Published in final edited form as:

Am J Cardiol. 2013 February 15; 111(4): 532–539. doi:10.1016/j.amjcard.2012.11.002.

Effect of Ezetimibe on Major Atherosclerotic Disease Events and All-Cause Mortality

Sami Hayek, MD^{a,*}, Fabrizio Canepa Escaro, MD^{a,*}, Assad Sattar, MD^{a,*}, Steven Gamalski, MD^{a,*}, Karen E. Wells, MPH^b, George Divine, PhD^b, Brian K. Ahmedani, PhD^c, David E. Lanfear, MD, MS^{a,c}, Manel Pladevall, MD, MS^d, and L. Keoki Williams, MD, MPH^{a,c}

^aDepartment of Internal Medicine, Henry Ford Health System, Detroit, Michigan, USA

^bDepartment of Public Health Sciences, Henry Ford Health System, Detroit, Michigan, USA

^cCenter for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Michigan, USA

^dResearch Triangle Institute Health Solutions, Barcelona, Spain

Abstract

Despite ezetimibe's ability to reduce serum cholesterol levels, there are concerns over its vascular effects and whether it prevents or ameliorates atherosclerotic disease (AD). Our objective was to estimate the effect of ezetimibe use on major AD events and all-cause mortality and to compare these associations to those observed for hydroxy-methylglutaryl-CoA reductase inhibitor (i.e., statin) use. We identified 367 new ezetimibe users between November 1, 2002 and December 31, 2009. These individuals were 18 years of age and had no prior statin use. One to four statin user matches were identified for each ezetimibe user resulting in a total of 1,238 closely matched statin users. Pharmacy data and drug dosage information were used to estimate a moving window of ezetimibe and statin exposure for each day of study follow-up. The primary outcome was a composite of major AD events (coronary heart disease, cerebrovascular disease, and peripheral vascular disease events) and all-cause death. Both ezetimibe use (odds ratio [OR] 0.33, 95% CI 0.13–0.86) and statin use (OR 0.61, 95% CI 0.36–1.04) were associated with reductions in the likelihood of the composite outcome. These protective associations were most significant for cerebrovascular disease events and all-cause death. Subgroup analyses by sex, race-ethnicity, prior history of AD, diabetes status, and estimated renal function showed consistent estimates across strata with no significant differences between ezetimibe and statin use. In conclusion, ezetimibe appeared to have a protective effect on major AD events and all-cause death which was not significantly different from that observed for statin use.

Keywords

ezetimibe; hydroxymethylglutaryl-CoA reductase inhibitors; pharmacoepidemiology; atherosclerosis; cardiovascular disease; all-cause death

© 2012 Excerpta Medica, Inc. All rights reserved.

Request for reprints and corresponding author: L. Keoki Williams, MD, MPH, Center for Health Policy and Health Services Research, Henry Ford Hospital, 1 Ford Place, 3A CHSR, Detroit, Michigan 48202, (313) 874-6693 (office), (313) 874-7137 (fax), kwillia5@hfhs.org.

*Denotes equal contribution as first author

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

A number of studies suggest that ezetimibe use reduces low density lipoprotein (LDL) cholesterol levels without a commensurate improvement in carotid intima-medial thickness (CIMT), a proxy measure of AD burden.^{1–3} However, one clinical trial in patients with chronic kidney disease showed that individuals randomized to using ezetimibe and a statin concomitantly had lower major AD events when compared with those assigned to placebo.⁴ Because of the seemingly conflicting findings regarding the ability of ezetimibe to improve AD, it is crucial to examine the independent effect of ezetimibe. However, to our knowledge there are no published studies of the effect of ezetimibe on either cardiovascular outcomes or all-cause mortality in the absence of concomitant statin use. Using data from a large health maintenance organization (HMO), we examined and compared the estimated effect of both ezetimibe use and statin use on these events. The large patient population allowed us to closely match individuals using each type of medication and detailed longitudinal clinical information enabled us to account for changing levels of drug exposure over time.^{5, 6}

METHODS

This study was approved by the institutional review board at Henry Ford Health System and was in compliance with its Health Insurance Portability and Accountability Act policy. Study individuals were members of a large HMO which serves southeast Michigan, including metropolitan Detroit. We identified all individuals with prescription coverage who had a medication fill for ezetimibe or a statin between November 1, 2002 and December 31, 2009. This time period was chosen to avoid the controversy over ezetimibe use starting at the end of 2009.^{3, 7} The first prescription fill in either class was considered the *index* prescription (and the time of that fill was the *index* date) provided that the patient had no record of earlier ezetimibe or statin use. Study individuals were 18 years of age on the index date and continuously enrolled in the health plan for 6 months prior to that date. We excluded individuals with a prior diagnosis of liver disease and those who died or had a major AD event within 3 months of the index prescription.

