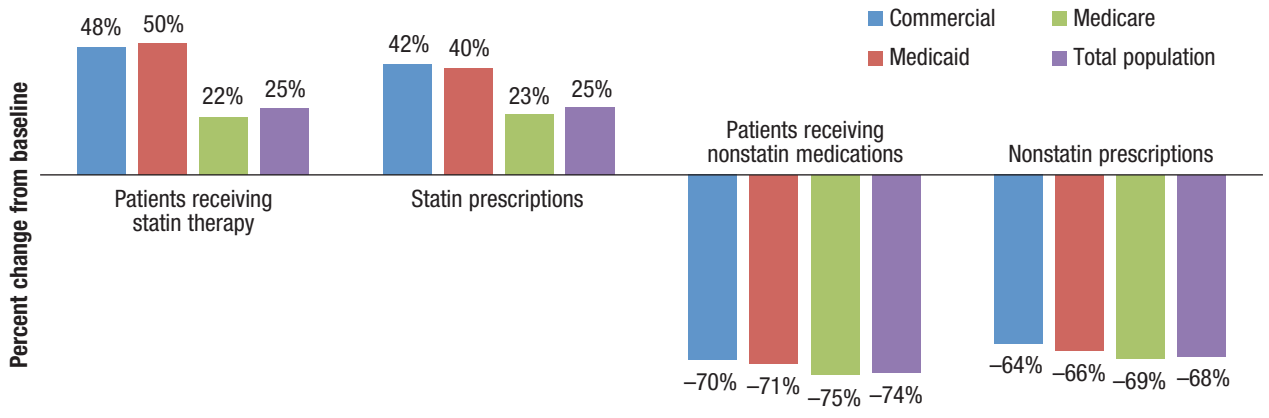
will be treated with a statin, with nearly 1 million more patients receiving a statin therapy under the new guidelines (**Figure 3**). Although more patients are starting statins in the Medicare population than in other groups, the commercial insurance and Medicaid populations have the greatest percentage change as a result of the lower initial number of patients receiving statin therapy at baseline. This increase in the number of patients receiving a statin is projected to result in a 25% overall increase in statin prescriptions (42%, 40%, and 23% in the commercial, Medicaid, and Medicare populations, respectively) and a 68% decrease in other nonstatin cholesterol-lowering medications (64%, 66%, and 69% in the commercial, Medicaid, and Medicare populations, respectively). The largest change in the statin drugs market share will be seen in the high-intensity medications, with the majority of patients starting or switching to this high-intensity class (**Figure 4**).

The sensitivity analysis showed that certain assumptions in the model will have a larger impact on utilization than other assumptions (**Figure 5**). The projected numbers of statin users and statin prescriptions are the most sensitive to the percentage of patients who are not receiving cholesterol-lowering medications, those who have hypertension, and patients who would start receiving statin therapy. Varying the percentage of patients with hypertension who would start receiving a statin therapy by ±25% (35%-85%) would result in a 5% change in the number of statin users and a 4% change in the number of statin prescriptions.

The projected number of patients receiving nonstatin cholesterol-lowering medications is the most sensitive to changes in the percentage of patients receiving concomitant statin and nonstatin cholesterol-lowering medications who would be discontinuing the nonstatin cholesterol-lowering medication, as well as the number of patients receiving a nonstatin cholesterol-lowering medication who would be switching to a statin therapy. Varying the percentage of patients receiving nonstatin cholesterol-lowering medications who would be switching to a statin therapy by ±25% (8%-58%) would result in a 37% change in the number of patients receiving a nonstatin cholesterol-lowering medication.

Lowering the percentage of patients receiving both a statin and a nonstatin cholesterol-lowering medication who would be discontinuing the nonstatin cholesterol-lowering therapy by 50% would lead to a 120% change in the number of patients receiving a nonstatin cholesterol-lowering medication. We also found that varying the statin persistence rate based on literature did

Figure 3 Change in Cholesterol-Lowering Medication Utilization from Baseline



Population by health plan type	Change in number of patients receiving statin, N (%)	Change in statin prescriptions, N (%)	Change in number of patients receiving nonstatin cholesterol-lowering medications, N (%)	Change in nonstatin cholesterol-lowering medication prescriptions, N (%)
Commercial (N = 4,402,866)	199,682 (48.4)	1,011,725 (42.1)	–57,767 (–69.6)	–275,823 (–63.6)
Medicaid (N = 2,173,914)	42,569 (49.8)	248,209 (40.4)	–12,743 (–70.8)	–83,614 (–66.0)
Medicare (N = 7,537,720)	741,011 (21.7)	4,647,888 (23.0)	–435,649 (–75.1)	–2,304,136 (–69.1)
Total population (N = 14,114,500)	983,261 (25.2)	5,907,823 (25.5)	–506,159 (–74.3)	–2,663,574 (–68.4)

not have a major impact on the use of cholesterol-lowering medications, and lowering persistence rates decreased statin prescriptions by 5%.

