

Trends in the Use of Nonstatin Lipid-Lowering Therapy Among Patients With Coronary Heart Disease

A Retrospective Cohort Study in the Medicare Population 2007 to 2011

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ABSTRACT

BACKGROUND Nonstatin lipid-lowering therapy is adjunctive therapy for high-risk individuals on statins or monotherapy among those who cannot tolerate statins.

OBJECTIVES This study determined time trends between 2007 and 2011 for statin and nonstatin lipid-lowering therapy (niacin, fibrates, bile acid sequestrants, and ezetimibe) use among Medicare beneficiaries with coronary heart disease (CHD) in light of emerging clinical trial evidence.

METHODS We conducted a retrospective cohort study using the national 5% random sample of Medicare beneficiaries (n = 310,091). We created 20 cohorts of individuals with CHD, representing calendar quarters from 2007 through 2011, to assess trends in use of statins and nonstatin lipid-lowering medications.

RESULTS Statin use increased from 53.1% to 58.8% between 2007 and 2011. Ezetimibe use peaked at 12.1% and declined to 4.6% by the end of 2011, declining among both patients on statins (18.4% to 6.2%) and not on statins (5.0% to 2.4%). Fibrate use increased from 4.2% to 5.0%, bile acid sequestrants did not change significantly, and niacin use increased from 1.5% to 2.4% and then declined in late 2011. Use of nonstatin lipid-lowering therapy was less common at older age, among African Americans, patients with heart failure, and patients with a higher Charlson comorbidity score. Nonstatin lipid-lowering therapy use was more common among men and patients with diabetes, those who had cardiologist visits, and among those taking statins.

CONCLUSIONS Declining ezetimibe and niacin use but not fibrate therapy among Medicare beneficiaries with CHD coincides with negative clinical trial results for these agents. (J Am Coll Cardiol 2015;66:1864–72)

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Statin therapy reduces cardiovascular events and mortality among patients with coronary heart disease (CHD) (1). However, many statin-treated patients with CHD experience cardiovascular events and premature mortality (2). This “residual risk” is mediated by multiple factors, including the burden of atherosclerosis, residual abnormalities in the lipid profile, poor control of nonlipid risk factors,

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and poor adherence or inability to tolerate prescribed therapies for secondary prevention. Among individuals with residual dyslipidemia on a statin, combination lipid-lowering therapy (statin plus niacin, fibrate, bile acid sequestrant, or ezetimibe) further lowers low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and may decrease triglycerides and increase high-density lipoprotein cholesterol (3). The evidence for additional reduction in cardiovascular risk with combination therapy is limited (4), although recent results from the IMPROVE-IT (IMPROved Reduction of Outcomes: Vytorin Efficacy International Trial) showed a modest reduction in cardiovascular events from additional low-density lipoprotein cholesterol-lowering with ezetimibe added to simvastatin compared to simvastatin monotherapy in patients with acute coronary syndrome (5). Nonstatin lipid-lowering therapy is also used among individuals unable to take statins given favorable outcomes with bile acid sequestrants, fibrates, and niacin in older randomized controlled outcomes trials and angiographic regression trials (3).

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Using pharmaceutical sales and prescription data from the United States and Canada, several reports have emphasized changes over time in the use of ezetimibe, niacin, and fibrates (6-11). However, these studies did not report trends of therapy among patients with CHD and did not assess clinical correlates of nonstatin lipid-lowering therapy. In this study, we report trends between 2007 and 2011 in the use of niacin, fibrates, bile acid sequestrants, and ezetimibe alone and in combination with statin therapy among Medicare beneficiaries with CHD.

METHODS

We conducted a retrospective cohort study of Medicare beneficiaries using the 2006-2011 national 5% random sample from the Centers for Medicare and Medicaid Services. Medicare is a U.S. federal benefit program that provides health insurance to individuals who are ≥ 65 years of age, on disability, or who have end-stage renal disease, through either fee-for-service reimbursement or through contracts with health care organizations (Medicare Advantage). For the current analysis, we used claims data from Medicare fee-for-service Parts A (inpatient), B (outpatient), and D (prescription drug). Medicare claims and assessment data are linked by beneficiary across the continuum of care. We excluded beneficiaries enrolled in Medicare Advantage plans (Medicare Part C) as claims for these individuals are not complete. Centers for Medicare

and Medicaid Services and the Institutional Review Board at the University of Alabama at Birmingham approved the study.