We adapted the method of Steiner and Prochazka to estimate medication exposure.⁸ As study individuals were members of the HMO with prescription coverage, we had a near complete record of all medication fills. We have previously shown for another class of medications that we capture ~99% of prescriptions filled.⁹ In calculating the *unweighted*, continuous measure of medication exposure (CMME) we assigned every day of medication supply the value of 1. We then summed all days supplied in a 3 month window (ending on each day of observation) and divided by 90 days. Each unweighted CMME took into account prescription fills prior to, but extending into, the 3-month observation window, as well as prescription fills in which the supply ran past the observation window (i.e., so as to include and truncate the supply estimates, respectively). Given the longitudinal study design, we calculated either an ezetimibe or a statin CMME for *each* patient for *every* day of follow-up. Therefore, patients had multiple CMME values, each of which represented a moving 3-month window of medication exposure for their particular lipid-lowering medication.

Unlike ezetimibe which was available as a single dose (10 mg per day), statin medications included multiple drugs and multiple dose preparations per drug. To account for potential differences in the magnitude of the effect on outcome by drug and dose, we developed a weighting schema based on the relative potency to reduce LDL levels. By request, we obtained data from a published meta-analysis by Weng et al.¹⁰ These data were used to model the relationship between dose (natural log transformed) and LDL reduction for each of the statin drugs. We rescaled the response variable (LDL reduction) as a proportion of the

maximum response (i.e., 55.7% reduction in LDL for the 40mg dose of rosuvastatin). This resulted in a fitted weight for each statin drug dose which ranged from 0.3 to 1.0 (see Table E1 in the online supplement). The appropriate drug- and dose-specific weight was therefore assigned to each day of medication supply. Days without an available statin supply were given a value of 0; therefore, daily weights ranged from 0 to 1. The calculation of the weighted CMME was the sum of the weights over the preceding 3 months divided by 90 days. Again, a moving weighted CMME was calculated for each day follow-up for individuals using statin medication.

Although much less frequently used by patients, separate exposure measures were created for the following classes of cholesterol lowering medication: bile acid sequestrants, fibrates, and niacin. Separate, unweighted CMMEs were calculated for these medication classes, and these measures were used to adjust our analytic models.

Available demographic information included patient age, sex, race-ethnicity, and median household income (for the census tract in which a patient resided). Laboratory data included measures of serum LDL cholesterol and creatinine levels. Patients' creatinine levels, age, sex, and race-ethnicity were used to derive estimated glomerular filtration rate (eGFR), a measure of kidney function, according the Modification of Diet in Renal Disease formula.¹¹ The creatinine level most proximal and within 1 year prior and 3 months following the index date was used in calculated eGFR.

Inpatient and outpatient clinical diagnoses were used to identify baseline co-morbid conditions. Baseline refers to meeting the following criteria at any time prior to the index date. Individuals were considered to have diabetes if they had ≥ 2 recorded diagnoses of diabetes or were taking a diabetes medication (i.e., an oral medication or insulin). Individuals were considered to have hypertension if they had ≥ 2 prior diagnoses of hypertension or were taking an oral anti-hypertensive medication. Individuals were considered to have AD at baseline if they had a prior diagnosis of coronary heart disease (i.e., myocardial infarction, unstable angina [USA], or coronary artery revascularization), cerebrovascular disease (i.e., either a cerebrovascular accident [CVA] or a transient ischemic attack [TIA]), or peripheral vascular occlusive disease (PVOD).

Atherosclerotic disease outcome variables were identified from *de novo* diagnoses and procedures, as we have done previously and which are described in Appendix E1 of the online supplement.⁵ We identified cardiovascular deaths from records maintained by the Division of Vital Records and Health Statistics, Michigan Department of Community Health and through death records maintained electronically by the health system.

Where possible we performed 1:4 matching between ezetimibe users and statin users. Individuals were matched on age in years (categorized as <49, 50–59, 60–69, 70–79, and ≥80), sex, race-ethnicity (white, African American, and other/unknown), baseline LDL cholesterol levels (categorized as <70mg/dL, 71–100 mg/dL, 101–130 mg/dL, 131–160 mg/dL, 161–190 mg/dL, and >190 mg/dL), presence of AD at baseline, presence of diabetes at baseline, presence of hypertension at baseline, and year of index prescription. When more than 4 statin initiator matches were available per ezetimibe initiator, 4 matches were randomly selected among the available pool. Of the 401 eligible patients on ezetimibe, 257 (64.1%) had 4 matched individuals using a statin, 110 (27.4%) individuals had less than 4 matches, and 34 (8.5%) did not have a matched statin user. Therefore, the analysis included 367 ezetimibe users and 1,238 statin user matches.

