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Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75): A Randomized Controlled Trial

Running Title: *Ouchi et al.; Ezetimibe and Cardiovascular Events in the Old-Old*

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Abstract

Background: Evidence regarding the primary prevention of coronary artery disease (CAD) events by LDL-C-lowering therapy in older individuals aged ≥75 years is insufficient. This trial tested whether LDL-C-lowering therapy with ezetimibe is useful for the primary prevention of cardiovascular events in older patients.

Methods: This multicenter, prospective, randomized, open-label, blinded end-point evaluation conducted at 363 medical institutions in Japan examined the preventive efficacy of ezetimibe for patients aged ≥75 years with elevated LDL-C without history of coronary artery disease. Patients, who all received dietary counseling, were randomly assigned (1:1) to receive ezetimibe (10 mg once daily) versus usual care with randomization stratified by site, age, sex, and baseline LDL-C. The primary outcome was a composite of sudden cardiac death, myocardial infarction, coronary revascularization, or stroke.

Results: Overall, 3,796 patients were enrolled between May 2009 and December 2014, and 1,898 each were randomly assigned to ezetimibe versus control. Median follow-up was 4.1 years. After exclusion of 182 and 203 patients because of lack of appropriate informed consent and other protocol violations, 1,716 (90.4%) and 1,695 (89.3%) patients were included in the primary analysis, respectively. Ezetimibe reduced the incidence of the primary outcome (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.50–0.86; *P*=0.002). Regarding the secondary outcomes, the incidences of composite cardiac events (HR, 0.60; 95% CI, 0.37–0.98; *P*=0.039) and coronary revascularization (HR, 0.38; 95% CI, 0.18–0.79; *P*=0.007) were lower in the ezetimibe group than in the control group; however, there was no difference in the incidence of stroke, all-cause mortality, or adverse events between trial groups.

Conclusions: LDL-C-lowering therapy with ezetimibe prevented cardiovascular events, suggesting the importance of LDL-C lowering for primary prevention in individuals aged ≥75 years with elevated LDL-C. Given the open label nature of the trial, its premature termination and issues with follow up, the magnitude of benefit observed should be interpreted with caution.

Clinical Trial Registration: URL: https://www.umin.ac.jp Unique identifier: UMIN000001988.

Key Words: elderly; atherosclerotic cardiovascular disease; ezetimibe; LDL-C-lowering therapy; primary prevention

Non-standard Abbreviations and Acronyms

EWTOPIA 75, Ezetimibe lipid-loWering Trial On PreventIon of Atherosclerosis in 75 or older; LDL-C, low-density lipoprotein-cholesterol; CAD, coronary artery disease; HR, hazard ratio; CI, confidence interval; ASCVD, atherosclerotic cardiovascular disease; RCT, randomized controlled trial; PROBE, prospective, randomized, open-label, blinded end-point; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; PAD, peripheral artery disease; JGS, Japan Geriatrics Society; PHRF, Public Health Research Foundation; CSP-LD, Clinical Research of Lifestyle-Related Disease; IDMC, independent data monitoring committee; ITT, intention-to-treat; PP, per-protocol; SD, standard derivation; GEE, generalized estimating equation; ALLHAT-LLT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; SAGE, Study Assessing Goals in the Elderly; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; PATE, Pravastatin Anti-atherosclerosis Trial in the Elderly; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

Clinical Perspective

What is new?

- Low-density lipoprotein-cholesterol (LDL-C)-lowering therapy with ezetimibe significantly reduced the risk of the primary outcome, a composite of sudden cardiac death, myocardial infarction, coronary revascularization, or stroke, for patients aged ≥75 years with elevated LDL-C at baseline.
- Analyses of secondary outcomes showed that ezetimibe reduced composite cardiac events, but not stroke.

What are the clinical implications?

- LDL-C-lowering therapy with ezetimibe prevented cardiovascular events in individuals aged ≥75 years with elevated LDL-C, supporting the importance of primary prevention for patients 75 years or older.

Introduction

In individuals aged ≥75 years, evidence to support primary prevention of atherosclerotic cardiovascular disease (ASCVD) events by LDL-C-lowering therapy is insufficient.[1-3] There is a need for obtaining randomized controlled trial (RCT)-based evidence as to whether LDL-C-lowering therapy can prevent ASCVD in older individuals because the number of individuals aged ≥75 years has dramatically increased worldwide.[4] Some studies showed that statin therapy for older patients was beneficial for primary prevention of ASCVD events[5-8], but a recent study did not show effectiveness in primary prevention.[9] A meta-analysis indicated that a reduction in LDL-C levels by statin and nonstatin therapies was associated with a lower incidence of coronary artery disease (CAD) events[10], but evidence for older individuals was still limited. Moreover, the clinical benefit of ezetimibe for the prevention of ASCVD in individuals aged ≥75 years remained unclear.[11] Therefore, we evaluated the effects of LDL-C-lowering therapy with ezetimibe in individuals aged ≥75 years with elevated baseline LDL-C without history of CAD.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Trial Design and Participants

This was a multicenter, prospective, randomized, open-label, blinded end-point (PROBE) trial performed in Japan. The trial enrolled men and women without a history of CAD who were aged ≥75 years between May 2, 2009, and December 29, 2014, at 363 medical institutions in Japan. The follow-up period defined in the protocol was for 3 years after the start date for the last patient enrolled. Inclusion criteria were as follows: the acquisition of written informed consent

for participation; age ≥75 years at the time of enrollment; being capable of visiting the participating site on an ambulatory basis; serum LDL-C level ≥140 mg/dL as estimated by the Friedewald formula.[12]: LDL-C = total cholesterol (TC) - (high-density lipoprotein cholesterol (HDL-C) + triglyceride (TG)/5); no use of a lipid-lowering drug for ≥4 weeks (in case of probucol for ≥8 weeks) prior to the measurement of baseline serum LDL-C level; and at least one of diabetes mellitus, hypertension, low HDL-C, hypertriglyceridemia, current smoker, a history of symptomatic, imaging-confirmed stroke, and peripheral artery disease (PAD).

Key exclusion criteria were as follows: a fasting serum TG level of ≥400 mg/dL; a history of myocardial infarction; a history of coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting); angina pectoris requiring treatment; stroke within 6 months of enrollment; severe liver disease with any one of the following 3 items: an aspartate aminotransferase level of ≥100 IU/L, an alanine aminotransferase level of ≥100 IU/L, and/or diagnosed cirrhosis; serum creatinine ≥3.0 mg/dL; malignancy; dementia; familial hypercholesterolemia diagnosed based on the Japan Atherosclerosis Society guidelines for prevention of atherosclerotic cardiovascular diseases 2007[13]; atrial fibrillation; a history of hypersensitivity to ezetimibe; participation in another clinical trial at the time of enrollment; and inappropriateness for enrollment as judged by the attending physician. Supplemental Table 1 and the online-only Data Supplement provide the full inclusion and exclusion criteria. The trial protocol was approved by the sponsors [the Japan Geriatrics Society (JGS) and Public Health Research Foundation (PHRF)] and the institutional review committee at each participating site. All of the patients provided written informed consent before enrollment. The trial was conducted in accordance with the principles of the Declaration of Helsinki.

Prior to randomization, the investigators examined concurrent treatments with lipid modifying, antihypertensive, antihyperglycemic, or antithrombotic drugs, determined

anthropometric variables (e.g., height, body weight, body mass index, and waist circumference), pulse rate, and gerontological index of competence, and conducted blood chemistry, urinalyses, and laboratory tests (eg, TC, HDL-C, non-HDL-C, LDL-C, TG, and fasting blood glucose). Supplemental Table 2 provides the details of and timing for observations, examinations, and assessments.