The calendar years of 2007 through 2011 were divided into 20 quarters defined as January 1 to March 31 (first quarter), April 1 to June 30 (second quarter), July 1 to September 30 (third quarter), and October 1 to December 31 (fourth quarter). For each calendar quarter, we defined an eligibility period as the 1 year before the start of the quarter (Online Figure 1). To be eligible for a calendar quarter, beneficiaries were required to meet the following criteria: 1) be ≥ 65 years of age at the start of the eligibility period; 2) have a history of CHD documented during the look-back period; and 3) have continuous "full coverage" for Medicare, be in the 5% Medicare sample, and live in the United States for the entire eligibility period and calendar quarter under study. We defined the look-back period as the time between the start of the eligibility period through the date of the first nonstatin lipid-lowering medication fill in the calendar quarter under study or as the midpoint of the calendar quarter for beneficiaries who did not fill a nonstatin lipid-lowering medication. Additionally, we excluded beneficiaries who died before the end of the calendar quarter under study. We used an algorithm based on International Classification of Diseases-Ninth Edition-Clinical Modification (ICD-9-CM) and current procedure terminology codes to define a history of CHD (Online Table 1). Full Medicare coverage was defined as enrollment in Medicare fee-for-service (Parts A and B) and Part D and not being enrolled in a Medicare Advantage plan.

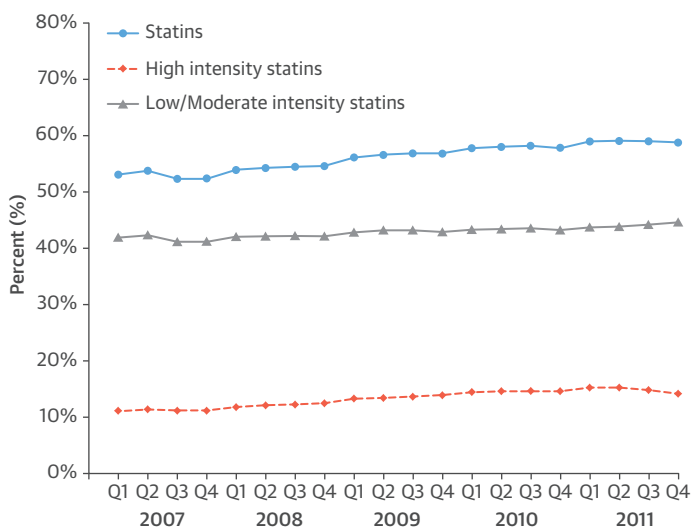
LIPID-LOWERING MEDICATION USE. We investigated the use of statins, overall and by intensity (high or low/moderate), and nonstatin lipid-lowering medications. Seven statins were studied (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin). High-intensity statins included a fill for atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, and simvastatin 80 mg. Nonstatin lipid-lowering medications included ezetimibe, fibrates, niacin, and bile acid sequestrants. Participants were considered to be taking a medication if they had a prescription fill during the calendar quarter under study. Medication use was identified using National Drug Codes and Medicare Part D pharmacy claims.

COVARIATES. We obtained age, sex, race/ethnicity, and receipt of a low-income subsidy under Medicare Part D or Medicare/Medicaid dual eligibility from the Medicare beneficiary enrollment file. Each beneficiary's age was based on the date of their first fill of a nonstatin lipid-lowering medication or the midpoint

ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease
CI = confidence interval
ICD-9-CM = International Classification of Diseases-Ninth Edition-Clinical Modification
RR = risk ratio

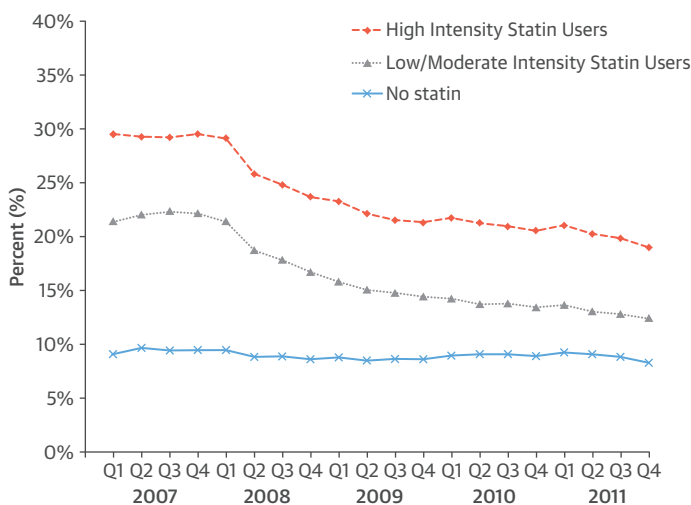
FIGURE 1 Use of Statins Among Medicare Beneficiaries With CHD in 2007 to 2011 by Calendar Quarter



