Lower Risk of Major Cardiovascular Events Associated with Adherence to Colesevelam HCI

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STUDY OBJECTIVE To examine the relationship between adherence to colesevelam and the risk of major cardiovascular events (acute myocardial infarction [AMI] and stroke) among patients newly treated with colesevelam.

DESIGN Retrospective cohort study using administrative claims data.

DATA SOURCE MarketScan commercial and Medicare databases (2005–2011).

PATIENTS A total of 42,549 adults with hyperlipidemia and/or type 2 diabetes mellitus who newly started colesevelam between January 1, 2005, and September 30, 2011, and who had continuous enrollment in employer-sponsored commercial health insurance or Medicare supplemental benefit plans for at least 6 months before and 12 months after the date of colesevelam initiation.

MEASUREMENTS AND MAIN RESULTS Adherence was measured as the proportion of days covered (PDC) by prescription claims for colesevelam during the 1-year period after the drug initiation date. Patients were assigned to one of three adherence cohorts: adherent, PDC of 0.8 or more; partially adherent, PDC of 0.5–0.8; or nonadherent, PDC of less than 0.5. The primary outcome was time to the first hospitalization with a primary diagnosis for AMI or stroke during the follow-up period. Association of colesevelam adherence with the primary outcome was examined by multivariate Cox regression models, adjusting for demographics, comorbidity, and concomitant drugs. A sensitivity analysis between propensity score-matched cohorts was conducted to compare the outcome between adherent and nonadherent groups. Of the 42,549 patients included in the analysis, 7968 (18.7%) were adherent, 6197 (14.6%) were partially adherent, and 28,384 (66.7%) were nonadherent. Compared with nonadherent patients, adherent patients were older, more likely to be male and from the Northeast or North Central regions of the United States, and had more cardiovascular risk factors and concomitant drugs. Controlling for patient demographic and clinical characteristics, adherent patients were more likely to experience an AMI or stroke hospitalization during the follow-up period compared with nonadherent patients (hazard ratio 0.57, 95% confidence interval[CI] 0.44–0.73, p<0.0001). Results of the sensitivity analysis using propensity score matching techniques were consistent.

CONCLUSION Adherence to colesevelam was associated with lower risk of major cardiovascular events (AMI and stroke) among patients with hyperlipidemia and/or type 2 diabetes. Research to assess interventions to improve adherence to colesevelam and subsequently to evaluate the effects of these interventions on cardiovascular outcomes is warranted.

KEY WORDS colesevelam, adherence, hyperlipidemia, diabetes, stroke, myocardial infarction.

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Bile acid sequestrants (BAS) were one of the first classes of drugs to show that cholesterol-lowering therapy decreases the risk of cardiovascular disease.1,2 According to the National Cholesterol Education Program Expert Panel (NCEP) guidelines, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), BAS, and nicotinic acid are recommended for the reduction of ele-
vated low-density lipoprotein cholesterol (LDL) levels for primary prevention of coronary heart disease. The use of combination therapy (i.e., BAS, nicotinic acid, or ezetimibe plus a statin) is also recommended by the 2004 NCEP guidelines in order to help certain patients reach recommended LDL goals. Although the use of first-generation BAS such as colestyrnate and colestipol has been limited due to poor tolerability and a relatively weak effect on lowering of LDL, use of second-generation BAS such as colesevelam and colestimide in combination with statins or antidiabetic agents or as monotherapy in patients with elevated LDL and/or glucose levels is being increasingly more recognized for their improved tolerance compared with first-generation agents and their proven glucose-lowering effect.