Randomization and Masking

At the time of enrollment, all patients received dietary counseling and were randomly assigned (1:1) by a centrally managed service at a sponsor PHRF−Comprehensive Support Project for Clinical Research of Lifestyle-Related Disease (CSP-LD) Data Center−to receive ezetimibe (10 mg once daily, after a meal) versus usual care with randomization (minimization method) stratified by site, age, sex, and baseline LDL-C level.

Because of the nature of a PROBE trial, patients and medical professionals (e.g., attending physicians and nurses) were not blinded. Blinded to randomized assignment, the outcome assessment committee assessed efficacy outcomes prior to the final analysis.

Procedures

After the acquisition of written informed consent for participation, we randomly assigned the patients in two groups; treatment consisting of dietary counseling plus ezetimibe (10 mg, once daily, after meals) as ezetimibe group or dietary counseling alone as control group. Patients in the ezetimibe group were prescribed the drug. Patients were instructed to visit the participating site every 12 months after randomization in order to examine the predefined assessment items (e.g., concurrent treatments with lipid modifying, antihypertensive, antihyperglycemic, or antithrombotic drugs, adverse events, and laboratory tests). Supplemental Table 2 provides the details of and timing for observations, examinations, and assessments.

An independent data monitoring committee (IDMC) reviewed the efficacy and safety data, provided oversight of the conduct, safety, and progression of the trial, and assumed the role of recommending whether or not to continue the trial. The IDMC had a meeting (November 20, 2015) to review the data and recommended the early closure of the trial because the anticipated number of 520 primary outcome events was unlikely to be achieved due to growing competing risks and increased losses to follow up. The IDMC judged that the incidence of events of the primary outcome would not increase during the scheduled follow-up period because of the following reasons: 1) the number of deaths other than the outcome events was greater than expected and 2) the incidence of the events slowed along with the elapsed period of treatment. The decision was subsequently endorsed by the principal investigator and the trial promotion committee, and the trial was closed on March 31, 2016. Median follow-up periods for survivors to death, loss to follow-up, or March 31, 2016 were equivalent between the two trial groups (4.1 years).

Outcomes

The primary outcome was a composite of sudden cardiac death, fatal/nonfatal myocardial infarction, coronary revascularization, or fatal/nonfatal stroke. The key secondary outcomes were sudden cardiac death, composite (fatal/nonfatal) myocardial infarction, fatal myocardial infarction, nonfatal myocardial infarction, coronary revascularization, composite (fatal/nonfatal) stroke, fatal stroke, nonfatal stroke, carotid artery revascularization (carotid artery stenting and carotid endarterectomy), deaths–all-cause mortality, cerebrovascular deaths, non-cerebrovascular deaths, non-cardiovascular deaths, death from malignant tumors, all-cause hospitalizations, atrial fibrillation, incident malignancy, fracture of the femoral neck, onset of dementia, Tokyo Metropolitan Institute index of competence, admission to a facility (admission to a center for geriatric care), adverse events, and length of hospital stay. The online Data Supplement provides

the full secondary outcomes. The trial promotion committee received reporting from the principal investigator (YO) on the outcomes.

Statistical Analysis

The trial was designed to have 90% power to detect a 25% reduction in the primary outcome, with a two-sided *P* value of <0.05. The trial was planned to continue until 520 events of the primary outcome occurred unless it was closed early. Planned sample size was 6,000 individuals when presuming a hazard ratio (HR) of 0.75, an incidence of the primary outcome in the control group of 3% per year, and a loss to follow-up rate of 20%. We conducted all statistical analyses according to the predefined statistical analysis plan and based on the intention-to-treat (ITT) and per-protocol (PP) principles, with outcomes assessed from the time of randomization. In the ITT analysis, patients lost to follow up during the trial period were censored at last date of contact. Patients in the ITT set, who met the following criteria, comprised the PP set: 1) those in the ezetimibe group who correctly started to receive ezetimibe; and 2) those in the control group who did not receive ezetimibe for 4 or more weeks. The primary outcome events were adjusted for the following covariates to analyze treatment effect: age (<85 years/≥85 years), sex (male/female), diabetes mellitus (absent/present), hypertension (absent/present), number of risk factors (1–2/≥3), PAD (absent/present), LDL-C at baseline (<160 mg/dL/≥160 mg/dL), decreased HDL-C (absent/present), metabolic syndrome (absent/present), chronic kidney disease (<60 mL/min per 1.73 m^2 in estimated glomerular filtration rate), plasma hemoglobin (<12 g/dL/≥12 g/dL), and pretrial history of dyslipidemia treatment (absent/present). We excluded urinary albumin and metabolic syndrome from covariates to be adjusted because the number of measurement of urinary albumin was small and metabolic syndrome was associated with other cofactors like hypertension, diabetes, and dyslipidemia. We imputed missing covariates for

adjustment to reduce missing effect by conducting multiple imputations with chained equations (25 rounds). No pre-specified interim analysis was conducted.

Summary statistics at baseline are reported as mean ± standard derivation (SD) and number (%) for continuous and categorical variables, respectively. Log-rank test p-values are presented for time-to-event analyses. The primary outcome was also analyzed by covariate-adjusted analysis and the competing risk-adjusted analysis using the Fine-Gray sub-distribution hazard model in the ITT and PP populations. The online-only Data Supplement provides the Fine-Gray proportional hazards regression model analyses. Cox regression modelling was used to calculate the point estimates for the HRs of group effect and their 95% confidence intervals (CIs). Kaplan-Meier estimates were used to calculate the incidences of outcome events and all-cause mortality in the two randomized groups. Summary statistics of changes from the baseline value were calculated for each group and for each time point. The between-group effect was tested and estimated according to the generalized estimating equation (GEE) using the baseline values as covariates. A GEE model with an interaction between treatment and categorized time, and one without an interaction were considered. Patients, whose follow-up was discontinued due to death, transfer to other hospitals, entry in centers for geriatric care, lost to follow up, etc., were handled as censored cases. A value of $P<0.05$ was considered statistically significant. Proportionality was checked by using the log(-log (survival probability)) plots. All statistical analyses were made with SAS version 9.4 (SAS Institute, NC, USA).

Role of the Funding Source

PHRF, Japan Heart Foundation, JGS, and Japan Atherosclerosis Society provided financial support for the trial. The company manufacturing and distributing the trial drug (MSD K.K.) and the company distributing the trial drug (Bayer Yakuhin, Ltd.) financed support for PHRF projects. None of these entities had a role in trial design, data analysis, data interpretation, or the writing

of the manuscript. YO had full access to all the data and final responsibility for the decision to submit for publication.

Results

Between May 2, 2009, and December 29, 2014, 5,333 patients were considered eligible. Of those, 17 patients at 13 institutions were excluded due to the violation of exclusion criteria and 1,520 patients were excluded from two medical institutions that were inadequate to conduct this trial because of their poor check-up and follow-up systems. Finally, 3,796 patients (1,898 each) were randomly assigned to the ezetimibe and control groups at 363 medical institutions (Figure 1). The groups were well balanced with respect to baseline characteristics (Table 1). All of the patients were Japanese. During the trial period, 182 and 203 patients were respectively excluded from the ezetimibe and control groups because of the lack of informed consent, etc (Figure 1). Subsequent to randomization, a total of 664 patients in the ezetimibe group (n = 339) and the control group (n = 325) were lost to follow up during the trial period. The median follow-up period in those lost to follow up was 2.6 years in ezetimibe group and 2.3 years in control group. The reasons of lost to follow up other than death were: 84 and 86 due to the transfer to other hospitals or admission to geriatric care facilities for long-term care; and 255 and 239 due to 1) the closure of hospitals/clinics because the investigators resigned/died during the trial period and 2) the failure in obtaining, through survey by mail or phone, any response from patients who stopped visiting the hospital/clinic. Consequently, 1,132 (59.6%) and 1,180 (62.2%) patients completed the trial, respectively. The number needed to treatment was 37.6 for the primary outcomes. After exclusion of patients who submitted the deficient consent form, the safety analysis sets comprised 1,742 and 1,726 patients in the respective groups.

