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Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With vs. Without Diabetes: Results from IMPROVE-IT

Running Title: *Giugliano et al.; Ezetimibe Added to Statin in Diabetics with ACS*

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Abstract

Background—Ezetimibe, when added to simvastatin, reduces cardiovascular events following acute coronary syndrome (ACS); we explored outcomes stratified by diabetes mellitus (DM).
Methods—In IMPROVE-IT, 18,144 patients post ACS with LDL-C 50-125 mg/dL were randomized to ezetimibe/simvastatin-40mg (E/S) or placebo/simvastatin-40mg (P/S). The primary composite endpoint was cardiovascular death, major coronary events, and stroke. DM was a prespecified subgroup.
Results—The 4933 (27%) patients with DM were more often older, female, with prior MI and revascularization, and presented more frequently with non-ST segment elevation ACS compared to non-DM (each p<0.001). The median admission LDL-C was lower among patients with DM (89 vs. 97 mg/dL, p<0.001). E/S achieved a significantly lower median time-weighted average LDL-C compared to P/S, irrespective of DM (DM: 49 vs. 67 mg/dL; No DM: 55 vs. 71 mg/dL, both P<0.001). In DM patients, E/S reduced the 7-year Kaplan-Meier primary endpoint event rate by 5.5% absolute (HR 0.85; 95% CI, 0.78-0.94); in non-DM patients the absolute difference was 0.7% (HR 0.98; 95% CI, 0.91-1.04; $P_{interaction}$=0.02). The largest relative reductions in DM patients were in MI (24%) and ischemic stroke (39%). No differences in safety outcomes by treatment were present regardless of DM. When stratified further by age, patients ≥75 years had a 20% relative reduction in the primary endpoint regardless of DM ($P_{interaction}$=0.91), while patients <75 years with DM had greater benefit than those without ($P_{interaction}$=0.011). When stratified by the TIMI risk score for Secondary Prevention, all patients with DM demonstrated benefit with E/S regardless of risk. In contrast, among non-diabetics, patients with a high risk score experienced a significant 18% relative reduction in the composite of cardiovascular death, MI, and ischemic stroke with E/S compared to P/S, whereas non-diabetics at low or moderate risk demonstrated no benefit with the addition of ezetimibe to simvastatin ($P_{interaction}$ 0.034).
Conclusions—In IMPROVE-IT the benefit of adding ezetimibe to statin was enhanced in patients with DM and in high-risk non-diabetics.
Clinical Trial Registration—URL: https://clinicaltrials.gov Unique Identifier: NCT00202878

Key Words: diabetes, ezetimibe, lipids, acute coronary syndromes

Clinical Perspective

What is new?

- In IMPROVE-IT, patients with recent acute coronary syndrome randomized to ezetimibe vs. placebo on top of background simvastatin, we found that patients with diabetes derived significantly greater relative and absolute benefit with the addition of ezetimibe relative to patients without diabetes.
- This enhanced benefit was driven by reductions of acute ischemic events, including myocardial infarction and ischemic stroke in diabetics, while non-diabetic patients who were >75 years of age or have a high risk score also significantly benefited from the addition of ezetimibe to simvastatin.
- The benefits of ezetimibe were achieved without an increase in safety events compared to placebo.

What is the clinical implication?

- In patients admitted with an acute coronary syndrome and LDL-C $\geq$50 mg/dL, health-care providers should consider adding ezetimibe to statin to reduce the risk of cardiovascular events.
- Two patient subgroups likely to achieve greater benefits with the addition of ezetimibe include patients with diabetes and patients without diabetes who have a high risk score.
- These findings support the 2017 American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease treatment goal of an LDL-C <55 mg/dL in patients with extreme risk, including diabetics with established clinical cardiovascular disease.