Colesevelam is the only second-generation BAS antihyperlipidemic agent approved by the United States Food and Drug Administration also has a glucose-lowering effect. It is indicated as an adjunct to diet and exercise to reduce elevated LDL levels in adults with primary hyperlipidemia, to improve glycemic control in adults with type 2 diabetes mellitus, and to reduce elevated LDL levels in patients with primary hyperlipidemia (Fredrickson type IIa) as monotherapy or in combination with a statin. The recommended dosage of colesevelam tablets in adults is 3750 mg once/day or 1875 mg twice/day. The recommended dosage of colesevelam oral suspension in adults and children aged 10–17 years is one 3.75 g packet once/day.

Although the effect of colesevelam on cardiovascular morbidity and mortality has not been determined, a meta-analysis of pooled data from eight trials investigating the efficacy of colesevelam in the reduction of glycemic and lipid outcomes found that colesevelam is associated with significant reductions in plasma fasting glucose, hemoglobin A1c (A1C) and LDL levels. Colesevelam may be of particular benefit in managing patients with type 2 diabetes mellitus and hyperlipidemia in whom elevated glucose and LDL levels are of particular concern. The American College of Endocrinology/American Association of Clinical Endocrinologists published a consensus statement for the treatment of type 2 diabetes mellitus. It recommends a wide range of antidiabetic therapies, including oral agents, injectable agents (incretin mimetics), and insulin for the achievement of glycemic control.

In the 2009 consensus statement, colesevelam was listed as one of the choices for dual therapy with metformin in patients with initial A1C levels of 6.5–7.5% who were unable to achieve glycemic control with metformin monotherapy. Poor adherence to drugs can decrease possible positive outcomes by reducing the potential preventive benefits of these drugs and by leading to an overestimation of therapeutic dosage. As many as 86,000 premature deaths each year in the U.S. are estimated to result from nonadherence with antihypertensive agents alone. Several studies have evaluated the association between adherence to drugs used to treat cardiovascular disease and clinical outcomes. A systematic review evaluated studies assessing the impact of adherence to statin monotherapy. High levels of adherence were associated with reductions in adverse clinical outcomes, including all-cause mortality and both fatal and nonfatal cardiovascular events; the most consistent benefits were witnessed at adherence levels of 80% or greater. In primary prevention cohorts, clinical benefits were seen after 1 year of therapy. As length of therapy increased, there was an associated incremental improvement in clinical outcomes. Researches conducted another systematic review to assess the general aspects of drug adherence in cardiovascular disease and found that the multifactorial nature of poor drug adherence implies that only a sustained, coordinated effort will ensure optimal drug adherence and realization of the full benefits of current therapies.

To our knowledge, the impact of adherence to colesevelam has not been evaluated in the published, peer-reviewed literature. Drug adherence in patients with hyperlipidemia and type 2 diabetes mellitus is a challenge, and it would be
helpful to know if colesevelam adherence is associated with better health outcomes as has been shown with other antihyperlipidemic and antidiabetic agents. Thus, the objective of this study was to examine the relationship between adherence to colesevelam and risk of major cardiovascular events—acute myocardial infarction (AMI) and stroke—among patients with hyperlipidemia and/or type 2 diabetes mellitus who were newly treated with colesevelam.

Methods

Study Design and Data Source

This was a retrospective cohort study using administrative claims data. The MarketScan commercial and Medicare databases from 2005–2011 were used for the analyses. The MarketScan databases include claims-based health data from approximately 70 million enrollees who are covered by employer-sponsored commercial health insurance or who are Medicare-eligible retirees with employer-sponsored supplemental benefit plans from more than 100 large employers, health plans, and government and public organizations. The databases contain data on enrollment and clinical utilization across inpatient, outpatient, and prescription drug services. The MarketScan databases are fully Health Insurance Portability and Accountability Act compliant and link paid claims and encounter data to detailed patient information across sites and types of providers over time.

This study was exempt from ethics approval from an institutional review board and informed consent because, according to the U.S. Department of Health and Human Services Exemption 4, the research involved the study of existing data, and the patients could not be identified directly or through identifiers linked to the patients.