High-intensity statins defined as 40 to 80 mg atorvastatin, 20 to 40 mg rosuvastatin, 80 mg simvastatin.

of the calendar quarter for beneficiaries who did not fill a nonstatin lipid-lowering medication. Comorbid conditions, Charlson comorbidity score, residence in a skilled nursing facility, having received cardiologist care, and the number of different medications filled

FIGURE 2 Use of Nonstatin Lipid-Lowering Medications Among Medicare Beneficiaries With CHD Taking High Potency Statins, Low/Moderate Potency Statins and Not Taking Statins in 2007 to 2011 by Calendar Quarter



High intensity statins defined as 40 to 80 mg atorvastatin, 20 to 40 mg rosuvastatin, 80 mg simvastatin.

were defined using previously published algorithms and ICD-9-CM codes (12-17). Hospitalizations in the look-back period were categorized as being CHD-related (myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention) or not.

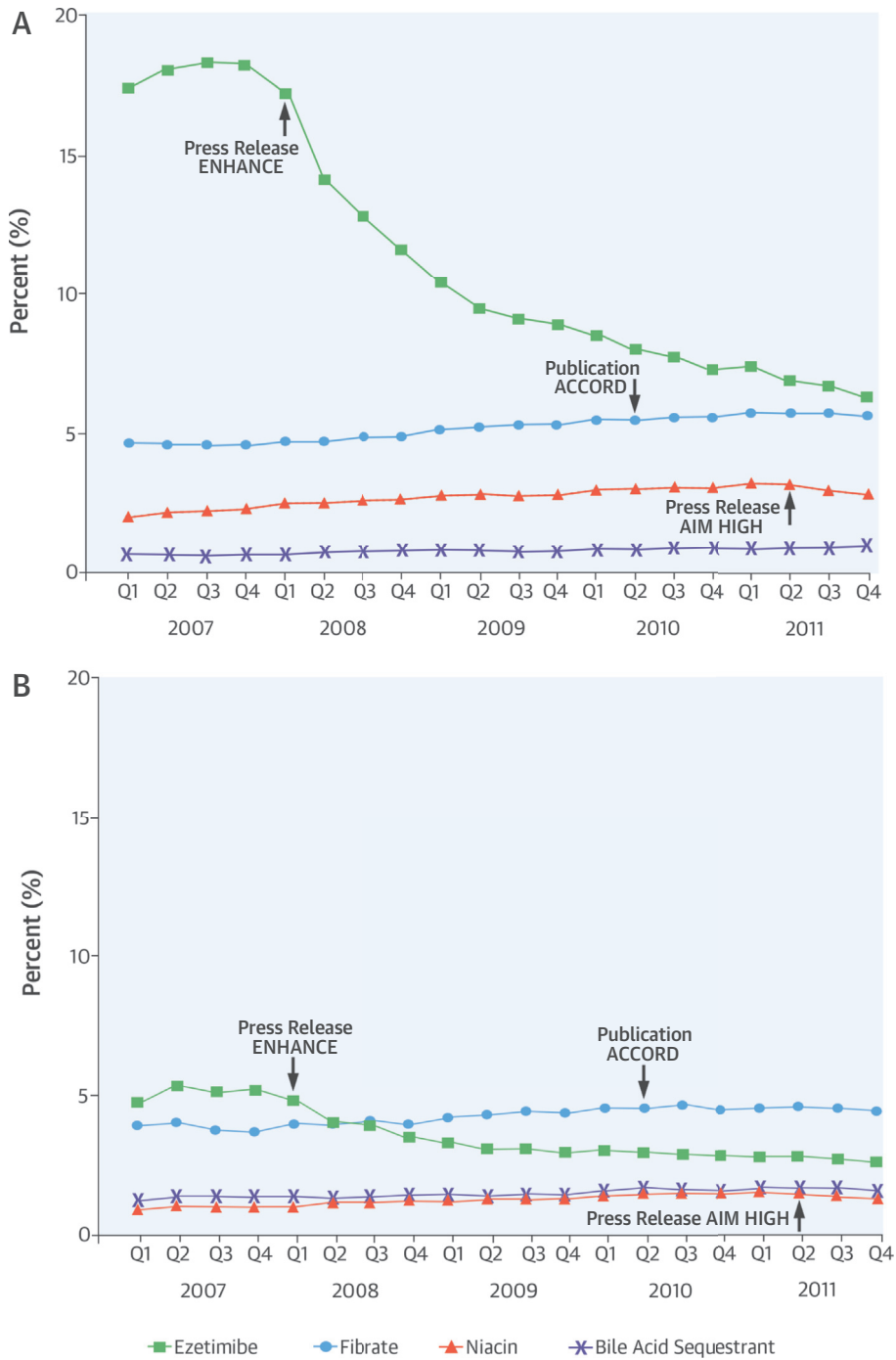
STATISTICAL ANALYSES. We first calculated the proportion of Medicare beneficiaries with CHD who filled a statin, overall and by intensity, and nonstatin lipid-lowering medication during each calendar quarter from January–March (quarter 1) 2007 through October–December (quarter 4) 2011. Taking nonstatin lipid-lowering medications was calculated overall and for beneficiaries taking and not taking statins, separately. Additionally, the proportion of Medicare beneficiaries with CHD taking ezetimibe, fibrates, niacin, and bile acid sequestrants, separately, was calculated for each calendar quarter.