Introduction

The number of individuals with diabetes mellitus (DM) has more than doubled in the last 3 decades,[1] affecting 9% of all adults worldwide in 2014.[2] Since patients with DM are both at increased risk of developing coronary artery disease[3] (CAD) and have poorer outcomes following acute coronary syndromes[4] (ACS), more effective treatments to prevent ischemic cardiovascular events in patients with DM are highly desirable. Statins, lifestyle modifications, and other interventions to reduce CAD risk factors, such as antihypertensive medications, are recommended for all patients with DM[5]. However, despite the recognition of this multifaceted approach, patients with DM who have experienced an acute coronary event remain at increased risk for subsequent coronary events, stroke, and vascular death.[6]

Ezetimibe is a non-statin that inhibits absorption of cholesterol from the small intestine, reducing low-density lipoprotein cholesterol (LDL-C) by 23-24% when added to a statin[7]. In patients with DM, ezetimibe not only lowers LDL-C, but also reduces levels of other atherogenic particles such as remnant-like particle cholesterol, small dense-LDL-C, malondialdehyde modified-LDL, apoliprotein B-48, and ratios of total cholesterol/HDL-C and ApoB/ApoA-I[8, 9]. While statins have been shown to improve cardiovascular outcomes in patients with DM in both patients with[6, 10, 11] and without prior clinically recognized CAD,[6, 12] guidelines for the management of patients with DM published in 2015[5] note that there has been insufficient evidence to support the addition of non-statin therapies (i.e., ezetimibe, niacin, fenofibrate, bile acid sequestrants) to further reduce cardiovascular risk in patients with DM.

As previously reported[13], the combination of ezetimibe and simvastatin (E/S) reduced the median time-weighted average LDL-C by 16 mg/dL compared to placebo and simvastatin (P/S), with a significant 2.0% absolute reduction (6.4% relative reduction, p=0.016) in the primary

composite endpoint (cardiovascular death, major coronary event, or stroke) after a median of 6 years in patients admitted with ACS. Of 19 subgroup analyses prespecified in the statistical analysis plan, two treatment-subgroup interactions (baseline diabetes status and age dichotomized at 75 years) had a nominally significant $P_{interaction}$ <0.05 for the primary endpoint. Here, we present an analysis of the efficacy and safety of E/S vs. P/S in patients enrolled in IMPROVE-IT stratified by the presence of DM at randomization is presented.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The IMPROVE-IT protocol has been described previously[14] and the main results published[13]. The ethics committee at each participating center approved the protocol and amendments, and all subjects provided informed consent. DM at hospital admission for the qualifying ACS event was determined by the investigators based on a history of DM (regardless of duration), treatment with an antidiabetic agent, or a fasting blood sugar >126 mg/dL. A sensitivity analysis was performed to also include patients identified from review of the trial database who had a fasting glucose >126 mg/dL, a non-fasting glucose >200 mg/dL, or a hemoglobin A1c $\geq$ 6.5% on the first sample obtained after randomization.

Baseline characteristics, medications, and laboratory test results were compared in patients with and without DM. Lipid levels (total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides) were measured locally upon admission with the qualifying ACS event (defined as within 24 hours after presentation, or if unavailable, a value from the prior 6 months was used provided the patient had been clinically stable with no changes in lipid-

lowering therapy). Lipid levels and high-sensitivity C-reactive protein (hsCRP) were measured at a core laboratory at randomization, post-randomization at 1, 4, and 8 months, and annually thereafter. A combined analysis of LDL-C and hsCRP at 30 days was conducted with the prespecified dual target achievement defined as <70 mg/dL for LDL-C and <2.0 mg/dL for hsCRP.[15]

The primary efficacy endpoint was a composite of cardiovascular death, major coronary event (which included myocardial infarction (MI), unstable angina requiring hospital admission, coronary revascularization occurring ≥30 days after randomization) or stroke, and was reported as a Kaplan Meier event rate at 7 years. Other efficacy endpoints and safety outcomes of special interest were as described in the main trial.[13] Efficacy endpoints and muscle-related adverse events were adjudicated by an independent clinical endpoint committee who were unaware of treatment assignment. Because patients ≥ 75 years of age derived particular benefit with E/S as compare to P/S[13], an analysis stratified by age and diabetes status was also performed. In addition, analyses were conducted in patients stratified by the TIMI Risk Score for Secondary Prevention, a simple 9-point risk stratification tool previously developed in a large population with atherothrombosis[16] to predict cardiovascular events that was subsequently validated in the IMPROVE-IT population.[17] Since patients treated with insulin represent an especially high-risk subgroup with more advanced DM, outcomes by treatment group, among patients with DM stratified by use of insulin, were also conducted.