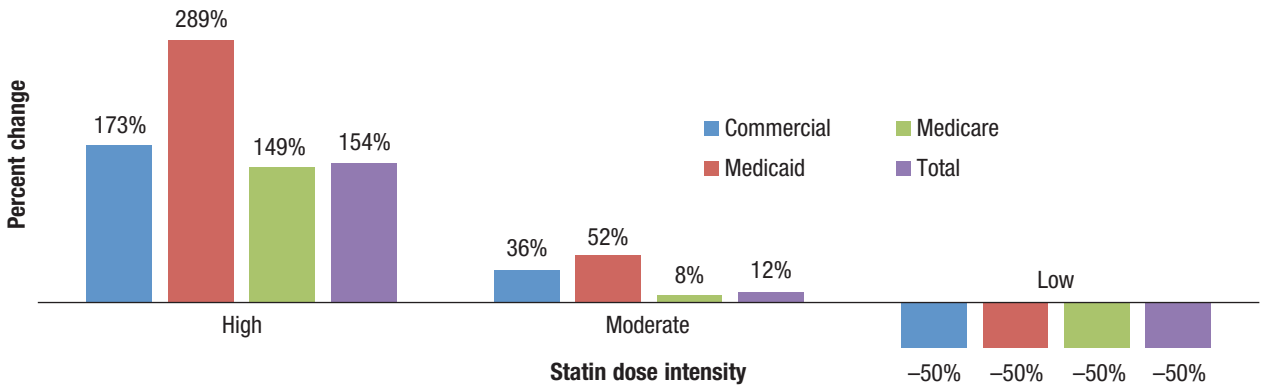
Discussion

In this analysis, we evaluated the potential impact of the new cholesterol treatment guidelines on the utilization of cholesterol-lowering medications in a real-world managed care setting and examined its potential impact in certain payer populations. Specifically, we applied real-world data and expert opinion from the practicing community in an attempt to determine the impact of the new guidelines. Our analysis suggests that the 2013 ACC/AHA guidelines will increase the overall number of patients who are treated with statins in the overall managed care population from 27.7% to 34.7% over the next 3-year period, with the greatest increase resulting from the new ASCVD primary prevention risk group defined by the 2013 guidelines. Patients who are not receiving any cholesterol-lowering medications and who are between the ages of 40 and 75 years comprise 30.8% of this managed care population. Of these patients, 30.2% receive treatment for diabetes or hypertension and could potentially be prescribed a statin.

Extrapolating data from the National Health and Nutrition Examination Survey to a population of 115.4 million US adults, Pencina and colleagues estimated that 56 million (48.6%) American adults would now be eligible for statin therapy.[5] They also projected that there would be 11.1% more statin users than previously would have been eligible under the ATP III guidelines.[5] Our estimates yielded a lower number of patients who would be eligible for a statin therapy in this managed care population; however, the projected change in statin utilization is expected to increase by approximately 25% over the next 3 years.

Similar to the study by Pencina and colleagues, our projections show that the greatest impact of the new