For the remainder of analyses, we pooled data for the 20 calendar quarters. Characteristics of Medicare beneficiaries with CHD taking and not taking nonstatin lipid-lowering medication were calculated. As beneficiaries could contribute to each of the 20 calendar quarters under study, generalizable estimating equations were used to determine the statistical significance of differences across these 2 groups. Using Poisson regression with sandwich estimators accounting for repeated measures, we calculated risk ratios (RRs) and 95% confidence intervals (CIs) for filling a nonstatin lipid-lowering medication associated with calendar year, age, sex, race/ethnicity, low socio-economic status, diabetes, CHD and non-CHD related hospitalization in the past year, history of stroke, history of heart failure, Charlson index, skilled nursing facility stay, cardiologist care, use of statins, and total number of medications being administered. RRs were calculated in unadjusted models, after age, sex, race/ethnicity adjustment, and in a model that included all covariates simultaneously. Poisson regression is a log-linear model that can be used with binary outcomes. When outcomes are common, it has the advantage of providing a more accurate estimate of an exposure-outcome association compared with odds ratios produced by logistic regression. In a final analysis, the fully adjusted model was also calculated for beneficiaries taking and not taking statins, separately. All data management and statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

The current analysis included 310,091 Medicare beneficiaries. In the first quarter of 2007, 53.1% of

CENTRAL ILLUSTRATION Nonstatin Lipid-Lowering Therapy in Medicare: Use of Ezetimibe, Fibrates, Niacin, and Bile Acid Sequestrants Among Medicare Beneficiaries With CHD in 2007 Through 2011 by Calendar Quarter



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(A) Shows data for Medicare beneficiaries on statins. **(B)** Shows data for Medicare beneficiaries not on statins. **Arrows** indicate time points when key study results were released. ENHANCE = Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; ACCORD = Action to Control Cardiovascular Risk in Diabetes; AIM HIGH = Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes.

TABLE 1 Characteristics of Medicare Beneficiaries With CHD Taking and Not Taking Nonstatin Lipid-Lowering Medication in 2007 to 2011

	Use of Nonstatin Lipid-Lowering Medication	
	No (n = 2,267,380)	Yes (n = 367,151)
Calendar year		
2007	367,698 (16.2)	75,247 (20.5)
2008	453,174 (20.0)	80,376 (21.9)
2009	471,383 (20.8)	71,582 (19.5)
2010	479,010 (21.1)	70,477 (19.2)
2011	496,115 (21.9)	69,469 (18.9)
Age, yrs		
<70	333,182 (14.7)	79,049 (21.5)
70-74	481,974 (21.3)	100,548 (27.4)
75-79	477,695 (21.1)	84,336 (23.0)
80-84	455,817 (20.1)	62,711 (17.1)
≥85	518,712 (22.9)	40,507 (11.0)
Male	1,011,652 (44.6)	188,939 (51.5)
Race/ethnicity		
White	1,924,531 (84.9)	327,484 (89.2)
African American	177,825 (7.8)	16,158 (4.4)
Other	41,052 (1.8)	6,311 (1.7)
Asian American	55,140 (2.4)	8,124 (2.2)
Hispanic American	68,832 (3.0)	9,074 (2.5)
Low income subsidy/dual eligible	908,203 (40.1)	132,297 (36.0)
History of diabetes	793,141 (35.0)	155,758 (42.4)
CHD hospitalization	166,020 (7.3)	25,975 (7.1)
Non-CHD hospitalization	792,471 (35.0)	101,214 (27.6)
History of stroke	185,798 (8.2)	22,709 (6.2)
History of heart failure	689,213 (30.4)	90,661 (24.7)
Charlson index		
0	386,173 (17.0)	67,512 (18.4)
1-3	909,130 (40.1)	155,469 (42.3)
≥4	972,077 (42.9)	144,170 (39.3)
Skilled nursing facility stay	291,266 (12.8)	25,174 (6.9)
Cardiologist care	1,433,906 (63.2)	273,661 (74.5)
Use of statins	1,218,466 (53.7)	264,960 (72.2)
Number of medications taken*		
<5	253,045 (11.2)	37,236 (10.1)
5-9	697,965 (30.8)	115,166 (31.4)
≥10	1,316,370 (58.1)	214,749 (58.5)