Statistical Analysis

The primary analyses were performed using the intention-to-treat principle, including all patients randomized, and counting first events between randomization and the final visit or last patient contact. A sensitivity analysis was conducted in the on-treatment population (including all

patients who took at least one dose of study drug), censoring events that occurred >30 days after the last dose of study drug. Continuous variables were reported as mean values ± standard deviation or median values with 25th and 75th percentiles depending upon their distribution, and compared using Wilcoxon rank sum test statistics. Categorical variables were compared using the chi square test. A *P*-value <0.05 was considered to represent nominal statistical significance. Adjustments for multiple testing were not performed for the analyses since all comparisons, other than the prespecified analysis of the primary endpoint stratified by the presence of diabetes at baseline, were considered exploratory. Cox proportional hazard models were developed to assess the time to the first clinical endpoint. Models were stratified by protocol specified stratification factors, to evaluate the presence of an interaction between diabetic status and randomized treatment. P-values for subgroup x treatment interactions were calculated using Cox Proportional Hazard or logistic regression models as appropriate, with a $P_{interaction}$ <0.05 indicative a significant interaction. P-values for comparisons of two groups on dichotomous/categorical responses controlled by a covariate were calculated using the Cochran-Mantel-Haenszel test or logistic regression (for binary outcomes). All analyses were performed using SAS (version 9.3, Cary, NC).

Results

Baseline characteristics

The investigators identified DM in 4933 (27%) of patients randomized (Table 1). On average, patients with DM were 2 years older; more likely to be female, have had a prior MI or CABG; but less likely to present with a ST-elevation MI, P <0.001 for each compared to patients without DM. Patients with DM were more likely to have been treated with guideline-supported therapies

(aspirin, beta-blocker, statins, angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers [ACE-I/ARB]) prior to the qualifying event. Prior to admission, statins were prescribed more frequently in patients with DM than those without. Three-quarters of patients with DM were being treated with an antidiabetic medication prior to admission, mostly commonly metformin (46%), sulfonylureas (25%), or insulin (21%), and 27% were treated with more than one antidiabetic agent. There were no differences in baseline characteristics, treatments, or laboratory values at admission between randomized treatment groups among patients with or without DM (Supplemental Table 1). Patient adherence to study drug was 2-3% higher among patients without DM (Supplemental Table 2).

Laboratory data at admission

The median LDL-C at admission was lower in patients with DM (89 mg/dL) as compared to those without DM (97 mg/dL, P <0.001, Table 1, Figures S1-S2). Patients with DM had lower median HDL-C and higher median triglycerides compared to patients without DM (both P<0.001).

Changes in lipids

In patients with DM, the median decline in LDL-C from admission to 1 year was 40 mg/dL (to a median achieved level of 46 mg/dL) with E/S, compared to a median decrease of 22 mg/dL (to a median achieved level of 65 mg/dL) with P/S, resulting in a median difference in LDL-C reduction between treatments in the first year of 18 mg/dL (P<0.001, Figure S2). In patients without DM, the median LDL-C values at 1 year decreased by 44 and 27 mg/dL and achieved median LDL-C values at 1 year were 51 and 68 mg/dL, with E/S and P/S, respectively (P<0.001 for both comparisons by treatment). The resultant median difference in LDL-C reduction from admission to year 1 in patients without DM between treatments of 17 mg/dL was similar to that