Mean age at baseline was 80.6±4.7 years for the two trial groups. Female patients, "never smoked" patients, patients with hypertension, "middle-risk (1 or 2 risk factors)" patients, as well as statin and calcium antagonist users were predominant (Table 1). The drug adherence rates in the ezetimibe group at 1, 2, 3, 4, and 5 years of follow-up were 87.0%, 87.8%, 86.7%, 85.1%, and 82.3%, respectively (Supplemental Table 3).

Time-course changes in mean serum lipid levels for 5 years after randomization in the ezetimibe group and the control group are shown in Figures 2A-D. The mean serum LDL-C levels at baseline in the ezetimibe group and the control group were 161.9 mg/dL and 161.3 mg/dL, respectively. At 5 years of follow-up, the mean serum levels of LDL-C, non-HDL-C, and TG significantly decreased from the baseline values in contrast to serum HDL-C levels that remained unchanged in the two trial groups (Supplemental Table 4); the reduction rates in the ezetimibe group were 25.9%, 23.1%, and 8.3%, respectively, against the counterparts of 18.5%, 16.5%, and 4.8%, respectively, in the control group. Therefore, the reduction rates of serum LDL-C, non-HDL-C, and TG levels during 5 years of follow-up were significantly greater in the ezetimibe group than in the control group ($P<0.001$, $P<0.001$, and $P=0.003$, respectively). The incidence of the primary outcome events was significantly lower in the ezetimibe group than in the control group by log-rank test (HR, 0.66; 95% CI, 0.50–0.86; $P=0.002$; Figure 3A and Table 2). Supplemental results from covariate-adjusted analysis and competing risk-adjusted analysis on the primary outcome events in the ITT and PP populations revealed no difference in *P* values as compared with the non-adjusted results (Supplemental Table 5). Between-group significant differences were found with respect to composite cardiac events (HR, 0.60; 95%, CI 0.37–0.98; $P=0.039$; Figure 3C and Table 2) and coronary revascularization (HR, 0.38; 95% CI, 0.18–0.79; $P=0.007$; Table 2), but not for composite stroke (HR, 0.78; 95% CI, 0.55–1.11; $P=0.17$; Figure

3B and Table 2) or all-cause mortality (HR, 1.09; 95% CI, 0.89–1.34; *P*=0.43; Figure 3D and Table 2).

The effects of treatment on the primary outcome were examined in the predefined subgroups by age (<85 years/≥85 years), sex (male/female), diabetes mellitus (absent/present), hypertension (absent/present), number of risk factors (1–2/≥3), PAD (absent/present), LDL-C at baseline (<160 mg/dL/≥160 mg/dL), decreased HDL-C (absent/present), metabolic syndrome (absent/present), chronic kidney disease (<60 mL/min per 1.73 m^2 in estimated glomerular filtration rate), plasma hemoglobin (<12 g/dL/≥12 g/dL), and pretrial history of dyslipidemia treatment (absent/present) (Figure 4). No significant heterogeneity of treatment effect was found in the prespecified subgroups (Figure 4). For the subgroups comprising small numbers of patients, between-group differences might not have been shown due to the lack of statistical power.

A total of 188 and 173 deaths occurred in the ezetimibe group and the control group due to the following causes: 29 and 45 cerebro- and cardiovascular deaths, one death each from the rupture of abdominal aneurysm, 120 and 98 noncerebro- and noncardiovascular deaths, and 38 and 29 deaths from malignant tumors, respectively (Table 2). Against patients in the control group, namely, patients in the ezetimibe group tended to die less frequently from cerebro- and cardiovascular causes and more frequently from noncerebro- and noncardiovascular causes and malignant tumors, although they were not significantly different (Supplemental Table 6). Adverse events including respiratory, gastrointestinal, and neurologic adverse events are listed in Table 3. Ezetimibe was not associated with all-cause mortality (Figure 3D).

Discussion

This is the first RCT demonstrating that LDL-C-lowering therapy with ezetimibe prevented cardiovascular events in older individuals aged ≥75 years with elevated LDL-C. Ezetimibe reduced the risks of primary outcome by 34% and composite cardiac events by 40% with directionally consistent effects seen for components of the primary outcome. Moreover, a subgroup analysis indicates consistent results both in men and women. Ezetimibe was well tolerated and did not increase the incidence of adverse events as compared with the control group. Furthermore, no statistically significant difference was found in the incidence of non-CAD causes of death, including deaths from cancer between the ezetimibe group and the control group. These results support lipid-lowering therapy for the primary prevention for older individuals aged ≥75 years with ezetimibe.

The Joint Committee of Japan Gerontological Society and JGS proposed redefining the older as aged ≥75 years in 2017.[14] The population of older individuals and the incidence of lifestyle-related disease in them are increasing in the world, especially in the U.S., Europe, and Asia including Japan. However, the efficacy of lipid-lowering therapy for older individuals aged ≥75 years who had elevated LDL-C remained unclear.[11] The results from the EWTOPIA 75 address the evidence gap as to whether the primary prevention by lipid-lowering therapy can prevent CAD events in older individuals.[1, 3]

Lipid-lowering therapy with statins was effective for patients aged 40–75 years with and without ASCVD.[3, 10, 15] Treatment of dyslipidemia is a keystone for preventive cardiology, and lowering of LDL-C in selected populations reduces the risk of CAD events in both primary and secondary prevention.[16] However, the majority of RCTs of lipid-lowering therapy have targeted at individuals under age 75.[5, 10, 17] A post-hoc analysis of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT-LLT) showed that pravastatin

did not reduce all-cause mortality or CAD when compared with usual care in older individuals aged ≥75 years who had well-controlled hypertension and moderately elevated LDL-C.[9] In contrast, the Study Assessing Goals in the Elderly (SAGE), in which a total of 893 ambulatory CAD patients 65 to 85 years of age were randomized to receive atorvastatin 80 mg/d or pravastatin 40 mg/d and were followed up for 12 months, showed that intensive statin therapy was beneficial for the primary prevention of CAD events.[5] The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), an RCT in which 5,804 individuals aged 70 to 82 years of age at high risk for ASCVD were assigned to receive pravastatin 40 mg or placebo, demonstrated the efficacy of pravastatin for ASCVD.[6] The Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE), an RCT that compared the effect of low-dose with standard dose pravastatin, an HMG CoA reductase inhibitor, on the incidence of ASCVD in elderly patients with hypercholesterolemia, also showed that standard-dose pravastatin was more effective in reducing the incidence of ASCVD than low-dose pravastatin in Japanese patients aged ≥60 years who had mild hypercholesterolemia.[7] However, these RCTs included older individuals aged <75 years. Moreover, the PROSPER showed the significant event-suppressive effect of pravastatin only for secondary prevention.[6] The EWTOPIA 75, which followed up only older individuals aged ≥75 years, used a nonstatin drug ezetimibe to evaluate the efficacy of the primary prevention for ASCVD. From these viewpoints, the EWTOPIA 75 was different from previous studies, which provided the first evidence that ezetimibe was effective for the primary prevention of ASCVD in older individuals aged ≥75 years.