Values are n (%). *Not including statins or other lipid-lowering medications. As described in the Methods, beneficiaries could contribute multiple records between 2007 and 2011. Overall, there were 310,091 unique beneficiaries included in this analysis (n = 62,638 using nonstatin lipid-lowering medication). All p values for comparisons are <0.001. Though statistically significant, some differences are likely unimportant.
CHD = coronary heart disease.

Medicare beneficiaries with CHD filled a statin prescription with 11.1% having received a high-intensity statin (Figure 1). The use of statins increased over time and 58.8% and 14.2% of Medicare beneficiaries with a history of CHD filled any statin and a high-intensity statin, respectively, in the fourth quarter of 2011. The use of nonstatin lipid-lowering medication did not change substantially between the first

quarter of 2007 and 2008, but declined thereafter from 16.8% in the first quarter of 2008 to 11.7% in the fourth quarter of 2011. Use of nonstatin lipid-lowering therapy decreased substantially more among statin users than non-users (Figure 2).

In the overall population with CHD, ezetimibe use peaked at 12.1% in 2007 and declined to 4.6% by the end of 2011. Fibrate use increased from 4.2% to 5.0%, bile acid sequestrants did not change significantly, and niacin use increased from 1.5% to 2.4% and then modestly declined in late 2011. Among those on statins, ezetimibe use declined from a peak of 18.4% in 2007 to 6.2% by the fourth quarter of 2011 (Central Illustration). Niacin use increased from 2.2% in the first quarter of 2007 to a peak of 3.1% in the first quarter of 2011 and declined to 2.7% by the fourth quarter of 2011. Fibrate use gradually increased from 4.7% to 5.5% over this period. Bile acid sequestrant use was low (0.5% to 0.8%) throughout the study period. Patterns of use of nonstatin lipid-lowering medications were similar for high-intensity statin and low-/moderate-intensity statin users (Online Figure 2).

Among those not on statins (Central Illustration), ezetimibe use was less common throughout the study period than among statin users. Temporal trends, however, were similar with ezetimibe use declining from 5.0% in the fourth quarter of 2007 to 2.4% in the fourth quarter of 2011. In contrast, fibrate use was more common among those not on statins than those on statins and increased over time among those not on statins, surpassing ezetimibe use by the third quarter of 2008. Only a small percentage of nonstatin users were on bile acid sequestrants or niacin. Publication dates of key clinical trials concerning nonstatin lipid-lowering medications are shown in the Central Illustration and Online Figure 2 and suggest a temporal relationship between negative trial announcement or publication for ezetimibe and niacin, but not for fibrates.

Differences in demographics, comorbidities, and health care use between Medicare beneficiaries with CHD taking and not taking nonstatin lipid-lowering medications are detailed in Table 1. These differences were similar across the study period (Online Table 2). In both crude and age-, sex-, and race/ethnicity-adjusted models, the use of nonstatin lipid-lowering medication decreased over successive calendar years and was lower at older age and among African Americans, Asian Americans, and Hispanics, compared to whites (Table 2). Being male, having diabetes, receiving care from a cardiologist, taking statins, and taking more medications overall were associated with a higher RR of nonstatin

lipid-lowering medication use. In contrast, nonstatin lipid-lowering medication use was less common among beneficiaries with CHD- or non-CHD-related hospitalizations in the prior year, with a history of heart failure or stroke, or with a stay in a skilled nursing facility.

