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,*]

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). The aims of this study were to estimate the effect of ezetimibe use on major AD events and all-cause mortality and to compare these associations to those observed for hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) use. A total of 367 new ezetimibe users were identified from November 1, 2002, to December 31, 2009. These subjects were aged ≥18 years and had no previous statin use. One to 4 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. Ezetimibe use (odds ratio 0.33, 95% confidence interval 0.13 to 0.86) and statin use (odds ratio 0.61, 95% confidence interval 0.36 to 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 gender, race or ethnicity, 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 that was not significantly different from that observed for statin use. © 2013 Elsevier Inc. All rights reserved. **(Am J Cardiol 2013;111:532−539)**

A number of studies suggest that ezetimibe use reduces low-density lipoprotein (LDL) cholesterol levels without a commensurate improvement in carotid intima-media thickness (CIMT), a proxy measure of atherosclerotic disease (AD) burden.[1−3] However, 1 clinical trial in patients with chronic kidney disease showed that patients randomized to using ezetimibe and a statin concomitantly had fewer major AD events compared to those assigned to placebo.[4] Because of the seemingly conflicting findings regarding the ability of ezetimibe to reduce 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, we examined and compared the estimated effect of ezetimibe use and statin use on these events. The large patient population allowed us to closely match patients 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 subjects were members of a large health maintenance organization that serves southeastern Michigan, including metropolitan Detroit. We identified all subjects with prescription coverage who had medication fills for ezetimibe or statins from November 1, 2002, to 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

[a]Department of Internal Medicine, [b]Department of Public Health Sciences, and [c]Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Michigan; and [d]Research Triangle Institute Health Solutions, Barcelona, Spain. Manuscript received September 18, 2012; revised manuscript received and accepted November 1, 2012.

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See page 538 for disclosure information.

*Corresponding author: Tel: +313-874-6693; fax: +313-874-7137.
E-mail address: kwillia5@hfhs.org (L.K. Williams).

† Drs. Hayek, Canepa Escaro, Sattar, and Gamalski contributed equally to this works.

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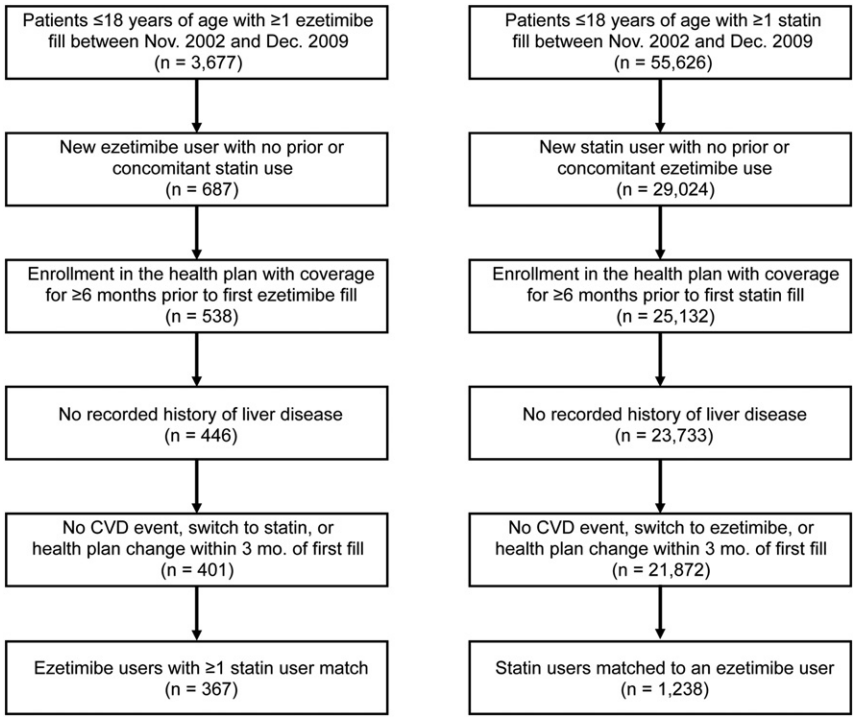

Figure 1. Flow diagram of ezetimibe users and statin users who were included in the present analysis. Depending on the number of suitable matches, each ezetimibe user was matched with up to 4 comparable statin users. Subjects were matched on age, gender, race or ethnicity, baseline LDL cholesterol level, history of cardiovascular disease (CVD), diabetes status, presence of hypertension, and year of index prescription.

was the index date), provided the patient had no record of earlier ezetimibe or statin use. Study subjects were aged $\geq$18 years on the index date and were continuously enrolled in the health plan for $\geq$6 months before that date. We excluded patients with previous diagnoses of liver disease and those who died or had major AD events within 3 months of the index prescription.

We adapted the method of Steiner and Prochazka[8] to estimate medication exposure. Because study subjects were members of the health maintenance organization 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 about 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 before, but extending into, the 3-month observation window, as well as prescription fills in which the supply ran past the observation window (i.e., 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 CMMEs, each of which represented a moving 3-month window of medication exposure for their particular lipid-lowering medications.

Unlike ezetimibe, which was available as a single dose (10 mg/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 on the basis of 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 relation 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 40-mg 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 on-line 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 subjects using statin medications.

Although much less frequently used by patients, separate exposure measures were created for the following classes of cholesterol-lowering medications: 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, gender, race or 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. Creatinine level, age, gender, and race or ethnicity were used to derive estimated glomerular filtration rate (eGFR), a measure of kidney function, according to the