Observational studies have raised questions regarding benefits of cholesterol lowering in older adults. A meta-analysis on 61 prospective observational studies indicated the association of lower TC with lower ASCVD mortality and suggested the less involvement of ASCVD mortality for older individuals than for the middle-aged.[18] A 10-year cohort trial showed that each 1

mmol/L (38.7 mg/dL) increase in TC corresponded to a 15% decrease in mortality in 724 participants aged ≥85 years; mortality from cancer and infection was lower in the highest TC category than in the other categories.[19] A 6-year cohort trial in Japanese-American men aged 71 to 93 years revealed a significant U-shaped relationship between the age-adjusted rates of ASCVD and both TC and LDL-C, suggesting increased ASCVD risk at lower TC in older individuals.[20] However, these observational studies involve multiple biases and confounding factors. Our results showed the efficiency of lipid-lowering therapy for preventing CAD events in older individuals aged ≥75 years with elevated LDL-C.

Our trial did not demonstrate the efficacy of ezetimibe therapy for cerebrovascular events, although stroke events were numerically lower in the ezetimibe group. This finding may be attributable to the facts that the inclusion criteria of our trial included not patients with CAD but those with stroke occurring at ≥6 months prior to enrollment and that the test was underpowered for stroke events. Moreover, our trial could not assess asymptomatic stroke. This finding is in line, at least in part, with a meta-analysis on 29 cohort studies in the Asia-Pacific region that indicated a positive association between TC and CAD death but not between serum lipid levels and stroke in the <60, 60–74, and ≥75 years old groups.[21] On the other hand, interestingly, our trial showed reductions in LDL-C in the control group after baseline. We have speculated the reasons about this fact: 1) the improving effect of dietary counseling on the overall risk factor profile; 2) the potentially natural course of decreasing LDL-C levels in older individuals ≥ 75 years; and 3) some effects of the fact that a minimum proportion of patients received statins. We cannot exclude the possibility of "regression to the mean" but consider that the above reasons mainly caused the relevant reductions.

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that the combination of ezetimibe and simvastatin improved cardiovascular outcomes

compared with simvastatin monotherapy.[22] The subanalysis showed that patients aged ≥75 years had a 20% relative reduction in the primary outcome.[23] In addition, the combination of ezetimibe and simvastatin prevented CAD events in patients with advanced chronic kidney disease.[24] The EWTOPIA 75 is the first clinical study to demonstrate the clinical benefits of ezetimibe monotherapy. The number needed to treatment for the primary outcome in the present trial was 37.6, a value lower than 47.1 in PROSPER[6] and 50.0 in IMPROVE-IT[22]. Hence, ezetimibe monotherapy was suggested to be a potentially useful option to treat dyslipidemia in older adults, especially those with statin-related adverse events (eg, rhabdomyolysis).[25]

The magnitude of observed risk reductions by ezetimibe in the EWTOPIA 75 was greater than expected based on LDL differences between trial groups. The mechanisms by which ezetimibe was associated with large relative reductions in the incidence of CAD events through such a small reduction in LDL-C remain unclear. Until these findings are replicated in other studies on ezetimibe monotherapy for primary prevention, caution is required when interpreting the magnitude of treatment effect. The exaggerated magnitude of treatment effect may reflect the play of chance, and the early closure of the trial might have exaggerated the true treatment effect.

Our trial has several important limitations. First, this was a prospective RCT with blinded outcome assessment, but not a blinded placebo-controlled trial. We could not use matching placebo as control because of cost considerations. We consider that this determination is acceptable because most of the outcomes were objective variables and were analyzed by the event evaluation committee in a blinded manner. Second, 385 patients were excluded after randomization, and 664 patients were lost to follow up thereafter during the trial period. It is a major limitation which may have contributed to inflate treatment effect because this was PROBE in study design, even though the PROSPER trial also showed similar numbers of patients who were excluded before randomization.[6] The follow-up rates at 1, 2, and 3 years were 100.0%,

97.9%, and 93.9% in ezetimibe group and 100.0 %, 97.9.%, and 94.3 % in control group, respectively (Supplemental Table 3). The outcomes obtained at 4 and 5 years were compatible with those obtained up to 3 years. The follow-up rates at 5 years in the ezetimibe group and the control group were 53.4 % and 52.9 %, respectively. Third, the recruitment of this trial was slow and the trial was terminated after 3,796 of 6,000 planned participants were enrolled. This was a nationwide trial that included not only hospitals but also small clinics. More than half of 363 participating sites were represented by sites where only a small mall number of patients were enrolled: 1, 2, and 3 patients at 90, 63, and 40 sites, respectively. We consider that these participating sites affected the recruitment rate. However, the strong point of this trial was that we included trial patients on the nationwide scale, which suggested less area bias. Fourth, the low incidence of adverse events in our trial may reflect reporting bias. Ezetimibe is well-known for the lower incidence of adverse events compared to statins. Moreover, subjects of the present trial were very old, and there was a possibility that some doctors failed to report minor adverse events because they could consider that some adverse events came from aging effects. Fifth, this trial did not achieve the planned sample size or the estimated number of the primary outcome events in the initial protocol. The initial statistical analysis plan established “6,000 patients” as the target number of patients to detect a significant difference between the trial groups for the incidence of the primary outcome events. However, the IDMC recommended the earlier closure of the trial than expected due to increments in competing risks. Although statistically significant differences were found in the primary outcome, composite cardiac events, and coronary revascularization, other outcomes of interest may be subject to type II error. Additionally, the larger than expected treatment effect may reflect the lower precision of the outcome rates due to the small numbers of events. Finally, the number of censored individuals in the trial groups increased due to increments in competing risks (eg, losses to follow up due to noncardiac death,

and transfer to nursing homes), which led to the earlier closure of the trial that was recommended by the IDMC. Post-hoc competing risk-adjusted analysis revealed the similar results as the primary analysis. The impact of competing risks increased with aging, suggesting that we should take it into account when designing RCTs for older individuals.

Conclusions

LDL-C-lowering therapy with ezetimibe prevented cardiovascular events in older individuals aged ≥75 years, suggesting the importance of LDL-C lowering for primary prevention in individuals aged ≥75 years with elevated LDL-C. Given the open label nature of the trial, its premature termination and issues with follow up, the magnitude of benefit observed should be interpreted with caution.

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References

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019:73:e285-e350.
2. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014:129:S1-45
3. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, Jr., Garcia FA, Gillman MW, Kemper AR, Krist AH, , et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2016;316:1997-2007.
4. Gurwitz JH, Go AS and Fortmann SP. Statins for Primary Prevention in Older Adults: Uncertainty and the Need for More Evidence. *JAMA*. 2016;316:1971-1972.
5. Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, Luo D, Ouyang P, Piotrowicz R, Schenck-Gustafsson K, Sellier P, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation*. 2007;115:700-7.
6. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623-30.
7. Ito H, Ouchi Y, Ohashi Y, Saito Y, Ishikawa T, Nakamura H and Orimo H. A comparison of low versus standard dose pravastatin therapy for the prevention of cardiovascular events in the elderly: the pravastatin anti-atherosclerosis trial in the elderly (PATE). *J Atheroscler Thromb*. 2001;8:33-44.
8. Ishikawa T, Ito H, Ouchi Y, Ohashi Y, Saito Y, Nakamura H, Orimo H and Pate I. Increased risk for cardiovascular outcomes and effect of cholesterol-lowering pravastatin therapy