Study Sample Selection

Patients were included in the study if they met the following criteria: had at least one prescription for colesevelam during the time period from January 1, 2005-September 30, 2011 (the fill date of the first prescription for colesevelam was defined as the index date); were continuously enrolled for at least 180 days before index date and at least 365 days after the index date; and had a diagnosis of diabetes mellitus (International Classification of Diseases, Ninth Revision [ICD-9] codes 250.xx, 249.xx, 357.2x, 362.0x, 996.57, V45.85, V53.91, V58.67, and V65.46) and/or hyperlipidemia (ICD-9 codes 272.0x, 272.1x, 272.2x, 272.3x, 272.4x, and 272.9x). Patients were excluded if they met the following criteria: had a diagnosis of type 1 diabetes mellitus (ICD-9 codes 250.x1 and 250.x3); were younger than 18 years of age; were taking another BAS during the baseline period or within 365 days after the index date; or had a diagnosis for AMI or stroke during the baseline or the 1-year period after the index date.

Study Period

The study period was from January 1, 2005–September 30, 2011. The 180-day period before the index date was defined as the baseline period; the 365-day period after the index date was the adherence cohort assignment period (ACAP). The follow-up period consisted of the period of time from the end of ACAP to the end of continuous enrollment or September 30, 2011, whichever occurred first (Figure 1).

Measures and Analyses

Adherence was measured by using the proportion of days covered (PDC) by prescription claims for colesevelam. The PDC was calculated as the total number of days supplied over the 1-year ACAP divided by 365. Patients were assigned to one of three cohorts based on PDC (adherent: PDC ≥ 0.8, partially adherent: 0.5 ≤ PDC < 0.8, or nonadherent: PDC < 0.5). The primary outcome was the time to hospitalization with a primary diagnosis for AMI or stroke. The primary independent variable of interest was adherence status. Other covariates included patient demographics (age, sex, and region), comorbidities (listed in Table 1), and concomitant drug use (listed in Table 1).

The continuous variable (age) was summarized using mean and standard deviation. Categorical variables were summarized using numbers and percentages. Treatment comparisons for the primary outcome were performed by using univariate Cox regression and multivariate Cox regression with stepwise selection for covariates in the final model.

A stratified analysis of patients older and younger than 65 years of age was conducted since Medicare patients (those > 65 yrs old) in the MarketScan database may be also be covered through a Medicare Part D plan in addition to...
Figure 1. Timeline of the study period (January 1, 2005–September 30, 2011) illustrating the 6-month baseline period before the index date (date of the first prescription for colesevelam), the 1-year adherence cohort assignment period, and the follow-up period.

Table 1. Baseline Demographic and Clinical Characteristics by Level of Adherencea