After multivariable adjustment, declining use of nonstatin lipid-lowering medication by calendar year was more evident among statin users than nonusers (Table 3). History of diabetes, cardiologist care, and number of medications administered were associated with an increased risk of nonstatin lipid-lowering medication use in both groups, but the association was more pronounced among those not taking statins. History of skilled nursing facility stay was associated with a lower risk for nonstatin lipid-lowering medication use in both groups. Having CHD hospitalizations were more strongly associated with not using nonstatin lipid-lowering therapy among statin users. The Charlson index was more strongly associated with lower use of nonstatin lipid-lowering medications among those not taking statins.

DISCUSSION

Among Medicare beneficiaries with CHD, use of nonstatin lipid-lowering therapy has declined between 2008 and 2011 primarily due to a marked reduction in the use of ezetimibe, even though national cholesterol guidelines and treatment targets remained unchanged during the study period. This decrease in nonstatin lipid-lowering therapy occurred both among patients taking statins and not taking statins, but was more pronounced among statin users. Time trends in use of nonstatin lipid-lowering medications other than ezetimibe were less pronounced and heterogeneous. In any given calendar quarter, <60% of Medicare beneficiaries with CHD filled a statin. Statin use was low at the beginning of the observation period and increased only modestly over time despite good evidence for efficacy to at least age 75 years and likely beyond and guideline recommendations in favor of statin use in these high-risk individuals.

As others have reported based on data from IMS Health (Danbury, Connecticut) and pharmacy benefit managers (10,11,18), the decline in ezetimibe therapy in this Medicare cohort with CHD temporally coincides with the announcement and publication of the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial (a small trial that assessed changes in carotid intimal medial thickness among patients with

TABLE 2 Risk Ratios for Taking Nonstatin Lipid-Lowering Medications Among Medicare Beneficiaries With CHD

	Risk Ratio (95% CI)		
	Crude	Age, Sex, Race/Ethnicity Adjusted	Multivariable Adjusted
Calendar year			
2007	1.00 (ref)	1.00 (ref)	1.00 (ref)
2008	0.89 (0.88-0.89)	0.88 (0.88-0.89)	0.87 (0.86-0.88)
2009	0.78 (0.77-0.79)	0.77 (0.76-0.78)	0.75 (0.74-0.75)
2010	0.76 (0.74-0.77)	0.75 (0.74-0.76)	0.71 (0.70-0.72)
2011	0.72 (0.71-0.73)	0.72 (0.71-0.73)	0.67 (0.66-0.68)
Age, yrs			
<70	1.00 (ref)	1.00 (ref)	1.00 (ref)
70-74	0.90 (0.88-0.92)	0.90 (0.88-0.92)	0.91 (0.89-0.93)
75-79	0.78 (0.76-0.80)	0.79 (0.77-0.80)	0.81 (0.79-0.83)
80-84	0.63 (0.61-0.65)	0.64 (0.62-0.65)	0.69 (0.68-0.71)
≥85	0.38 (0.37-0.39)	0.38 (0.37-0.40)	0.48 (0.47-0.50)
Male			
	1.27 (1.24-1.29)	1.11 (1.09-1.13)	1.09 (1.07-1.11)
Race/ethnicity			
White	1.00 (ref)	1.00 (ref)	1.00 (ref)
African American	0.57 (0.55-0.60)	0.56 (0.54-0.59)	0.59 (0.57-0.62)
Other	0.92 (0.85-0.98)	0.85 (0.80-0.92)	0.86 (0.80-0.92)
Asian American	0.88 (0.83-0.94)	0.88 (0.83-0.93)	0.82 (0.77-0.88)
Hispanic American	0.80 (0.76-0.85)	0.84 (0.79-0.89)	0.82 (0.77-0.86)
Low income subsidy/dual eligible			
	0.86 (0.85-0.88)	0.97 (0.95-0.99)	1.00 (0.98-1.02)
History of diabetes			
	1.31 (1.29-1.33)	1.28 (1.26-1.30)	1.30 (1.28-1.32)
CHD hospitalization			
	0.97 (0.95-0.99)	0.94 (0.92-0.96)	0.81 (0.80-0.83)
Non-CHD hospitalization			
	0.74 (0.73-0.75)	0.81 (0.80-0.82)	0.85 (0.84-0.87)
History of stroke			
	0.77 (0.75-0.79)	0.85 (0.82-0.87)	0.93 (0.90-0.96)
History of heart failure			
	0.78 (0.77-0.79)	0.88 (0.87-0.90)	0.89 (0.88-0.91)
Charlson index			
0	1.00 (ref)	1.00 (ref)	1.00 (ref)
1-3	0.98 (0.96-1.00)	1.02 (1.00-1.04)	0.93 (0.92-0.95)
≥4	0.87 (0.85-0.89)	0.97 (0.95-1.00)	0.95 (0.92-0.97)
Skilled nursing facility stay			
	0.54 (0.53-0.55)	0.65 (0.64-0.67)	0.80 (0.78-0.82)
Cardiologist care			
	1.59 (1.56-1.62)	1.45 (1.42-1.47)	1.38 (1.35-1.40)
Use of statins			
	2.01 (1.98-2.05)	1.86 (1.83-1.90)	1.77 (1.74-1.81)
Total number of medications taken*			
<5	1.00 (ref)	1.00 (ref)	1.00 (ref)
5-9	1.10 (1.08-1.13)	1.18 (1.15-1.20)	1.10 (1.08-1.13)
≥10	1.09 (1.07-1.12)	1.21 (1.18-1.25)	1.19 (1.16-1.22)