The primary study outcome was a composite of major AD events and all-cause death. The former included fatal and non-fatal acute myocardial infarction (AMI), USA, coronary revascularization, fatal and non-fatal CVA, cerebrovascular revascularization, TIA, and

PVOD events (i.e., hospitalization, revascularization, amputation, or death from PVOD). Secondary outcomes included separate analyses for each of the following: major AD events, coronary heart disease (CHD) events (i.e., fatal and non-fatal AMI, USA, and coronary revascularization), cerebrovascular disease events (i.e., fatal and non-fatal CVA, TIA, and cerebrovascular revascularization), PVOD events, and all-cause death.

As has been described by Allison,^{12, 13} our analyses employed logistic regression to perform the time-dependent survival analysis whereby each day of observation per patient was treated as a separate record. This approach has the benefit of more easily managing the multiple daily-updated exposure variables over Cox regression models. We adjusted for matching by treating each of the matching categories as strata as implemented in PROC LOGISTIC.¹⁴ We also accounted for other potential confounders, such as use of other lipid lowering drugs and household income. The assessment period began 3 months after the index date (i.e., the earliest time possible for assessing outcomes given the 3-month drug exposure windows) and continued until the patient experienced the outcome being assessed, disenrolled from the health system, switched medications (i.e., ezetimibe to a statin or *vice versa*), or died.

We performed three separate analyses to assess and compare the relationship between ezetimibe and statin use on major AD events and all-cause death. For our first set of comparisons we simply coded whether individuals were ezetimibe or statin users with a single dichotomous variable (i.e., ezetimibe use = 1 and statin use = 0). This provided a direct comparison of the two therapies, but it did not account for changing use over time, nor did it assess the effect of increasing levels of exposure within class.

The second set of analyses had separate continuous and time-updated measures for ezetimibe and statin use (i.e., unweighted CMME) for each day of study follow-up. These non-negative, continuous exposure measures mostly ranged from 0–1 (occasionally greater), and represented the range of daily use. Likewise, the effect estimates for ezetimibe and statins each represented the effect of going from no use to daily use. Differences in the effect estimates for both treatments were compared using the Wald test. This approach accounted for changing patterns of use over time, measured the effect of each drug class, and compared differences in effect between drug classes.

The final, principal set of analyses as shown in the results section tables also had separate CMME estimates for ezetimibe use and statin use. However, the CMME estimates for statin use were weighted to account for differences in dosage and differences in the relative strength of the various statin preparations. Therefore, these weighted exposure measures represented the range of no use to daily use of the strongest statin at the highest dose. Since ezetimibe had a single daily dose, the unweighted CMME estimates for ezetimibe use had the same interpretation. As a result, the effect estimates for *both* drug classes represented the effect of going from no use to daily use at maximum strength (i.e., a similar scale for the *within* drug class effects of increasing exposure). *Between* treatment differences (i.e., ezetimibe vs. statin) were compared using the Wald test. Therefore, this final, analytic approach accounted for changing patterns of medication use over time, measured the within drug class effect while accounting for differences in dose and preparation, and compared differences in effect between drug classes. This approach was also used in analyzing the secondary outcomes and for the subgroup analyses. In the subgroup analyses, we assessed the relationship between ezetimibe and statin use on the primary outcome after stratifying within the following categories: sex, race-ethnicity (African American and white), history of atherosclerotic disease, diabetes status, and baseline eGFR (<60 and ≥60 mL/min per 1.73 m²).

Based on both the available sample and application of an exemplary dataset calculation,^{15, 16} we estimated 80% power to detect an OR of 0.26 for the ezetimibe dose effect and an OR of 0.47 for the statin dose effect on the composite outcome. The OR for comparing the ezetimibe and statin dose effects (i.e., the ratio of the dose effects) would need to be 0.24 in order for a difference between them to be detectable with 80% power. All calculations assumed a two-sided analysis and a significance level (α) of 0.05. Analyses were performed using the statistical software, SAS version 9.2.¹⁴

RESULTS

As shown in Figure 1, we identified 401 new ezetimibe users who met the inclusion criteria. Of these individuals, 367 (92%) had at least one suitable statin user match. We identified 21,872 potential statin initiators who similarly had no history of prior or concomitant ezetimibe use, liver disease, or a major AD event within 3 months of the first statin fill. We selected up to 4 statin user matches for each ezetimibe user, and we randomly selected among the available statin users when >4 potential matches were available. This process resulted in 1,238 statin user matches.