| Group                              | Adherent (n=7968) (%) | Partially Adherent Group (n=6197) (%) | Nonadherent Group (n=28,384) (%) | p Value |
|------------------------------------|-----------------------|---------------------------------------|----------------------------------|---------|
| Male sex                           | 4316 (54.2)           | 3104 (50.1)                           | 11,687 (41.2)                    | <0.0001 |
| Age (yrs), mean ± SD               | 60.2 ± 10.1           | 58.0 ± 10.5                           | 57.6 ± 11.3                      | <0.0001 |
| Region of United States            |                       |                                       |                                  |         |
| Northeast                          | 988 (12.4)            | 642 (10.4)                            | 2741 (9.7)                       | <0.0001 |
| North Central                      | 2436 (30.6)           | 1680 (27.1)                           | 7072 (24.9)                      |         |
| South                              | 3621 (45.4)           | 3156 (50.9)                           | 15,473 (54.5)                    |         |
| West                               | 923 (11.6)            | 719 (11.6)                            | 3098 (10.9)                      |         |
| Comorbidities                      |                       |                                       |                                  |         |
| Type 2 diabetes mellitus           | 3109 (39.0)           | 2306 (37.2)                           | 10,187 (35.9)                    | <0.0001 |
| Hyperlipidemia                     | 6645 (83.4)           | 5210 (84.1)                           | 23,729 (83.6)                    | 0.5419  |
| Hypertension                       | 3467 (43.5)           | 2561 (41.3)                           | 11,727 (41.3)                    | 0.0016  |
| Depression                         | 323 (4.0)             | 294 (4.7)                             | 1452 (5.1)                       | 0.0005  |
| Heart failure                      | 172 (2.2)             | 119 (1.9)                             | 503 (1.8)                        | 0.0746  |
| Coronary heart disease             | 1405 (17.6)           | 884 (14.3)                            | 3556 (12.5)                      | <0.0001 |
| Peripheral vascular disease        | 388 (4.9)             | 260 (4.2)                             | 1145 (4.0)                       | 0.0046  |
| Transient ischemic attack          | 64 (0.80)             | 41 (0.66)                             | 207 (0.73)                       | 0.6130  |
| Cerebral vascular disease          | 243 (3.0)             | 184 (3.0)                             | 810 (2.8)                        | 0.6234  |
| Chronic kidney disease             |                       |                                       |                                  |         |
| Concomitant drugs                  |                       |                                       |                                  |         |
| β blocker                          | 2910 (36.5)           | 1978 (31.9)                           | 8433 (29.7)                      | <0.0001 |
| Calcium channel blocker            | 1811 (22.7)           | 1272 (20.3)                           | 5728 (20.2)                      | <0.0001 |
| Angiotensin-converting enzyme      | 2724 (34.2)           | 1908 (30.8)                           | 8110 (28.6)                      | <0.0001 |
| Inhibitor                          |                       |                                       |                                  |         |
| Angiotensin receptor blocker       | 2187 (27.4)           | 1561 (25.2)                           | 6872 (24.2)                      | <0.0001 |
| Adrenolytic                        | 195 (2.4)             | 125 (2.0)                             | 637 (2.2)                        | 0.2293  |
| α blocker                          | 179 (2.2)             | 89 (1.4)                              | 421 (1.5)                        | <0.0001 |
| Vasodilator                        | 61 (0.77)             | 44 (0.71)                             | 206 (0.73)                       | 0.9142  |
| Diuretic                           | 3071 (38.5)           | 2308 (37.2)                           | 10,311 (36.3)                    | 0.0012  |
| Aliskiren                          | 93 (1.2)              | 75 (1.2)                              | 324 (1.1)                        | 0.8956  |
| Statin                             | 2659 (33.4)           | 2255 (36.4)                           | 11,843 (41.7)                    | <0.0001 |
| Fibrate                            | 1145 (14.4)           | 753 (12.2)                            | 3083 (10.8)                      | <0.0001 |
| Ezetimibe                          | 2059 (25.8)           | 1445 (23.3)                           | 6188 (21.8)                      | <0.0001 |
| Niacin                             | 777 (9.8)             | 488 (7.9)                             | 1892 (6.7)                       | <0.0001 |
| Sulfonylurea                       | 1141 (14.3)           | 795 (12.8)                            | 3406 (12.0)                      | <0.0001 |
| Metformin                          | 2021 (25.4)           | 1495 (24.1)                           | 6197 (21.8)                      | <0.0001 |
| Thiazolidinedione                  | 918 (11.5)            | 661 (10.7)                            | 2793 (9.8)                       | <0.0001 |
| Meglitinide derivative             | 109 (1.4)             | 88 (1.4)                              | 312 (1.1)                        | 0.0321  |
| Dipeptidyl peptidase-4 inhibitor   | 534 (6.7)             | 423 (6.8)                             | 1573 (5.5)                       | <0.0001 |
| Insulin                            | 764 (9.6)             | 593 (9.6)                             | 2873 (10.1)                      | 0.2121  |
| Exenatide                          | 256 (3.2)             | 182 (2.9)                             | 778 (2.7)                        | 0.076   |
| Antiplatelet agent                 | 771 (9.7)             | 482 (7.8)                             | 1980 (7.0)                       | <0.0001 |

*aAdherence was measured as the proportion of days covered (PDC) by prescription claims for colesevelam during the 1-year follow-up period after the drug initiation date. Adherent = PDC ≥ 0.8; partially adherent = 0.5 ≤ PDC < 0.8; and nonadherent = PDC < 0.5.*
their employer-sponsored plan; thus, all their prescriptions may not be captured in the database. Stratified analysis by the use of statin (yes vs no) was also conducted.