*Not including statins or nonstatin lipid-lowering therapy. Multivariable adjusted model includes all variables listed in a single model.
CHD = coronary heart disease; CI = confidence interval.

familial hypercholesterolemia), related media coverage, and an announcement by the U.S. Food and Drug Administration of an ongoing review of the drug after the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial raised the possibility of an increased risk of malignancy (19,20). This malignancy risk was not confirmed in subsequent pooled analyses of ezetimibe data (21). While much of the decline in ezetimibe use is likely related to fewer prescriptions written by physicians, increased nonpersistence with

TABLE 3 Risk Ratios for Taking Nonstatin Lipid-Lowering Medications Among Medicare Beneficiaries With CHD

	Multivariable Adjusted Risk Ratios (95% CI)	
	Not Taking Statins	Taking Statins
Calendar year		
2007	1.00 (ref)	1.00 (ref)
2008	0.91 (0.89-0.93)	0.86 (0.85-0.86)
2009	0.87 (0.85-0.89)	0.70 (0.69-0.71)
2010	0.89 (0.87-0.91)	0.65 (0.64-0.66)
2011	0.86 (0.83-0.88)	0.61 (0.60-0.62)
Age, yrs		
<70	1.00 (ref)	1.00 (ref)
70-74	0.96 (0.93-0.99)	0.89 (0.87-0.91)
75-79	0.88 (0.85-0.92)	0.79 (0.77-0.81)
80-84	0.78 (0.75-0.82)	0.67 (0.65-0.69)
≥85	0.51 (0.48-0.54)	0.48 (0.47-0.50)
Male	1.07 (1.04-1.11)	1.10 (1.08-1.12)
Race/ethnicity		
White	1.00 (ref)	1.00 (ref)
African American	0.50 (0.47-0.54)	0.63 (0.60-0.67)
Other	0.83 (0.74-0.93)	0.87 (0.81-0.95)
Asian American	0.97 (0.87-1.07)	0.78 (0.72-0.83)
Hispanic American	0.78 (0.71-0.86)	0.83 (0.78-0.89)
Low income subsidy/dual eligible	0.96 (0.93-1.00)	1.03 (1.01-1.05)
History of diabetes	1.53 (1.48-1.58)	1.22 (1.19-1.24)
CHD hospitalization	0.95 (0.91-0.99)	0.78 (0.76-0.80)
Non-CHD hospitalization	0.82 (0.80-0.84)	0.87 (0.86-0.89)
History of stroke	0.96 (0.92-1.01)	0.91 (0.88-0.94)
History of heart failure	0.83 (0.80-0.86)	0.92 (0.90-0.94)
Charlson index		
0	1.00 (ref)	1.00 (ref)
1-3	0.91 (0.88-0.95)	0.95 (0.93-0.97)
≥4	0.89 (0.85-0.93)	0.98 (0.96-1.01)
Skilled nursing facility stay	0.76 (0.73-0.79)	0.82 (0.80-0.85)
Cardiologist care	1.57 (1.52-1.62)	1.29 (1.27-1.32)
Total number of medications taken*		
<5	1.00 (ref)	1.00 (ref)
5-9	1.49 (1.42-1.55)	0.98 (0.95-1.00)
≥10	1.73 (1.65-1.81)	1.02 (0.99-1.05)

*Not including statins or nonstatin lipid-lowering therapy. Multivariable adjusted model includes all variables listed in a single model.
Abbreviations as in Table 2.

therapy by patients after the Food and Drug Administration communication has been reported (22). Interestingly, a similar decline in ezetimibe use was not seen in Canada during this same period (10). It is unknown why these changes in practice by physicians differ in the United States and Canada.