in patients with diabetes mellitus in the pravastatin anti-atherosclerosis trial in the elderly (PATE). *Curr Ther Res Clin Exp*. 2005;66:48-65.
9. Han BH, Sutin D, Williamson JD, Davis BR, Piller LB, Pervin H, Pressel SL, Blaum CS and Group ACR. Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial. *JAMA Intern Med*. 2017;177:955-965.
10. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E and Sabatine MS. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. *JAMA*. 2016;316:1289-97.
11. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, Umemoto S, Egusa G, Ohmura H, Okamura T, et al. Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. *J Atheroscler Thromb*. 2018;25:846-984.
12. Friedewald WT, Levy RI and Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499-502.
13. Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, et al. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. *J Atheroscler Thromb*. 2007;14:45-50.
14. Ouchi Y, Rakugi H, Arai H, Akishita M, Ito H, Toba K, Kai I, Joint Committee of Japan Gerontological Society (JGLS) and Japan Geriatrics Society (JGS) on the definition and classification of the elderly. Redefining the elderly as aged 75 years and older: Proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society. *Geriatr Gerontol Int*. 2017;17:1045-1047.
15. Long-Term Intervention with Pravastatin in Ischaemic Disease Study G. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-57.
16. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R and Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581-90.
17. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH and 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;333:1301-7.
18. Prospective Studies C, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R and Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370:1829-39.
19. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE and Westendorp RG. Total cholesterol and risk of mortality in the oldest old. *Lancet*. 1997;350:1119-23.
20. Curb JD, Abbott RD, Rodriguez BL, Masaki K, Popper J, Chen R, Petrovitch H, Blanchette P, Schatz I and Yano K. Prospective association between low and high total and

low-density lipoprotein cholesterol and coronary heart disease in elderly men. *J Am Geriatr Soc*. 2004;52:1975-80.
21. Zhang X, Patel A, Horibe H, Wu Z, Barzi F, Rodgers A, MacMahon S, Woodward M and Asia Pacific Cohort Studies C. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol*. 2003;32:563-72.
22. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med*. 2015;372:2387-97.
23. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalan R, Spinar J, Park JG, White JA, Bohula EA, Braunwald E et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation*. 2018;137:1571-1582.
24. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, et al. 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;377:2181-92.
25. Armitage J. The safety of statins in clinical practice. *Lancet*. 2007;370:1781-90.

Table 1. Baseline Patient Characteristics

	Control Group (n=1,695)	Ezetimibe Group (n=1,716)
Age (years)	80.6±4.7	80.6±4.7
Patients aged ≥85 years	325 (19.2)	323 (18.8)
Sex		
Male	432 (25.5)	440 (25.6)
Female	1263 (74.5)	1276 (74.4)
Height (cm)	150.6±8.6	150.7±8.7
Body weight (kg)	53.4±10.4	53.8±10.0
Body mass index (kg/m^2)	23.5±3.7	23.6±3.5
Waist circumference (cm)	84.1±10.1	84.5±10.1
Total cholesterol (mg/dL)	244.1±24.4	245.6±25.5
High-density lipoprotein cholesterol (mg/dL)	56.6±13.9	57.3±14.2
Triglycerides (mg/dL)	131.1±55.9	132.1±54.5
Low-density lipoprotein cholesterol (mg/dL)	161.3±19.4	161.9±20.1
Non-high-density lipoprotein cholesterol (mg/dL)	187.5±23.3	188.4±23.8
Decreased high-density lipoprotein cholesterol	156 (9.2)	146 (8.5)
Hypertriglyceridemia	520 (30.7)	526 (30.7)
Systolic blood pressure (mmHg)	135.8±15.9	137.0±15.8
Diastolic blood pressure (mmHg)	74.0±10.4	74.4±10.4
Heart rate (beats/min)	72.7±10.5	73.0±11.2
TMIG-IC	10.7±3.1	10.7±3.1
Smoking status		
Never smoked	1456 (85.9)	1466 (85.4)
Former smoker	157 (9.3)	161 (9.4)
Current smoker	82 (4.8)	89 (5.2)
Complications		
Hypertension	1509 (89.0)	1520 (88.6)
Diabetes mellitus	434 (25.6)	433 (25.2)
Metabolic syndrome	276 (16.3)	290 (16.9)
Others	176 (10.4)	186 (10.8)
Peripheral artery disease	49 (2.9)	52 (3.0)
Number of risk factors*		
0	0 (0.0)	0 (0.0)
1-2	1470 (86.7)	1488 (86.7)
≥3	225 (13.3)	228 (13.3)
Anamnesis		
Cerebral infarction	118 (7.0)	117 (6.8)
Fracture	35 (2.1)	45 (2.6)
Treatment history of malignant tumors	24 (1.4)	27 (1.6)
Chronic obstructive pulmonary disease	17 (1.0)	14 (0.8)
Cerebral hemorrhage	9 (0.5)	8 (0.5)
Transient ischemic attack	5 (0.3)	3 (0.2)
Others	129 (7.6)	144 (8.4)

Data are expressed as mean±SD or number (%). n, number of patients; TMIG-IC, Tokyo Metropolitan Institute index of competence *: Diabetes mellitus, hypertension, low high-density lipoprotein cholesterol levels, hypertriglyceridemia, cigarette smoking, history of cerebral infarction, and peripheral arterial disease

Table 2. Outcomes of EWTOPIA 75

	Control, n (%) n=1,695	Ezetimibe, n (%) n=1,716	Hazard Ratio (95% CI)	*P* Value
Primary outcome Composite of sudden cardiac death, fatal/nonfatal myocardial infarction, coronary revascularization, or fatal/nonfatal stroke	133 (7.8)	89 (5.2)	0.66 (0.50-0.86)	0.002
Key secondary outcomes				
Composite cardiac events*	43 (2.5)	26 (1.5)	0.60 (0.37–0.98)	0.039
Sudden cardiac death	23 (1.4)	15 (0.9)	0.65 (0.34–1.25)	0.12
Composite myocardial infarction	20 (1.2)	11 (0.6)	0.55 (0.26–1.14)	0.10
Fatal myocardial infarction	4 (0.2)	3 (0.2)	0.75 (0.17–3.33)	0.70
Nonfatal myocardial infarction	16 (0.9)	8 (0.5)	0.50 (0.21–1.16)	0.10
Coronary revascularization†	26 (1.5)	10 (0.6)	0.38 (0.18–0.79)	0.007
Composite stroke‡	70 (4.1)	55 (3.2)	0.78 (0.55–1.11)	0.17
Fatal stroke	18 (1.1)	11 (0.6)	0.61 (0.29–1.29)	0.19
Nonfatal stroke	54 (3.2)	47 (2.7)	0.87 (0.59–1.28)	0.47
Composite cerebral infarction§	60 (3.5)	47 (2.7)	0.78 (0.53–1.14)	0.20
Fatal cerebral infarction	11 (0.6)	7 (0.4)	0.64 (0.25–1.64)	0.34
Nonfatal cerebral infarction	50 (2.9)	43 (2.5)	0.86 (0.57–1.29)	0.45
Transient ischemic attack	4 (0.2)	2 (0.1)	0.50 (0.09–2.74)	0.42
Composed cerebral hemorrhage‖	11 (0.6)	8 (0.5)	0.73 (0.29–1.81)	0.50
Fatal cerebral hemorrhage	7 (0.4)	4 (0.2)	0.57 (0.17–1.95)	0.36
Nonfatal cerebral hemorrhage	4 (0.2)	4 (0.2)	1.00 (0.25–3.99)	1.00
Carotid artery revascularization	0 (0.0)	0 (0.0)	NA	
Peripheral artery revascularization	1 (0.1)	0 (0.0)	NA	
Aortic dissection, rupture of aortic aneurysm, and surgery of aortic aneurysm	5 (0.3)	2 (0.1)	0.40 (0.08–2.05)	0.25
All-cause mortality	173 (10.2)	188 (11.0)	1.09 (0.89–1.34)	0.43
Noncerebro- and noncardiovascular deaths¶	98 (5.8)	120 (7.0)	1.23 (0.94–1.60)	0.13
Cerebro- and cardiovascular deaths	45 (2.7)	29 (1.7)	0.64 (0.40–1.03)	0.06
Death from malignant tumors	29 (1.7)	38 (2.2)	1.31 (0.81–2.13)	0.27
Death from the rupture of aortic aneurysm	1 (0.1)	1 (0.1)	NA	

The hazard ratios and 95% confidence intervals were calculated by Cox proportional hazards analysis, and the p values by log-rank test.