The baseline characteristics of the ezetimibe and statin users are shown in Table 1. As can be seen, these individuals were similar for all of the matching characteristics. However, we did observe a significant difference in the estimated median income for both groups. Although infrequent, use of other lipid lowering agents was significantly more common among ezetimibe users when compared with statin users (11% vs. 2%, respectively; $P < 0.001$). Average duration of follow-up for all study participants was 51 months (± 29 months standard deviation; range 3–105 months).

Assessing exposure dichotomously (i.e., ezetimibe use vs. statin use – data not shown), we observed a non-significant association favoring ezetimibe use for reducing the primary composite outcome of major AD events or all-cause death when compared with statin use (odds ratio [OR] 0.88, 95% confidence interval [CI] 0.59–1.33). When assessing both drug exposures continuously but without accounting for statin dose and strength, we found a protective association between increasing ezetimibe use and the primary composite outcome (OR 0.38, 95% CI 0.16–0.95; $P = 0.038$) and a borderline significant relation for statin use (OR 0.74, 95% CI 0.50–1.03; $P = 0.074$).

Accounting for the strength and dose of statins in the same model, we found similar relationships as described above for ezetimibe use (OR 0.33, 95% CI 0.13–0.86; $P = 0.024$) and statin use (OR 0.61, 95% CI 0.36–1.04; $P = 0.068$) on the primary outcome (Table 2). However, the magnitude of the effect estimates for ezetimibe use and statin use were not significantly different (Wald test P -value = 0.231).

We observed similar relationships for increasing ezetimibe use and increasing statin use on most secondary outcomes (Table 2). However, most of these relationships were non-significant, likely due in part to the much smaller number of analyzable events. Notable exceptions were a significant protective association between both ezetimibe use and statin use and cerebrovascular events. There was also a significant protective association for ezetimibe use and statin use on all-cause mortality. None of the effect estimates for ezetimibe use and statin use were significantly different.

Table 3 shows the types of deaths among the individuals in each treatment group. We did not observe a significant difference in the primary cause of death by group.

Subgroup analyses (Table 4) also showed consistent protective relationships for ezetimibe use and statin use on the primary outcome, although most did not reach statistical

significance. The exceptions included a significant protective relationship for both ezetimibe use and statin use among women. We also observed a protective association for statin users with a prior history of AD, ezetimibe users without a prior history of AD, and ezetimibe users with a history of diabetes. There were too few individuals with reduced eGFR (<60 mL/min per 1.73 m²) to estimate the effect of ezetimibe use on the primary composite outcome. However, among ezetimibe users with an eGFR ≥ 60 mL/min per 1.73 m² there was a protective association with the primary outcome (OR 0.44, 95% CI 0.14–1.38), albeit not statistically significant ($P=0.161$). None of the effect estimates for ezetimibe use and statin use were significantly different.

Although we accounted for the use of additional lipid lowering agents as covariates in our models, since their use was greater among ezetimibe users when compared with statin users, we also performed a post-hoc analysis which excluded individuals on these other cholesterol lowering medications from the analysis. Excluding these individuals actually strengthened the protective association observed for both ezetimibe use (OR 0.26, 95% CI 0.07–0.90; $P=0.034$) and statin use (OR 0.57, 95% CI 0.33–0.98; $P=0.044$) on the primary composite outcome (data not shown).

DISCUSSION

To our knowledge this is the first study to assess the independent association of ezetimibe use to major atherosclerotic events and all-cause death. Because of our approach we were able to estimate the effect of ezetimibe use in 2 ways. First, our continuous measures of drug exposure allowed us to assess a “dose-response” relation between increasing levels of ezetimibe use and outcomes. Second, by selecting a closely matched set of statin users, we were able to assess whether the aforementioned effect estimates for ezetimibe use differed from those of statin use. The benefit of the latter class of medications in reducing AD events and all-cause mortality has been established in a number of clinical trials,^{17–22} making statins a reasonable standard with which to compare ezetimibe. In short, we found that both ezetimibe use and statin use were associated with reductions in the primary composite outcome, and the effect estimates were not significantly different between these treatment groups.

Although the long-term, independent effects of ezetimibe use on cardiovascular events and all-cause mortality have not been well studied, our findings are consistent with existing clinical trials findings. For example, Baigent *et al.* showed that the combination of ezetimibe and simvastatin produced a 17% reduction in major atherosclerotic events when compared with individuals taking placebo.⁴ However, greater than 99% of this study population were on dialysis or had an eGFR <60 mL/min per 1.73 m². In contrast, our study population with an eGFR <60 mL/min per 1.73 m² was too small to examine, although we did find a consistent, albeit non-significant, protective association among ezetimibe users with an eGFR ≥ 60 mL/min per 1.73 m².