Rates of ezetimibe use in our Medicare population are substantially higher than those described by others. Rates of ezetimibe use in Express Script (St. Louis, Missouri) data were approximately one-fifth of the rates in this study (2.5% compared to 11.4%, respectively) (11). Data from IMS Health also

showed substantially lower rates of ezetimibe use (<1.2%) (10). Characteristics of patients included in Express Script and IMS Health were not reported. Although absolute rates of ezetimibe use differed in these 3 studies, declines in ezetimibe use over time were very similar suggesting that decision making by clinicians may have been driven more by perceptions about ezetimibe than individualized risk/benefit estimation based on specific patient characteristics.

Fibrate use in this Medicare cohort was substantially lower than in IMS Health, but we also saw no appreciable impact in the use of fibrates after publication of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial in 2010 (7). This large outcomes trial failed to show a benefit of combination therapy with a statin and fibrate compared to statin alone in 5,518 patients with type 2 diabetes mellitus, one-third of whom had a prior cardiovascular event (23).

Niacin use increased from 1.5% to 2.4% between the first quarter of 2007 and the first quarter of 2011 and declined to 2.0% by the fourth quarter of 2011. This modest decline temporally coincides with a May 26, 2011, National Heart, Lung, and Blood Institute press briefing about the premature termination of the AIM HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides) trial for reasons of futility and concern about increased rates of stroke with niacin/statin combination therapy. It is not known whether publication of the final AIM HIGH results in November of 2011 led to further declines in Niacin use in subsequent years (24).

Bile acid sequestrant use was uncommon throughout the study period and use did not increase concomitant with the ezetimibe decline. Such a substitution would have been rational given cardiovascular benefits in clinical trials of bile acid sequestrants and if additional lipid lowering through interference with cholesterol handling in the gastrointestinal tract was desired (25).

Patient characteristics independently associated with a higher prevalence of nonstatin lipid lowering use included younger age, male sex, white race, history of diabetes, cardiology care, and concomitant statin therapy. The lower use of nonstatin lipid-lowering agents among African Americans may be related to lower prevalence of low high-density lipoprotein cholesterol and high triglycerides in the African American population, but deserves further study. Use of nonstatin lipid-lowering therapy was more common among beneficiaries on more intense statin regimens. These data suggest that nonstatin

lipid-lowering therapy was not used as a substitute for statin therapy or in an attempt to minimize statin doses, but was instead targeted to individuals based on perceived higher risk of cardiovascular events and in need of further intensification of lipid-lowering therapy. In contrast, characteristics of patients on and off nonstatin lipid-lowering therapy did not change over time, suggesting that discontinuation of ezetimibe therapy was not guided by consideration of specific patient characteristics but instead by concerns specific to this medication.

STUDY STRENGTHS AND LIMITATIONS. Our study has a number of strengths. We analyzed data from a national cohort of older U.S. adults with CHD, a high-risk group most likely to benefit from intensive lipid-lowering therapy. We had data on demographics, comorbid conditions, and prescription data that allowed us to identify factors associated with nonstatin lipid-lowering medication use. However, our study also has limitations. Lipid values are not available in Medicare claims limiting our ability to address appropriateness of therapy with specific lipid-lowering agents. We were unable to distinguish whether the decline in ezetimibe and niacin use was a consequence of fewer prescriptions being written by physicians or patient decisions to no longer fill their prescriptions. Many formularies may have excluded ezetimibe after publication of ENHANCE. As there are more than 100 drug plans available in Medicare Part D, examining the association of formularies and use of ezetimibe was not feasible. Niacin use in our analysis may be underestimated because many formulations of niacin are available without prescription.

CONCLUSIONS

Nonstatin lipid-lowering therapy is not commonly used in the Medicare population with CHD. Temporal trends in ezetimibe and niacin therapy appeared to coincide with the announcement and publication of negative clinical trials evaluating these agents while an impact of negative trial evidence was not evident for fibrates use. Studies are needed to better understand the response to clinical evidence by prescribing clinicians, their patients, regulatory agencies and guideline panels. Such data will be essential for the development of better knowledge translation strategies.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: Nonstatin lipid-lowering therapy with ezetimibe, niacin, and/or fibrates, either alone or in combination with statins, is uncommon in the Medicare population with CHD and has decreased over time. Many patients with CHD are not taking statins.

TRANSLATIONAL OUTLOOK: Studies are needed to better understand the response to evolving clinical evidence by prescribing clinicians, their patients, regulatory agencies, and guideline panels.

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APPENDIX For supplemental tables and figures, please see the online version of this article.