Propensity score matching techniques were used as a sensitivity analysis to compare the outcome between the adherent and nonadherent groups. Patients in these two adherence cohorts were matched in a 1:1 ratio based on the propensity score that summarized the likelihood of being adherent according to their demographics, comorbidities, and concomitant drug use. SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC) was used for all analyses. A p value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Patient Characteristics

The total number of patients meeting the study criteria was 42,549. Figure 2 illustrates patient identification and sample attrition after applying the inclusion and exclusion criteria. Of the 42,549 patients included in the analysis, 7968 (18.7%) were adherent, 6197 (14.6%) were partially adherent, and 28,384 (66.7%) were nonadherent. The mean follow-up period after ACAP was 591 days (maximum 1827 days). Table 1 presents the baseline characteristics of the patients by adherence group. Compared with the nonadherent group, patients in the adherent group were older, were more likely to be male and from the Northeast or North Central regions of the U.S. Compared with the nonadherent group, a greater proportion of the adherent group had type 2 diabetes, hypertension, coronary heart disease, and peripheral vascular disease, and a greater proportion of the nonadherent group had depression compared with the adherent group. Patients in the adherent group also had greater use of concomitant drugs including β blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, α blockers, diuretics, fibrates, ezetimibe, niacin, sulfonylureas, metformin, thiazolidinediones, meglitinide derivatives, dipeptidyl peptidase-4 inhibitors, and antiplatelet agents compared with the nonadherent group. More patients in the nonadherent group used statins compared with patients in the adherent group.

Primary Outcome Analyses

The overall cardiovascular event (AMI or stroke) rates during the follow-up period were 5.4/1000 person-years, 5.6/1000 person-years, and 7.5/1000 person-years among patients who were adherent, partially adherent, and nonadherent, respectively. The unadjusted hazard ratio

**Table 1.** Baseline characteristics of patients by adherence group.

| Characteristics                                      | Adherent (N=7968) | Partially Adherent (N=6197) | Nonadherent (N=28,384) |
|------------------------------------------------------|-------------------|------------------------------|------------------------|
| Age                                                  | 61.6 (±10.0)      | 60.2 (±10.0)                 | 62.1 (±10.0)           |
| Gender                                               | Male: 55.5%       | Male: 55.9%                  | Male: 54.8%            |
| Race                                                 | White: 78.3%      | White: 76.4%                 | White: 78.8%           |
| Ethnicity                                            | Hispanic: 6.9%    | Hispanic: 7.3%               | Hispanic: 5.9%         |
| Comorbidities                                        |                   |                              |                        |
| Hypertension                                         | 46.0%             | 46.2%                        | 46.0%                  |
| Diabetes                                             | 32.7%             | 32.2%                        | 33.3%                  |
| Coronary heart disease                               | 22.0%             | 21.6%                        | 22.9%                  |
| Peripheral vascular disease                          | 14.7%             | 14.3%                        | 15.6%                  |
| Depression                                           | 12.2%             | 11.9%                        | 13.1%                  |
| Concomitant drug use                                  |                   |                              |                        |
| β blockers                                           | 63.3%             | 63.5%                        | 62.8%                  |
| Calcium channel blockers (CCBs)                      | 53.6%             | 55.0%                        | 53.9%                  |
| Angiotensin-converting enzyme inhibitors             | 46.7%             | 46.5%                        | 46.8%                  |
| Angiotensin receptor blockers                        | 31.2%             | 31.4%                        | 31.1%                  |
| A blockaders                                         | 17.8%             | 18.0%                        | 17.5%                  |
| Diuretics                                            | 11.9%             | 11.5%                        | 12.0%                  |
| Fibrates                                             | 10.2%             | 10.3%                        | 10.2%                  |
| Ezetimibe                                            | 7.8%              | 7.7%                         | 7.9%                   |
| Niacin                                               | 6.3%              | 6.1%                         | 6.4%                   |
| Sulfonylureas                                        | 5.3%              | 5.2%                         | 5.4%                   |
| Metformin                                            | 4.8%              | 4.7%                         | 4.9%                   |
| Thiazolidinediones                                   | 4.3%              | 4.2%                         | 4.3%                   |
| Meglinidine derivatives                              | 3.9%              | 3.8%                         | 3.9%                   |
| Dipeptidyl peptidase-4 inhibitors                    | 3.6%              | 3.5%                         | 3.7%                   |
| Antiplatelet agents                                  | 3.3%              | 3.2%                         | 3.3%                   |
| Statins                                              | 27.8%             | 28.0%                        | 27.7%                  |