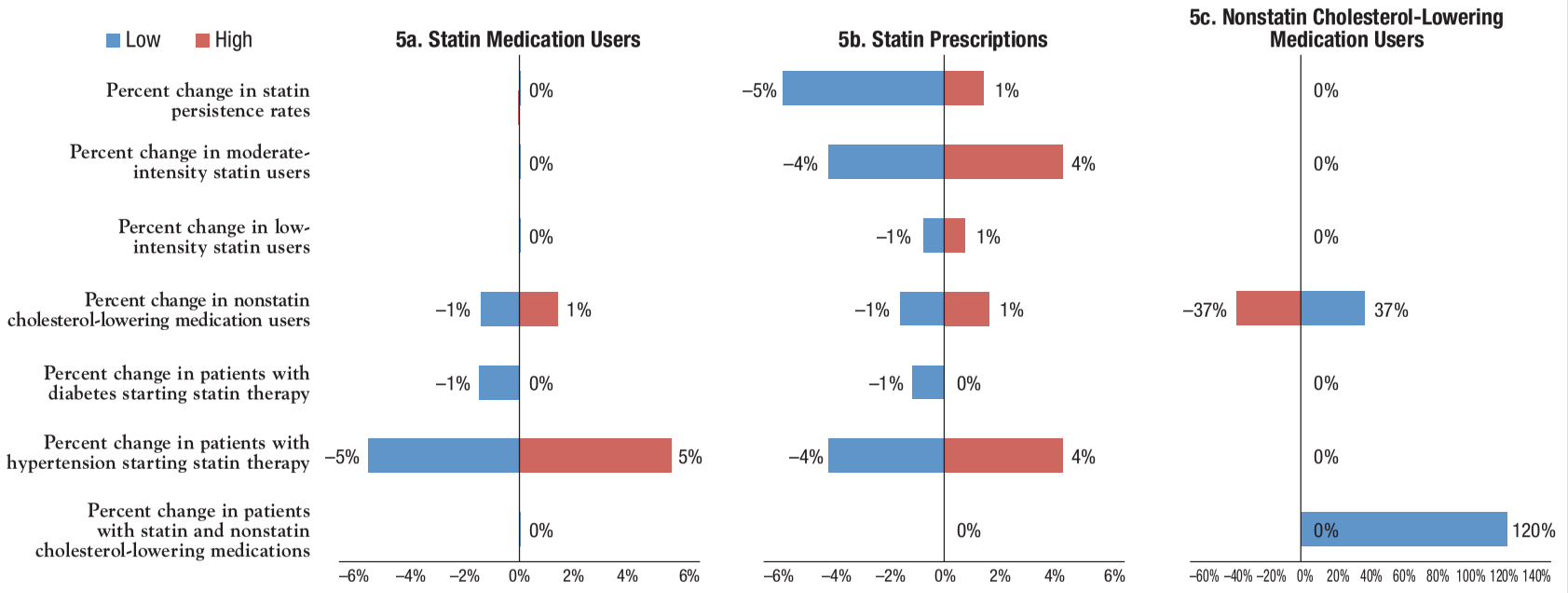
Figure 4 Expected Shift in Statin Dose-Intensity Utilization



Population by health plan type	Statin dose intensity[a]	Current patients, N	Projected patients, N	Percent change, %
Commercial (N = 4,402,866)	High	70,329	192,302	173.4
	Moderate	287,968	392,928	36.4
	Low	54,503	27,252	–50.0
Medicaid (N = 2,173,914)	High	7196	28,021	289.4
	Moderate	59,556	90,642	52.2
	Low	18,684	9342	–50.0
Medicare (N = 7,537,720)	High	535,758	1,336,627	149.5
	Moderate	2,377,955	2,566,826	7.9
	Low	497,458	248,729	–50.0
Total population (N = 14,114,500)	High	613,283	1,556,950	153.9
	Moderate	2,725,479	3,050,396	11.9
	Low	570,645	285,323	–50.0

[a]See Table 1 for statin dosing intensity information.

Figure 5 Sensitivity Analysis Varying Different Model Assumptions



Label	Description	Base case, %	Low, %	High, %
Percent change in patients with statin and nonstatin cholesterol-lowering medications	Patients receiving a statin and a nonstatin cholesterol-lowering medication, with the percentage of patients who will discontinue their nonstatin cholesterol-lowering medication removed	100	50	100
Percent change in patients with hypertension starting statin therapy	Percentage of patients aged 40-75 years who are not receiving a cholesterol medication but are receiving an antihypertensive medication and will start taking a statin	60	35	85
Percent change in patients with diabetes starting statin therapy	Percentage of patients aged 40-75 years who are not receiving a cholesterol-lowering medication but are receiving an antidiabetes medication who will start taking a statin	100	75	100
Percent change in nonstatin cholesterol-lowering medication users	Percentage of patients receiving a nonstatin cholesterol-lowering medication who will switch to a statin therapy	33	8	58
Percent change of low-intensity statin users	Percentage of patients receiving low-intensity statin therapy who will switch to a moderate-intensity or high-intensity statin	50	25	75
Percent change of moderate-intensity statin users	Percentage of patients receiving moderate-intensity statin therapies who will switch to a high-intensity statin	25	0	50
Percent change of statin persistence rates	Percentage of patients newly starting statin therapy who are projected to be persistent over time	67	40	73

guidelines is with patients between the ages of 40 and 75 years who were not receiving therapy at baseline and who will be starting statin therapy for the primary prevention of ASCVD. Although we did not specifically evaluate the patients' ages, we found that the Medicare population, which generally covers patients aged ≥65 years, is estimated to have the largest change in cholesterol utilization.