* Includes sudden cardiac death and fatal/nonfatal myocardial infarction.

† Includes percutaneous coronary intervention or coronary artery bypass grafting.

‡ Includes fatal/nonfatal stroke.

§ Includes fatal/nonfatal cerebral infarction but excludes transient ischemic attack.

‖ Includes fatal/nonfatal cerebral hemorrhage.

¶ Does not include death from malignant tumors.

EWTOPIA 75, ezetimibe lipid-lowering trial on prevention of atherosclerosis in patients aged 75 years or older; n, number of patients; CI, confidence interval; NA, not available

Table 3. Adverse Events

	Number of Episodes	
	Control Group (n=1,726)	Ezetimibe Group (n=1,742)
Respiratory	23	22
Gastrointestinal (including the hepatobiliary tract)	21	24
Neurologic	6	13
Cardiovascular	23	14
Renal	5	8
Endocrinologic	5	7
Orthopedic (including muscle and bone)	41	40
Otorhinolaryngologic	16	12
Urologic	4	4
Ophthalmologic	1	3
Dermatologic	5	14
Dental and oral surgery	1	0
Infections	3	4
Hematologic abnormalities	3	7
Others	9	13
Total	166	185

n, number of patients

Figure Legends

Figure 1. Trial profile. A total of 385 excluded patients are detailed as follows: 1) Withdrew consent: 47 patients who gave written consent and were then enrolled. They withdrew the consent prior to the onset of trial treatment because of their worry about trial treatment or hospital visits for a long period of time; 2) Deficient consent form: 85 patients about whom independent on-site monitoring revealed that the investigators had not obtained written informed consent at the time of written consent acquisition; 3) No information after trial onset: 196 patients were transferred to other hospitals, admitted to centers for geriatric care, etc. at 1 or subsequent years of treatment; and 4) Ineligible: 57 patients who were found to be ineligible by on-site monitoring that was conducted to ensure the quality of the trial data. Concretely, 3 patients had a history of cardiovascular events, 6 and 8 patients had confirmed stroke and unconfirmed stroke, respectively, which was less than 6 months after onset at the time of enrollment, 7 patients had a malignant tumor that was less than 5 years after onset, and 33 patients had dementia prior to enrollment.

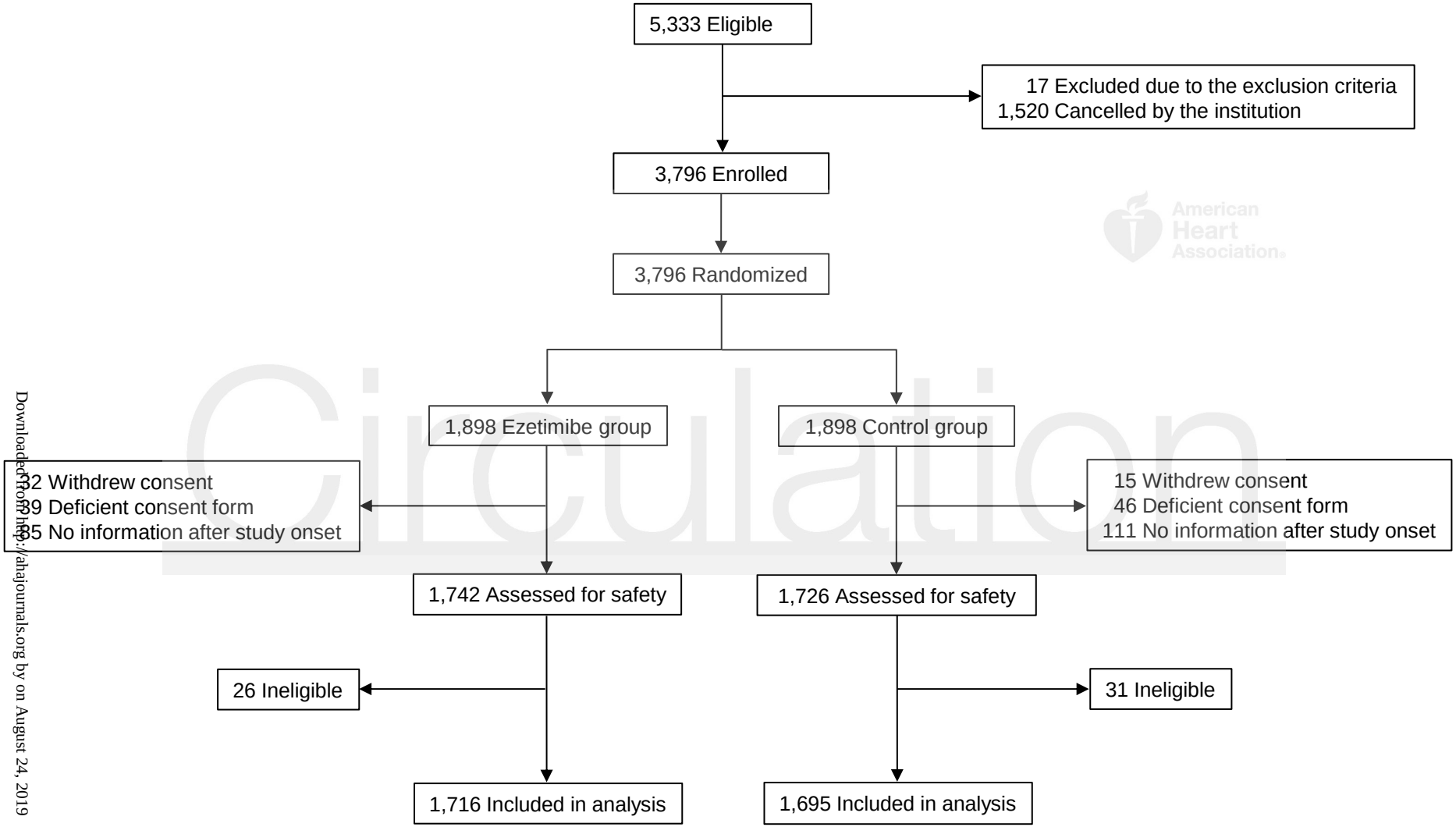
Figure 2. Time-course changes in the serum levels of LDL-C (A), HDL-C (B), non-HDL-C (C), and TG (D) for 5 years after randomization in the ezetimibe group and the control group. LDL-C was calculated according to the Friedewald's formula: LDL-C=TC - (HDL-C + TG/5), and non-HDL-C as "total cholesterol minus HDL-C."