Figure 2. Schematic of the patient selection process illustrating patient identification and attrition after applying the inclusion and exclusion criteria. AMI = acute myocardial infarction; ACAP = adherence cohort assignment period.
(HR) was 0.72 (95% CI 0.56–0.92, p=0.0092) comparing adherent patients with nonadherent patients. After adjusting for patient demographics, baseline comorbidities, and concomitant drug use, adherent patients were about 43% less likely to experience AMI or stroke hospitalization during the follow-up period (HR 0.57, 95% CI 0.44–0.73, p=0.0001) compared with nonadherent patients (Table 2). Other factors associated with significantly lower risk of AMI or stroke hospitalization included younger age; female sex; absence of baseline hypertension; absence of coronary heart disease; absence of concomitant β blocker, CCB, vasodilator, metformin, insulin, and antiplatelet use; and concomitant statin use. The results of stratified analyses by age and statin use were consistent with the finding that adherent patients had lower associated risk of AMI or stroke hospitalization than nonadherent patients (data not shown).

Sensitivity Analysis with Propensity Score Matching

Propensity score matching eliminated most of the baseline characteristic differences seen between adherent and nonadherent patients. Only differences in the proportion of patients with depression (adherent 4.0% and nonadherent 4.9%, p=0.0125) and chronic kidney disease (adherent 7.7% and nonadherent 8.6%, p=0.0391), and the proportion of patients taking fibrates (adherent 14.3% and nonadherent 13.2%; p=0.0477), metformin (adherent 25.3% and nonadherent 23.9%, p=0.0375), or pramlintide (adherent 0.39% and nonadherent 0.20%, p=0.0284) remained after propensity score matching. Stepwise regression results using the above-mentioned covariates after propensity score matching confirmed that adherent patients were significantly associated with lower risk of AMI or stroke hospitalization than nonadherent patients (HR 0.58, 95% CI 0.43–0.77, p=0.0002).

Discussion

This study provides insight into real-world (i.e., drug treatment in everyday practice) utilization and associated clinical outcomes of colesvelam as recorded by health insurance claims records that track health care activities for the purposes of reimbursing for medical services provided and drugs dispensed. Adherent patients were about 43% less likely to experience AMI or stroke hospitalization during the follow-up period.
period after adjustment for confounders. Female sex, younger age, absence of baseline hypertension or coronary heart disease, absence of concomitant use of β blockers, CCBs, vasodilators, metformin, insulin or antiplatelet agents, and concomitant statin use were other factors associated with significantly lower risk of AMI or stroke hospitalization. A sensitivity analysis using propensity score matching techniques confirmed that high adherence was associated with significantly lower risk of AMI or stroke hospitalization.