observed in patients with DM (18 mg/dL, $P_{interaction}$ =0.58). The reduction in LDL-C with E/S as compared to P/S persisted throughout follow-up (Figure S1), although the difference between treatment groups in the time-weighted reduction in LDL-C after admission was 3 mg/dL greater in patients with DM (17 mg/dL) compared to patients without DM (14 mg/dL, $P_{interaction}$=0.03) Patients treated with E/S as compared to P/S, also achieved greater reductions in total cholesterol, triglycerides, and non-HDL-C during the trial both among patients with and without DM. The median time-weighted average reduction in total cholesterol with E/S vs. P/S was greater in patients with DM (19 mg/dL) than in patients without DM (16 mg/dL; $P_{interaction}$ 0.022), while reductions with the addition of ezetimibe in triglycerides (DM: 11 mg/dL, no DM: 8 mg/dL; $P_{interaction}$ 0.58), and non-HDL-C (DM: 19 mg/dL, no DM: 17 mg/dL; $P_{interaction}$ 0.10) were similar regardless of diabetic status.

Reduction hsCRP at 1 month

The median hsCRP levels at randomization were 9.7 and 9.5 mg/L among patients with vs. without DM, respectively (P=0.74). E/S as compared to P/S, reduced hsCRP to a similar degree in patients with DM (-0.3 mg/dL) as compared to non-DM (-0.2 mg/dL, $P_{interaction}$ 0.93).

Achievement of prespecified dual targets of LDL-C and hsCRP

The pre-specified dual targets of LDL-C <70 mg/dL and hsCRP <2.0 mg/L were achieved more frequently with E/S than with P/S, both among patients with DM (46 vs. 30%, P<0.001) and in those without DM (52 vs. 31%, P<0.001). There was evidence of statistical heterogeneity indicating an even greater likelihood of achieving the dual targets with E/S in patients without DM (Cochran-Mantel-Haenszel P <0.001 with P 0.02 for treatment arm difference in odds ratios).

Clinical Efficacy

Efficacy outcomes occurred more frequently in patients with DM as compared to those without DM. For the primary composite endpoint, the Kaplan-Meier event rates at 7 years in patients with DM were 40.0 vs. 45.5% in patients treated with E/S vs. P/S (HR 0.85, 95% CI 0.78 to 0.94), and the corresponding rates in patients without DM were 30.2 vs. 30.8% (HR 0.98 [0.91, 1.04], Figures 1-2, Table S3). This difference in treatment benefit with the addition of ezetimibe in patients with DM vs. no DM was significant (P-value of 0.023 for interaction). Among patients with DM, combination E/S prevented 1 event for every 18 (95% CI 12-42) patients treated on average for 6 years compared with P/S.

The HRs comparing E/S with P/S for the 3 secondary efficacy composite endpoints and the tertiary composite endpoint are shown in Figure 2 and Table S3. For two of these composite endpoints (secondary composite III: cardiovascular death, MI, unstable angina, all revascularization on/after 30 days, stroke; tertiary composite of CHD death, unstable angina, MI, and ischemic stroke) the $P_{interaction}$ values were significant (0.021 and 0.006, respectively). For the two other secondary composite endpoints the HRs comparing E/S with P/S were numerically lower in patients with DM, although the $P_{interaction}$ values were not significant (0.11 and 0.074, respectively).

The results for other endpoints are shown in Table S4. Patients with DM exhibited significantly lower HRs with E/S vs. P/S for the endpoints of MI (HR 0.76 [0.66, 0.88]), ischemic stroke (HR 0.61 [0.46, 0.82]), and the composite of cardiovascular death, MI, or stroke (HR 0.80 [0.71, 0.90]) as compared to patients without DM (interaction P-values of 0.028, 0.031, and 0.016, respectively). Urgent revascularization was significantly and similarly reduced in patients with DM (HR 0.76 [0.62, 0.93]) and without DM (HR 0.84 [0.73, 0.97], $P_{interaction}$ 0.40).