Unlike the study by Pencina and colleagues, our analysis did not focus solely on statin therapy but also examined the impact to all cholesterol-lowering medications. We assumed that patients receiving a statin and a concomitant nonstatin cholesterol-lowering medication would stop the latter medication. This is based on the assumption that these nonstatin cholesterol-lowering medications were added to augment the statin therapy to get the patient to an LDL-C target. Because the treat-to-target approach is no longer a recommended strategy, it was assumed that these nonstatin cholesterol-lowering medications would be removed. This may underestimate the number of patients who may be taking these nonstatin cholesterol-lowering medications for other cholesterol-lowering benefits, such as for lowering elevated triglyceride levels.

In our sensitivity analysis, we varied the percentage of patients, currently using statin and nonstatin cholesterol-lowering medications, who would be stopping their nonstatin cholesterol-lowering agent between 50% and 100%. By decreasing the percentage of patients who would be discontinuing their nonstatin cholesterol-lowering therapy to 50%, we calculated a 120% increase in the number of patients using a nonstatin cholesterol-lowering medication. In addition, we assumed that 33% of patients receiving a nonstatin cholesterol-lowering medication are projected to start a statin therapy, because it is likely that some of these patients were potentially not receiving a statin previously because of intolerance.

The prevalence of true statin intolerance in the medical literature has been shown to be 5% to 10%, with a higher percentage of patients (10%-20%) having statin-associated muscle problems.[6-8] By varying the percentage of patients receiving a nonstatin cholesterol-lowering medication who would be projected to switch to a statin therapy between 8% and 58%, we observed a large impact on the utilization of nonstatin cholesterol-lowering medications.

In addition, the 2013 guidelines do not recommend treatment with low-intensity statins; however, based on expert opinion, we assumed that 50% of the patients using low-intensity statins may not be able to tolerate a higher-intensity statin therapy. Varying this estimate in our sensitivity analysis by 25% did not greatly affect other utilization rates. Based on the 2013 guidelines, certain patients (eg, diabetic patients aged <40 years with LDL-C levels between 70 mg/dL and 189 mg/dL) who were previously receiving statin medications may now be taken off therapy, because they are no longer defined as an ASCVD high-risk group. However, we did not assume that such patients would discontinue therapy during the initial phase that the 2013 guidelines are being implemented. A possible reason for this is because of the reluctance of providers and patients to stop a statin therapy as a result of the long-perceived benefits of statin therapy in this population. As a result, we may be overestimating the number of patients who would continue to receive a statin therapy during the next 3 years.

In this study we also assumed that among patients who are not receiving cholesterol-lowering therapy, those with diabetes or hypertension have a higher risk for ASCVD. Based on the 2013 guidelines, all diabetic patients between the ages of 40 and 75 years should be receiving a statin therapy. By contrast, based on expert opinion, we assumed that approximately 60% of patients in this group who are receiving antihypertensive medications should also start receiving a statin. Some of the patients receiving an antihypertensive medication are assumed to have their hypertension controlled with therapy, or be at a lower risk for ASCVD and, therefore, do not have to use statin therapy. Our sensitivity analysis showed that a 25% change in the percentage of patients receiving antihypertensive medications that would be starting to use statin therapy (between 35% and 85%) will change the projected number of statin users by 5%.

In another part of our analysis we applied adherence to therapy and market share to determine which medications will be used after the 2013 ACC/AHA guidelines. Karter and colleagues examined adherence and persistence in a cohort of new medication users (ie, antidiabetes agents, antihypertensives, lipid-lowering medications) during a 2-year period, and found that 4.7% of patients were primary nonadherent to their medication regimen (ie, no dispensing), 17.6% were early nonpersistent (ie, only 1 prescription fill), and 4.4% discontinued therapy without either provider consultation or switching therapies.[10] This amounts to approximately 26.7% of patients who discontinued therapy or who did not start therapy during a 2-year period.