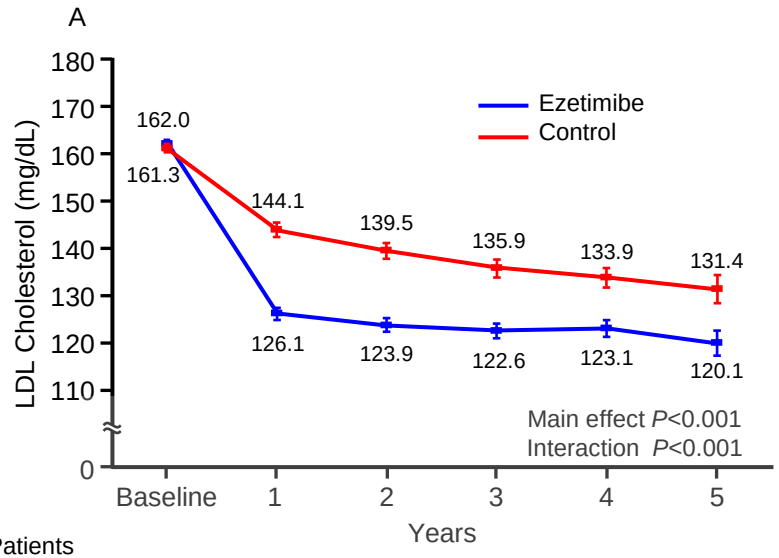
LDL-C; low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglycerides

Figure 3. Kaplan-Meier estimates of the incidences of outcome events in the ezetimibe group and the control group. Primary outcome (**A**). Composed stroke (**B**). Composite cardiac events (**C**). All-cause mortality (**D**).HR, hazard ratio; CI, confidence interval

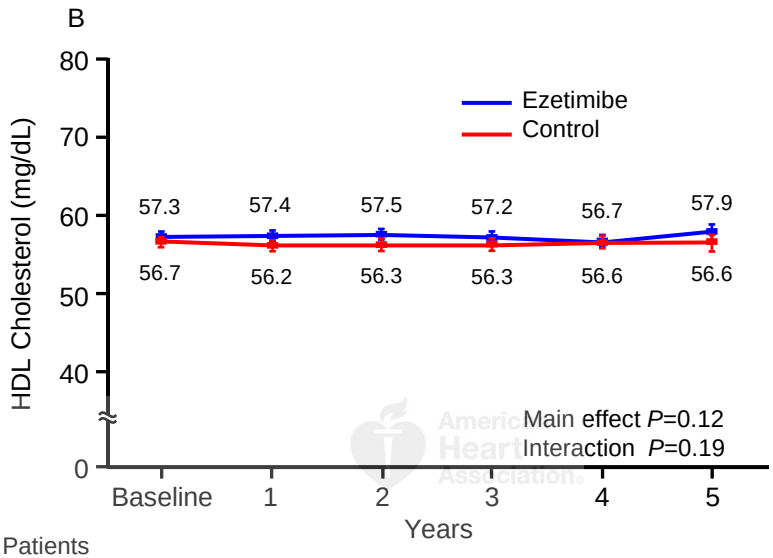
Figure 4. Subgroup analyses of the primary outcome events.

*: Includes diabetes mellitus, hypertension, decreased high-density lipoprotein cholesterol, hypertriglyceridemia, cigarette smoking, history of cerebral infarction, and peripheral artery disease. n, number of patients; CI, confidence interval; LDL-C, low-density cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

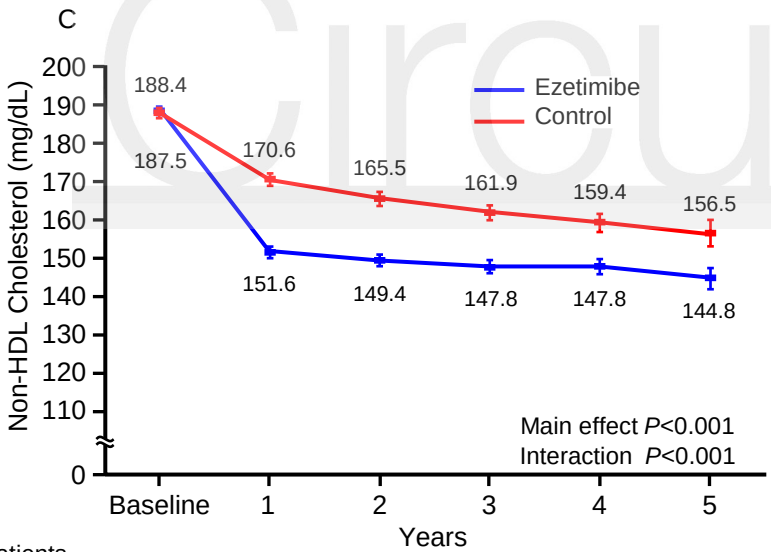




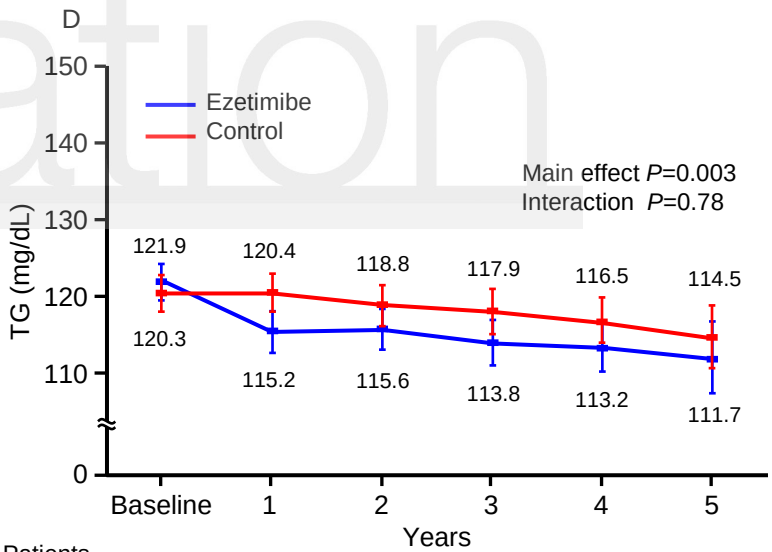
Number of Patients						
Ezetimibe	1700	1489	1245	1009	685	311
Control	1685	1464	1227	1023	706	314



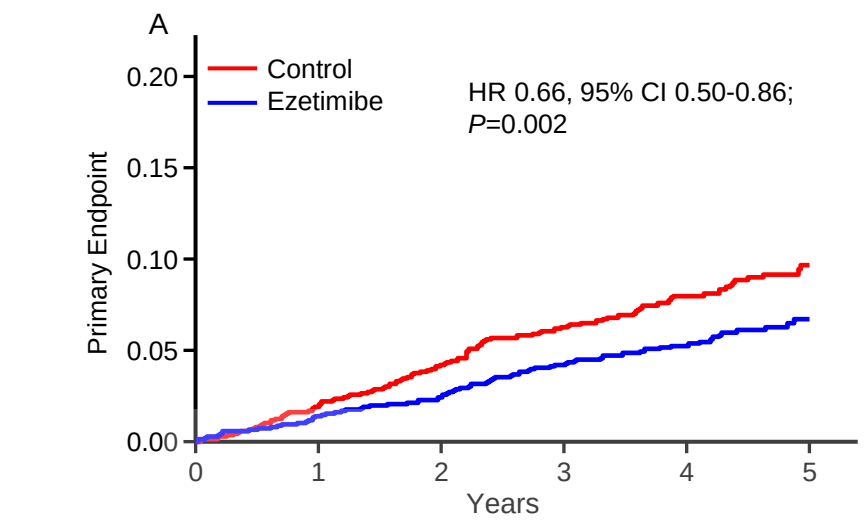
Number of Patients						
Ezetimibe	1700	1508	1259	1018	701	318
Control	1685	1484	1244	1028	718	319



Number of Patients						
Ezetimibe	1700	1490	1247	1009	687	311
Control	1685	1466	1230	1024	707	314