In this study, we did not measure the effect of ezetimibe use or statin use on proxy measures of AD, such as CIMT.²³ It has been in studies examining this latter outcome where the benefit of ezetimibe therapy has been most strongly called into question.^{2, 3, 24} However, a number of recent studies cast doubt on the utility of CIMT as a predictive measure for AD events.²⁵ For example, in data from 41 trials representing 18,307 individuals using a variety of lipid lowering treatments, Costanzo *et al.* did not find a significant relationship between treatment-related changes in CIMT and future CHD events, cerebrovascular disease events, and all-cause death.²⁶ Similarly, Lorenz *et al.* used CIMT data of 36,984 individuals derived from general population studies worldwide.²⁷ They found no relationship between CIMT

progression and the outcomes of myocardial infarction, stroke, combined vascular events, and all-cause death.

There are multiple study limitations to consider. First, as with any observational study, there may be additional unmeasured confounders, which explain all or part of the observed associations. To minimize this possibility we carefully matched ezetimibe users and statin users by many potential confounders *a priori*, and our large patient population made this possible. However, there were other risk factors, such as obesity and smoking status, which we did not have complete data on and could not account for in our analyses.

Despite our large sample size, we were underpowered on many of the secondary and subgroup analyses. Nevertheless, the consistency of effect estimates across nearly all of these analyses supports a protective association for ezetimibe use on the composite outcome. Our findings are in keeping with Morrone *et al.* who found consistent response to ezetimibe as part of statin combination therapy in multiple population subgroups.²⁸

To combine and account for the different statin preparations, we extrapolated findings from a recent meta-analysis¹⁰ and derived weights based on the comparative efficacy in lowering LDL levels. Since LDL reduction is just one way in which statins may reduce the risk of atherosclerotic disease and death, it would have been preferable to have weights which reflected efficacy in reducing the composite outcome, but these data were not available. As a result, we may have misestimated the true effect of statins.

We also did not use propensity scores to match individuals or adjust for differences between the ezetimibe and statin user groups. It is important to note that these propensity methods do not account for unmeasured confounders,^{29, 30} and they do not guarantee similarities within any given characteristic across groups. Since we had a very large population of statin users, we were able to directly match on all of the factors which we would have used in building a propensity score. Therefore, rather than rely on a single summary (i.e., propensity) metric for matching or adjusting, we were able to assure that ezetimibe and statin users were similar in all of the following characteristics: age, sex, race-ethnicity, baseline LDL levels, year of index prescription, prior atherosclerotic events, and other co-morbidities (i.e., hypertension and diabetes).

Lastly, this is the first study to examine and report on the independent relationship between ezetimibe use and clinical end outcomes. Therefore, additional studies of ezetimibe are needed to support our findings, especially those focusing on hard clinical endpoints rather than uncertain predictive measures of major AD events, such as CIMT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants from the Fund for Henry Ford Hospital (D.E.L. and L.K.W.), the National Heart Lung and Blood Institute (R01HL079055 [L.K.W.], R01HL103871 [D.E.L.], and K23HL085124 [D.E.L.]), the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK064695 [L.K.W.]), and the National Institute of Allergy and Infectious Diseases (R01AI079139 [L.K.W.]), National Institutes of Health. These funding agencies did not have a role in the study design, analysis, drafting of the manuscript, or revision of the manuscript.

References

1. Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, Silverman A, Galloway JM, Henderson JA, Weir MR, Wilson C, Stylianou M, Howard WJ. Effect of statins alone versus statins

- plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. *J Am Coll Cardiol*. 2008; 52:2198–2205. [PubMed: 19095139]
2. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, Visseren FL, Sijbrands EJ, Trip MD, Stein EA, Gaudet D, Duivenvoorden R, Veltri EP, Marais AD, de GE. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008; 358:1431–1443. [PubMed: 18376000]
 3. Taylor AJ, Villines TC, Stanek EJ, Devine PJ, Griffen L, Miller M, Weissman NJ, Turco M. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med*. 2009; 361:2113–2122. [PubMed: 19915217]
 4. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de ZD, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011; 377:2181–2192. [PubMed: 21663949]
 5. Habib ZA, Tzogias L, Havstad SL, Wells K, Divine G, Lanfear DE, Tang J, Krajenta R, Pladevall M, Williams LK. Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis. *Pharmacoepidemiol Drug Saf*. 2009; 18:437–447. [PubMed: 19235778]
 6. Wells KE, Peterson EL, Ahmedani BK, Severson RK, Gleason-Comstock J, Williams LK. The relationship between combination inhaled corticosteroid and long-acting beta-agonist use and severe asthma exacerbations in a diverse population. *J Allergy Clin Immunol*. 2012; 129:1274–1279. [PubMed: 22281166]
 7. Singer N. Study raises questions about cholesterol drug's benefit. *The New York Times*. 2009 Nov 16. Sect A:16.
 8. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol*. 1997; 50:105–116. [PubMed: 9048695]
 9. Williams LK, Joseph CL, Peterson EL, Wells K, Wang M, Chowdhry VK, Walsh M, Campbell J, Rand CS, Apter AJ, Lanfear DE, Tunceli K, Pladevall M. Patients with asthma who do not fill their inhaled corticosteroids: a study of primary nonadherence. *J Allergy Clin Immunol*. 2007; 120:1153–1159. [PubMed: 17936894]
 10. Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. *J Clin Pharm Ther*. 2010; 35:139–151. [PubMed: 20456733]
 11. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis*. 2003; 41:1–12. [PubMed: 12500213]
 12. Allison PD. Discrete-Time Methods for the Analysis of Event Histories. *Sociol Methodol*. 1982; 13:61–98.
 13. Allison, PD. Survival analysis using the SAS system: A Practical Guide. Cary, NC: SAS Institute Inc; 1995. Analysis of Tied or Discrete Data with the LOGISTIC, PROBIT, and GENMOD procedures; p. 211–231.
 14. SAS Institute Inc. SAS/STAT Users Guide. Cary, NC: SAS Institute Inc; 2008. Version 9.2 ed
 15. O'Brien, RG. Using the SAS System to Perform Power Analyses for Log-linear Models. Proceedings of the Eleventh Annual SAS Users Group International Conference; Cary, NC: SAS Institute Inc; 1986. p. 778–782.
 16. Divine G, Kapke A, Havstad S, Joseph CL. Exemplary data set sample size calculation for Wilcoxon-Mann-Whitney tests. *Stat Med*. 2010; 29:108–115. [PubMed: 19890884]
 17. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998; 279:1615–1622. [PubMed: 9613910]

18. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med.* 1995; 333:1301–1307. [PubMed: 7566020]
19. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994; 344:1383–1389. [PubMed: 7968073]
20. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med.* 1996; 335:1001–1009. [PubMed: 8801446]
21. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005; 352:1425–1435. [PubMed: 15755765]
22. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendixen FS, Lindahl C, Szarek M, Tsai J. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA.* 2005; 294:2437–2445. [PubMed: 16287954]
23. Stein EA. Additional lipid lowering trials using surrogate measurements of atherosclerosis by carotid intima-media thickness: more clarity or confusion? *J Am Coll Cardiol.* 2008; 52:2206–2209. [PubMed: 19095140]
24. Khanderia U, Regal RE, Rubenfire M, Boyden T. The ezetimibe controversy: implications for clinical practice. *Ther Adv Cardiovasc Dis.* 2011; 5:199–208. [PubMed: 21636623]
25. Goldberger ZD, Valle JA, Dandekar VK, Chan PS, Ko DT, Nallamothu BK. Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. *Am Heart J.* 2010; 160:701–714. [PubMed: 20934565]
26. Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, Chiariello M. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. *J Am Coll Cardiol.* 2010; 56:2006–2020. [PubMed: 21126642]
27. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Volzke H, Tuomainen TP, Sander D, Plichart M, Catapano AL, Robertson CM, Kiechl S, Rundek T, Desvarieux M, Lind L, Schmid C, DasMahapatra P, Gao L, Ziegelbauer K, Bots ML, Thompson SG. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet.* 2012; 379:2053–2062. [PubMed: 22541275]
28. Morrone D, Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, Shah AK, Tershakovec AM. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: A pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis.* 2012; 223:251–261. [PubMed: 22410123]
29. Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol.* 2006; 98:253–259. [PubMed: 16611199]
30. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. *Am J Epidemiol.* 1999; 150:327–333. [PubMed: 10453808]

Figure 1.

Flow diagram of ezetimibe users and statin users who were included in the current analysis. Depending on the number of suitable matches, each ezetimibe user was matched with up to four comparable statin users. Individuals were matched on age, sex, race-ethnicity, baseline LDL cholesterol level, history of cardiovascular disease, diabetes status, presence of hypertension, and year of index prescription.