Overall, 39% of patients in the study by Karter and colleagues were persistent with their therapy at 2 years, with the remainder of discontinuations resulting from changes in therapy initiated by the provider.[10] Based on this, we assumed that approximately 66% of patients in the model would be persistent with therapy at 3 years, which we examined in our sensitivity analysis. Varying the persistence estimates between 40% and 73%, we found that lowering the persistence rate to 40% decreased statin prescriptions by 5%. It is unknown what

the rate of acceptance or provider adherence to the 2013 guidelines would be, and thus, we assumed that these projections would take place during a 3-year period.

Limitations

Our study has several limitations. First, because of the nature of the claims data, we were not able to apply LDL-C levels or the new risk calculator to determine the specific CV event risk for each patient. Pharmacy claims data were examined, so proxy medications were used to identify patients with diabetes or hypertension. In addition, the 2013 guidelines do not apply to patients with stage II to IV heart failure and hemodialysis, who could not be easily identified in our pharmacy claims database and were not accounted for in the projections. To evaluate the impact of the 2013 guidelines in a real-world setting, we used expert specialist opinion where there was limited medical information or uncertainty in the clinical application of the guidelines. Because these estimates were used directly in the projection, we varied them in a sensitivity analysis to determine their impact.

Another limitation is that there are several unknown impacts of the guidelines, including provider uptake of the guidelines and patient adherence to the guidelines. Thus, assumptions were made to estimate the impact of the guidelines' uptake. Because of the timing of the guidelines' release, there were controversies regarding the risk calculator that may affect acceptance of the guideline; these were not taken into consideration in our projections.

One other limitation in this model is that we did not take into consideration the age of patients who may be starting or switching to moderate- or high-intensity statins. The 2013 guidelines recommend the use of moderate-intensity statins for patients aged ≥75 years. Because the Medicare population is the largest utilizer of statin therapy in our population, we might have overestimated the number of patients who could potentially be receiving high-intensity statins in this population, by not accounting for the proportion of these members who may actually be using moderate-intensity statin therapy.

Furthermore, the cholesterol drugs market share in this managed care population was used to determine how statins would be utilized, which may change with any changes in statin utilization or with formulary changes in the future.

Conclusions

The 2013 ACC/AHA guidelines for the management of cholesterol are projected to increase the number of statin users by 25% in a managed care population with more than 25 million members. The largest increase in statin use will be in the population of patients aged 40 to 75 years who are not currently receiving any cholesterol-lowering therapy. Because the 2013 guidelines focus on the use of higher-intensity statins in these high-risk groups, we expect to see an increase in the use of these agents as more patients start therapy or switch from lower-intensity statins. In addition, the 2013 ACC/AHA guidelines are also projected to have a large impact on the use of nonstatin cholesterol-lowering medications as patients are gradually being switched to statin therapy as recommended by the new guidelines. Of the entire managed care population, the Medicare population, which includes mainly older patients, is expected to see the greatest impact of the new guidelines in cholesterol-lowering drug utilization. ■

Acknowledgments

Dr Tran, Dr Caglar, Dr Stockl, Dr Lew, Dr Solow, and Dr Chan were responsible for the writing of this manuscript. Dr Tran and Dr Caglar validated the data. Dr Tran is the guarantor of the quality and validity of this article. Dr Chan provided clinical consultation for this article.

Author Disclosure Statement

Dr Tran, Dr Caglar, Dr Stockl, Dr Lew, and Dr Solow are employees of OptumRx; Dr Chan is a consultant to and is on the advisory board of OptumRx. OptumRx did not receive any external funding for this study.