Although, to our knowledge, the impact of adherence to colesevelam has not been evaluated in the published, peer-reviewed literature, there is significant evidence that increased adherence to statins results in improved clinical outcomes. A systematic review identified 19 studies that assessed the direct relationship between adherence or persistence to statin monotherapy and clinical outcomes. Most studies reported adherence as PDC or medication possession ratio (MPR), and the most common accepted threshold for full or high adherence was a PDC or MPR of 80% or greater over the observation period. Some trends in the findings of the systematic review underscored the important aspects of adherence and persistence; high levels of adherence and longer durations of persistence with statins were associated with progressively increasing reductions in all-cause mortality and fatal and nonfatal cardiovascular events.

The PDC measure used to assess adherence in the current study offers an improvement over the often-used MPR because it does not count overlapping days of drug supply in the estimation. The PDC avoids some of the common problems of MPR such as the overestimation of adherence for patients who switch drugs or who use dual therapy within a drug category. The PDC also captures the impact of a patient’s discontinuation of a drug regimen, whereas some versions of MPR do not. Comparisons of PDC and MPR have shown that the PDC tends to give a more conservative and accurate estimation of adherence for patients on complex therapy.

The PDC measures of adherence have been endorsed by the National Quality Forum and have been adopted by the Centers for Medicare & Medicaid Services (CMS) to evaluate all Medicare Part D plans and have also been recommended by CMS for use by Quality Improvement Organizations.

There are some limitations associated with this study. This was an observational study and the results may be biased due to unmeasured confounders. The analysis was restricted to variables present in this particular database, and other factors that were not measured in the database may have confounded the observed relationship between high adherence to colesevelam and lower risk of cardiovascular events. The observational design and potential unobserved confounding provides a weaker framework for causal inference of exposure-disease associations than randomized studies.

In particular, a “healthy adherer” effect might exist. Some studies have shown that patients who are adherent to drug exhibit behaviors that are healthy in general. Adherence with placebo (and not just with active drugs) has been associated with significant (and similarly robust) improvements in health outcomes. Thus, it is unknown whether improvements in adherence with colesevelam per se would result in improved outcomes. Since some of these factors cannot be measured in claims-based analyses, it is difficult to discern the extent to which each factor is responsible for the observed effect. This was seen in a recent study of patients initiating statin therapy. After adjustment for demographic and clinical covariates, patients who initiated statins were more likely to receive recommended preventive services than noninitiators matched by age, sex, and state (HR 1.10, 95% CI 1.06–1.14 for men, HR 1.09, 95% CI 1.07–1.11 for women) and appeared to have a lower risk of a range of adverse outcomes (HR 0.87, 95% CI 0.85–0.89) thought to be unrelated to statin use.

This possibility may, in fact, be supported by the extent to which colesevelam reduced cardiovascular events in adherent patients in our study. Results showed that adherent patients were 43% less likely to experience AMI or stroke hospitalization during the follow-up period compared with nonadherent patients after adjustment for confounders. This reduction in events is greater than what would be expected from the impact of colesevelam on cholesterol (LDL level lowering of 15–19%) and A1C (reduction of approximately 0.5%) compared with the impact of statins on cholesterol and their associated impact on cardiovascular events. A meta-analysis of statin trials involving data from 90,056 individuals in 14 randomized trials showed an overall reduction of 23% in myocardial infarction or coronary death (risk ratio [RR] 0.77, 95% CI 0.74–0.80, p<0.0001), a reduction of 24% in the need for coronary
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Adherence to colesevelam was significantly associated with lower risk of major cardiovascular events (AMI and stroke) among patients with hypercholesterolemia and/or type 2 diabetes mellitus who used colesevelam. Research to assess interventions to improve adherence to colesevelam and subsequently to evaluate the effects of these interventions on cardiovascular outcomes is warranted.

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