Table 1

Baseline characteristics of study participants stratified by whether they received ezetimibe or statin therapy.*

Characteristic	Patients receiving ezetimibe (n=367)	Patients receiving statins (n=1,238)	P-value
Age (years) – mean ± SD	58.9 ± 12.6	58.5 ± 12.4	0.585
Sex (female)	211 (57%)	712 (58%)	0.995
Race-ethnicity			0.350
African American	72 (20%)	232 (19%)	
White	278 (76%)	967 (78%)	
Other/unknown	17 (5%)	39 (3%)	
Household income (dollars) – mean ± SD*	59,000 ± 24,000	56,000 ± 25,000	0.023
LDL cholesterol level (mg/dL) [†]			0.354
70	10 (3%)	15 (1%)	
71–100	21 (6%)	61 (5%)	
101–130	80 (24%)	284 (24%)	
131–160	121 (36%)	445 (38%)	
161–190	88 (26%)	295 (25%)	
>190	20 (6%)	61 (5%)	
Atherosclerotic disease [‡]	101 (28%)	302 (24%)	0.225
Diabetes mellitus [§]	87 (24%)	250 (20%)	0.147
Hypertension	270 (74%)	911 (74%)	0.995
Estimated GFR	78 ± 23	81 ± 37	0.088
(mL/min per 1.73 m ²) – mean ± SD [¶]			
1 additional lipid lowering medication use [#]	41 (11%)	29 (2%)	<0.001
Type of statin medication used			
Atorvastatin	--	287 (23%)	
Fluvastatin	--	3 (<1%)	
Lovastatin	--	60 (5%)	
Pravastatin	--	29 (2%)	
Rosuvastatin	--	7 (1%)	
Simvastatin	--	852 (69%)	
Type of additional lipid lowering medication used			
Bile salts	5 (1%)	4 (<1%)	0.034
Fibrates	33 (9%)	21 (2%)	<0.001
Niacin	4 (1%)	4 (<1%)	0.086

SD denotes standard deviation and LDL, low density lipoprotein.

*Based on the median house hold income in the census tract for the listed primary residence.

[†]Defined as the value in the year prior and closest to the index prescription.

[‡]Individuals were considered to have atherosclerotic disease at baseline if they had a prior diagnosis of coronary heart disease (i.e., myocardial infarction, unstable angina, or coronary revascularization), cerebrovascular disease (i.e., a cerebrovascular accident, a transient ischemic attack, or carotid revascularization), or peripheral vascular occlusive disease at any time prior to their index prescription for ezetimibe or a statin.

^{\$}Individuals were considered to have diabetes if they had at least 2 recorded diagnoses of diabetes or were taking a diabetes medication (i.e., an oral medication or insulin).

^{//}Individuals were considered to have hypertension if they had at least 2 prior diagnoses of hypertension or were taking an oral anti-hypertensive medication.

[¶]The glomerular filtration rate was estimated using the Modification of Diet in Renal Disease formula.¹¹

[#]Denotes whether patients were taking any other class of lipid lowering medication at the time of their initial prescription fill for ezetimibe or a statin.

Table 2
Relation of ezetimibe use and statin use with major atherosclerotic disease events and death^{*}

Outcome	Model	Number of events	OR (95% CI)	P-value	Wald test – P-value [*]
Primary outcome[†]		180			0.231
	Ezetimibe		0.33 (0.13–0.86)	0.024	
	Statin		0.61 (0.36–1.04)	0.068	
Secondary outcomes					
Major atherosclerotic disease events [‡]		137			0.336
	Ezetimibe		0.55 (0.20–1.52)	0.250	
	Statin		0.93 (0.51–1.69)	0.801	
Coronary heart disease [§]		75			0.509
	Ezetimibe		0.96 (0.28–3.32)	0.944	
	Statin		1.48 (0.66–3.32)	0.341	
Cerebrovascular disease		65			0.324
	Ezetimibe		0.13 (0.02–0.99)	0.048	
	Statin		0.37 (0.16–0.89)	0.027	
Peripheral vascular occlusive disease [¶]		12			0.543
	Ezetimibe		3.78 (0.35–40.63)	0.272	
	Statin		1.70 (0.17–17.37)	0.655	
All-cause death		71			
	Ezetimibe		0.03 (0.01–0.49)	0.013	0.242
	Statin		0.17 (0.07–0.42)	<0.001	

OR denotes odds ratio and CI, confidence interval.

^{*} In all of the models, ezetimibe use and statin use are estimated as continuous measures of medication exposure (CMME). However, statin use is weighted to account for differences in statin dose and preparation. The models also account for household income and the use of other lipid lowering medications (i.e., separate CMME for bile acid sequestrants, fibrates, and niacin).

[†] The primary study outcome was a composite of all-cause death and major atherosclerotic disease (AD) events (i.e., acute myocardial infarction [AMI], unstable angina, coronary revascularization, cerebrovascular accidents [CVA], transient ischemic attacks [TIA], carotid revascularization, and peripheral vascular occlusive disease [PVOD] events).