References

1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 pt B):2889-2934. Erratum in: *J Am Coll Cardiol.* 2014;63(25 pt B):3024-3025.
2. Downs J, Good C. New cholesterol guidelines: has Godot finally arrived? *Ann Intern Med.* 2014;160:354-355.
3. Krumholz HM. The new cholesterol and blood pressure guidelines: perspective on the path forward. *JAMA.* 2014;311:1403-1405.
4. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106:3143-3421.
5. Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr, et al. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med.* 2014;370:1422-1431.
6. Grundy SM. Statin discontinuation and intolerance: the challenge of lifelong therapy. *Ann Intern Med.* 2013;158:562-563.
7. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. *Ann Intern Med.* 2013;158:526-534.
8. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation.* 2006;114:2788-2797.
9. Shenolikar RA, Balkrishnan R. Oral antidiabetes medication adherence and health care utilization among Medicaid-enrolled type 2 diabetic patients beginning monotherapy. *Diabetes Care.* 2008;31:e5.
10. Karter AJ, Parker MM, Moffet HH, et al. New prescription medication gaps: a comprehensive measure of adherence to new prescriptions. *Health Serv Res.* 2009;44(5 pt 1):1640-1661.
11. Raebel MA, Ellis JL, Carroll NM, et al. Characteristics of patients with primary non-adherence to medications for hypertension, diabetes, and lipid disorders. *J Gen Intern Med.* 2012;27:57-64.

Stakeholder Perspective next page

STAKEHOLDER PERSPECTIVE

Real-World Consequences of the 2013 ACC/AHA Cholesterol Guidelines for the Prevention of Cardiovascular Disease

By Joseph D. Jackson, PhD
Program Director, Applied Health Economics and Outcomes Research, Jefferson School of Population Health, Thomas Jefferson University, Philadelphia, PA

RESEARCHERS/PROVIDERS: From the approval of the first statin, lovastatin (Mevacor), in 1987 in the United States, there have been naysayers, despite the overwhelming scientific (and clinical) evidence in support of the cholesterol hypothesis, namely, the persistent use of prescribed statins to reduce heart disease events.[1,2] In 1989, Thomas Moore wrote a commentary discussing "The Cholesterol Myth" in the *Atlantic Monthly*,[3] and as recently as 2013, Abramson and Redberg[4] and Kolata,[5] writing in the *New York Times*, panned the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (published in 2014) for the management of high blood cholesterol with statins to reduce the risk for cardiovascular disease.[2]

In more than a dozen randomized controlled trials (RCTs), statins have been conclusively proved to significantly reduce all-cause mortality, cardiac death, stroke, coronary revascularization, and major coronary events in at-risk populations for the primary and secondary prevention of heart disease.[6] One of the key concerns of the naysayers is the incidence of side effects, particularly muscle pain (myopathy), in the populations of patients using statins, especially in the primary prevention setting. Critics cite the rates of side effects with statins to be as high as 18% to 20% based largely on observational evidence.

By contrast, Dr Rory Collins, Head of the Cholesterol Treatment Trialists' (CTT) Collaboration, cites the rate of 5% as statin-related side effects, based on dozens of RCTs in the CTT and on a Cochrane review.[7] The side effects seen with statins can usually be managed by a change in the statin dose or by switching the statin. Therefore, the 2013 ACC/AHA guideline authors, and most physicians who practice evidence-based medicine, believe that more individuals who are at risk for cardiovascular disease because of elevated blood cholesterol should be treated with a statin.[2]

PAYERS: Are statins worth the cost? An important aspect of drug cost and value is the question of who will be receiving the treatment in the real world. In this issue of *American Health & Drug Benefits*, Tran and colleagues provide a guided tour of what the 2013 ACC/AHA guidelines mean for managed care organizations in the real world.[8] Epidemiologically, the new guidelines were projected to add 13 million new patients for treatment with cholesterol-lowering drugs, and most of the population would come from adults aged 60 to 75 years.[9]

An important provision in the new guidelines is the recommendation for a risk assessment to guide cholesterol-lowering treatment rather than treatment based on a laboratory measure of cholesterol levels, which has not been supported by event-level evidence from RCTs. This change to risk-based prescribing is consistent with the evidence of benefit versus risk and with best medical practice.

Pharmacologic treatment in addition to diet and exercise (which are increasingly emerging as important) are the best ways to manage cardiovascular disease. Risk assessment is an important aspect of optimal medical practice and of assessing the economic value of treatment.[10,11] The 2013 ACC/AHA guidelines specify a risk rate of ≥7.5% over 10 years as a criterion for treatment with a statin.[2] In 2003, using evidence of event-level data from RCTs, Caro and colleagues found that the price of branded statins would be cost-effective at a threshold of $50,000 per a life-year gained, with a 10-year risk of 7.5%.[11]

Furthermore, based on the price of generic statins, which is applicable to most statins today, cost-effectiveness threshold levels would actually yield a cost-savings—that is, more money would be spent on managing the cardiovascular events (ie, heart attack, stroke, death, percutaneous coronary intervention, and surgery) than the cost spent on all at-risk patients who would be using a generic statin. Thus, the projected increased utilization of statins that Tran and colleagues highlight may actually save money for health insurance plans and other payers.