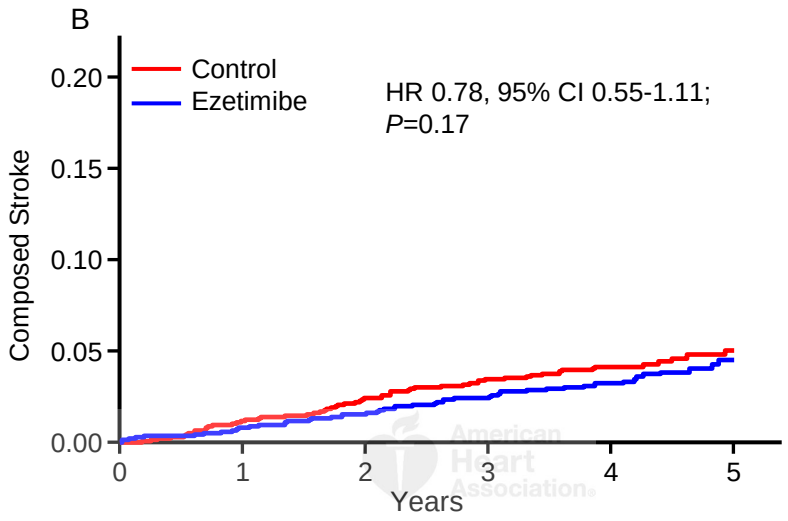


Number of Patients						
Ezetimibe	1700	1507	1258	1019	699	317
Control	1685	1484	1242	1029	717	321



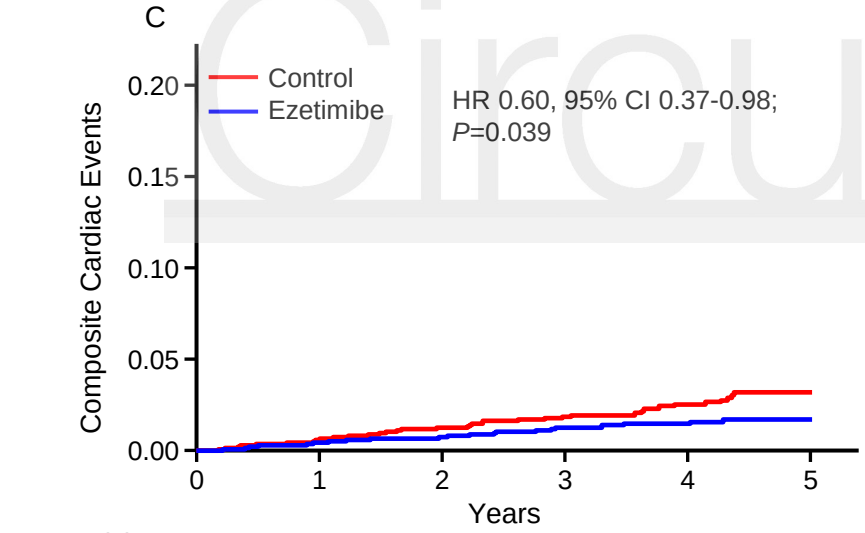
No. at Risk

Control	1695	1582	1418	1217	887	383
Ezetimibe	1716	1617	1445	1219	897	387



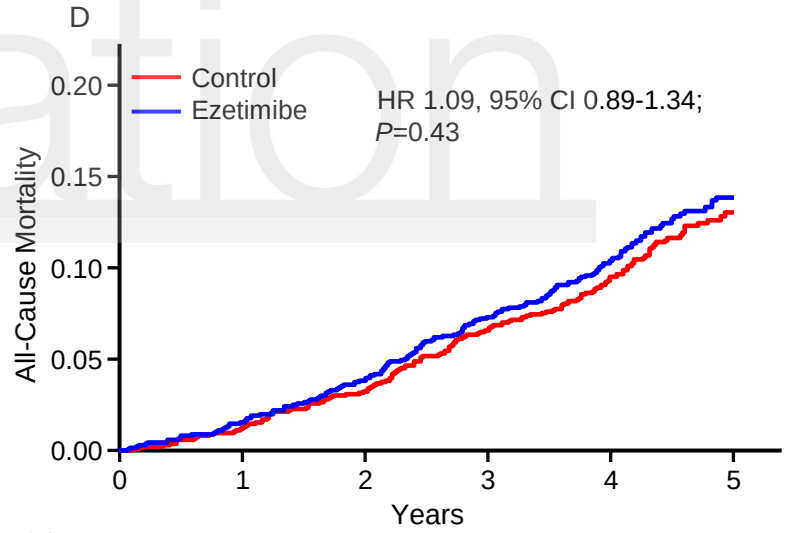
No. at Risk

Control	1695	1590	1435	1238	906	397
Ezetimibe	1716	1619	1447	1226	903	391



No. at Risk

Control	1695	1603	1454	1260	920	405
Ezetimibe	1716	1629	1464	1249	919	402



No. at Risk

Control	1695	1608	1463	1268	926	410
Ezetimibe	1716	1630	1466	1252	922	403

Subgroup	Control (n=1,695)		Ezetimibe (n=1,716)		Hazard Ratio (95% CI)	*P* Value	*P* Value for Inter-Action
	No. of Patients	No. with Events	No. of Patients	No. with Events			
Age							
<85 years	1,370	102	1,393	60	0.58 (0.42–0.80)	0.001	0.17
≥85 years	325	31	323	29	0.93 (0.56–1.54)	0.78	
Sex							
Male	432	43	440	26	0.60 (0.37–0.98)	0.041	0.63
Female	1,263	90	1,276	63	0.69 (0.50–0.95)	0.024	
Diabetes mellitus							
Absent	1,261	96	1,283	64	0.66 (0.48–0.91)	0.010	1.00
Present	434	37	433	25	0.66 (0.40–1.10)	0.11	
Hypertension							
Absent	186	8	196	11	1.08 (0.46–2.54)	0.86	0.24
Present	1,509	125	1,520	78	0.63 (0.47–0.83)	0.001	
Number of risk factors*							
1-2	1,470	109	1,488	73	0.66 (0.49–0.89)	0.006	0.93
≥3	225	24	228	16	0.64 (0.34–1.21)	0.17	
History of cerebral infarction							
Absent	1,577	123	1,599	83	0.67 (0.51–0.89)	0.005	0.53
Present	118	10	117	6	0.49 (0.18–1.35)	0.17	
Peripheral artery disease							
Absent	1,646	130	1,664	87	0.66 (0.51–0.87)	0.003	0.82
Present	49	3	52	2	0.55 (0.09–3.32)	0.52	
LDL-C at baseline							
<160 mg/dL	996	76	993	53	0.71 (0.50–1.01)	0.05	0.49
≥160 mg/dL	689	57	707	35	0.59 (0.38–0.89)	0.013	
Decreased HDL-C							
Absent	1,529	117	1,554	76	0.65 (0.49–0.86)	0.003	0.70
Present	156	16	146	12	0.75 (0.36–1.59)	0.46	
Hypertriglyceridemia							
Absent	1,165	91	1,174	60	0.65 (0.47–0.91)	0.011	0.92
Present	520	42	526	28	0.68 (0.42–1.08)	0.10	
Metabolic syndrome							
Absent	1,419	109	1,426	76	0.72 (0.53–0.97)	0.029	0.35
Present	276	24	290	13	0.50 (0.26–0.99)	0.047	
Chronic kidney disease							
<60 mL/min/1.73 m^2 in eGFR	893	58	900	36	0.61 (0.40–0.92)	0.020	0.61
≥60 mL/min/1.73 m^2 in eGFR	796	74	814	53	0.71 (0.50–1.00)	0.05	
Plasma hemoglobin							
<12 mg/dL	431	49	384	22	0.51 (0.31–0.85)	0.009	0.19
≥12 mg/dL	1,252	83	1,321	67	0.76 (0.55–1.05)	0.10	
Pretrial history of dyslipidemia treatment							
Absent							
Present	1,337	107	1,355	76	0.66 (0.50–0.86)	0.002	0.39
	358	26	361	13	0.50 (0.26–0.98)	0.044