[‡] Major AD events included the following: fatal and non-fatal AMI, unstable angina, coronary revascularization, fatal and non-fatal CVA, TIA, carotid revascularization, and PVOD events.

[§]Coronary heart disease was a composite of fatal and non-fatal AML, unstable angina, and coronary revascularization.

^{//}Cerebrovascular disease was a composite of fatal and non-fatal CVA, TIA, and carotid revascularization.

[¶]PVOD was a composite of hospitalization, peripheral revascularization, amputation, and death.

Table 3

Primary cause of death among ezetimibe and statin users

Cause of death – no. (% of all users)	Ezetimibe users (n=367)	Statin users (n=1,238)
Infectious	0	7 (0.6%)
Malignancy – total	4 (1.1%)	18 (1.5%)
Solid tumor	2 (0.5%)	15 (1.2%)
Hematologic	2 (0.5%)	2 (0.2%)
Unknown	0	1 (0.1%)
Cardiac – total	8 (2.2%)	22 (1.8%)
Atherosclerotic heart disease	7 (1.9%)	12 (1.0%)
Other heart disease	1 (0.3%)	10 (0.8%)
Cerebrovascular	1 (0.3%)	2 (0.2%)
Peripheral vascular	1 (0.3%)	1 (0.1%)
Other vascular	2 (0.5%)	2 (0.2%)
Pulmonary	0	5 (0.4%)
Gastrointestinal	1 (0.3%)	6 (0.5%)
Injury	3 (0.8%)	2 (0.2%)
Other	3 (0.8%)	9 (0.7%)
TOTAL	23 (6.3%)	74 (6.0%)

Table 4

Relation of ezetimibe monotherapy and statin monotherapy with the primary composite outcome stratified by subgroups.*

Outcome	Treatment	Number of events	OR (95% CI) [†]	P-value	Wald test – P-value [‡]
Sex					
Male		81			0.188
	Ezetimibe		0.55 (0.15–2.04)	0.373	
	Statin		1.37 (0.61–3.07)	0.448	
Female		99			0.747
	Ezetimibe		0.25 (0.06–0.96)	0.043	
	Statin		0.31 (0.15–0.64)	0.001	
Race-ethnicity					
African American		33			0.343
	Ezetimibe		0.11 (0.01–2.19)	0.148	
	Statin		0.47 (0.12–1.79)	0.267	
White		145			0.745
	Ezetimibe		0.50 (0.19–1.36)	0.176	
	Statin		0.60 (0.33–1.08)	0.091	
History of atherosclerotic disease [§]					
Yes		84			0.631
	Ezetimibe		0.56 (0.18–1.76)	0.324	
	Statin		0.42 (0.19–0.94)	0.034	
No		96			0.073
	Ezetimibe		0.11 (0.01–0.88)	0.037	
	Statin		0.75 (0.37–1.55)	0.441	
History of diabetes					
Yes		68			0.102
	Ezetimibe		0.15 (0.03–0.81)	0.027	
	Statin		0.61 (0.26–1.45)	0.263	
No		112			0.840

Outcome	Treatment	Number of events	OR (95% CI) [†]	P-value	Wald test – P-value [‡]
Estimated GFR (mL/min per 1.73 m ²) [§]	Ezetimibe		0.59 (0.19–1.80)	0.353	
	Statin		0.67 (0.33–1.32)	0.245	
<60	Ezetimibe	52	--	--	--
	Statin		0.47 (0.15–1.48)	0.198	
60	Ezetimibe	123	0.44 (0.14–1.38)	0.161	0.429
	Statin		0.72 (0.36–1.41)	0.333	

OR denotes odds ratio; CI, confidence interval; and GFR, glomerular filtration rate.

* The primary study outcome was a composite of all-cause death and major atherosclerotic disease (AD) events (i.e., acute myocardial infarction, unstable angina, coronary revascularization procedures, cerebrovascular accidents [CVA], transient ischemic attacks [TIA], carotid revascularization, and peripheral vascular occlusive disease [PVOD] events).

[†] Ezetimibe use and statin use are estimated as continuous measures of medication exposure (CMME). However, statin use is weighted to account for differences in statin dose and preparation. Effect estimates represent the difference in going from no use to use of the maximal strength preparation every day.

[‡] The Wald test assesses differences in the effect estimates for ezetimibe and statins.

[§] Individuals were considered to have AD at baseline if they had a prior diagnosis of coronary heart disease (i.e., myocardial infarction, unstable angina, or coronary revascularization), cerebrovascular disease (i.e., CVA, TIA, or carotid revascularization), or PVOD.

// The glomerular filtration rate was estimated using the Modification of Diet in Renal Disease formula.¹¹