PATIENTS: The 2013 ACC/AHA cholesterol guidelines are good news for patients with high cholesterol who are at risk for cardiovascular events. We know

STAKEHOLDER PERSPECTIVE *Continued*

that of the approximately 100 million Americans aged 40 to 75 years, 31 million would meet the ACC/AHA risk definition to qualify for treatment with a statin. We also know that 60% of these 31 million patients will have a cardiovascular event in their lifetime.[12] The ACC/AHA guidelines also indicate that physicians should discuss risk status with their patients.[2] This means that in addition to prescribing a statin, with an alert to watch for side effects (especially muscle pain), providers should talk to their patients about diet and exercise levels, according to best medical practice.

Furthermore, Tran and colleagues note that there has been a decrease in the use of nonstatin treatments in this patient population.[8] This is an important observation, because patients should not use unproved treatments. The best current example of this is niacin for the treatment of heart disease, which is intended to increase high-density lipoprotein (HDL) levels.

The HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events) and the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) studies, as well as studies with cholesterylester transfer protein inhibitors (eg, torcetrapib and anacetrapib), have demonstrated no reduction in cardiovascular events for drugs that raise HDL levels, such as niacin: the side effects of niacin are well known, and the drug is difficult for patients to tolerate.[13,14]

Tran and colleagues have provided a real-world analysis of probable treatment scenarios under the new 2013 ACC/AHA cholesterol treatment guidelines. This should help us to appreciate the benefits, risks, and costs that are likely to be the consequences of these new recommendations. ■

1. Vagelos PR, Galambos L. *Medicine, Science, and Merck*. Cambridge, UK: Cambridge University Press; 2004:155-156.
2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 pt B):2889-2934. Erratum in: *J Am Coll Cardiol*. 2014;63(25 pt B):3024-3025.
3. Moore TJ. The cholesterol myth. *The Atlantic Monthly*. September 1989:37-59.
4. Abramson JD, Redberg RF. Don't give more patients statins. *New York Times*. November 13, 2013. www.nytimes.com/2013/11/14/opinion/dont-give-more-patients-statins.html?_r=0. Accessed November 5, 2014.
5. Kolata G. Bumps in the road to new cholesterol guidelines. *New York Times*. November 25, 2013. www.nytimes.com/2013/11/26/health/heart-and-stroke-study-hit-by-a-wave-of-criticism.html?pagewanted=all. Accessed November 5, 2014.
6. Shah RV, Goldfine AB. Statins and risk of new-onset diabetes mellitus. *Circulation*. 2012;126:e282-e284.
7. Wood S. Statin papers stand: expert panel endorses the *BMJ*'s stance on retraction request. *Medscape*. August 1, 2014. www.medscape.com/viewarticle/829298. Accessed November 5, 2014.
8. Tran JN, Caglar T, Stockl KM, Lew HC, et al. Impact of the new ACC/AHA guidelines on the treatment of high blood cholesterol in a managed care setting. *Am Health Drug Benefits*. 2014;7:426-439.
9. Pencina MJ, Navar-Boggan AM, D'Agostino RB, et al. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med*. 2014;370:1422-1431.
10. L'Italien GL, Ford I, Jackson JD, et al. The cardiovascular event reduction tool (CERT)—A simplified cardiac risk prediction model developed from the West of Scotland Coronary Prevention Study (WOSCOPS). *Am J Cardiol*. 2000;85:720-724.
11. Caro JJ, Huybrechts KF, Jackson JD, et al. Allocating funds for cardiovascular disease prevention in light of the NCEP ATP III guidelines. *Am J Manag Care*. 2003;9:477-489.
12. Smith SC Jr, Wood S. Who's at risk? A defense of the CV risk calculator. *Medscape*. November 20, 2013. www.medscape.com/viewarticle/814711. Accessed November 5, 2014.
13. Mandrola JM. Five lessons from the niacin failure. *Medscape*. July 21, 2014. www.medscape.com/viewarticle/828580. Accessed November 5, 2014.
14. Stetka B, Aronow W. Niacin with statins? No dice. *Medscape*. September 19, 2014. www.medscape.com/viewarticle/829961. Accessed November 5, 2014.