Mortality endpoints and hospitalization for unstable angina were not reduced with E/S vs. P/S either in patients with or without DM.

Efficacy Outcomes Stratified by Age and Diabetes Status

Among patients ≥75 years E/S when compared to P/S significantly reduced the primary endpoint to a similar degree in patients with DM (HR 0.80) and without DM (HR 0.79, $P_{interaction}$ 0.91, Table 2, Figure S3). The high event rates in elderly patients at 7 years (Figure 3) resulted in numbers needed to treat (NNT) of 10 [95% CI 5 to 73]) in patients with DM and 12 [95% CI 7 to 28] in patients without DM.

In contrast, among patients <75 years, there was evidence of a significant treatment-DM subgroup interaction. In these patients with DM, E/S significantly reduced the primary endpoint compared to P/S (HR 0.87 [0.78, 0.96], P=0.008, NNT = 21 [95% CI 12 to 73]), while in patients <75 years without DM there was no difference between treatments (HR 1.02 [0.95, 1.10], $P_{interaction}$= 0.01). Likewise, there was evidence of similar interactions in patients <75 years for several secondary endpoints (Table 2, Figure S3), whereby the treatment benefit with E/S was greater among such patients with DM than in such patients without DM.

Risk stratification and outcomes in patients with and without DM

When patients were stratified by the TIMI Risk Score for Secondary Prevention[16], more patients with DM vs. no DM were classified as high risk (3 or more risk indicators: 55% vs. 13%), while far fewer patients with DM were classified as low risk (0-1 risk indicators: 9% vs. 59%, P<0.001 for both, Figure S4). In patients with DM, the benefit of E/S over P/S in reducing the composite of cardiovascular death, MI, and ischemic stroke was consistent across the risk strata ($P_{interaction}$ 0.59, Figure 4A). In contrast, in patients without DM, there was significant effect modification by the risk score ($P_{interaction}$ 0.034), with non-diabetics at high risk experiencing a significant 18%

reduction with E/S compared to P/S whereas non-diabetics with moderate and low risk did not demonstrate a significant difference between treatments (Figure 4B).

Safety Outcomes

Overall, patients with and without DM had similar rates of transaminase elevation and cancer, however patients with DM were more likely to experience gall-bladder and muscle-related adverse events than those without DM (Table 3). Rates of prespecified safety events of special interest were similar between E/S and P/S, irrespective of diabetes status, with the possible exception of hemorrhagic stroke. In patients with DM the rates of hemorrhagic stroke were 0.9% with E/S vs. 0.4% with P/S (P=0.023), however the treatment-subgroup interaction P-value was not statistically significant (P=0.092).

Sensitivity Analyses

In the first sensitivity analysis using a definition of existing DM that incorporated glucose values at randomization, the 5284 patients who met this broader definition of DM who were randomized to E/S vs. P/S had a greater reduction the primary composite (HR 0.84) as compared to those without DM (HR 0.99, $P_{interaction}$ 0.006). There were similar significant interactions for the 3 secondary and 1 tertiary composite endpoint demonstrating consistently greater benefit of E/S among patients with this alternative definition of existing DM (Table S5). There were no differences in the safety outcomes of special interest when patients were stratified by this definition of DM.

In the second sensitivity analysis of primary composite endpoints conducted in 17.706 patients while on-treatment (Table S6), a qualitatively similar pattern of greater relative benefit was seen with E/S vs. P/S among patients with DM (HR 0.85) as compared to those without DM (HR 0.96), although the p-interaction was of borderline significance (0.067). The pattern of

greater relative efficacy with E/S in patients with DM was directionally consistent in other prespecified composite efficacy endpoints in the on-treatment analysis (HRs ranging from 0.76-0.86 in patients with DM vs. HRs 0.94-0.96 in patients without DM, Table S6), with statistically significant subgroup-treatment interactions observed for 2 of these 4 additional composite efficacy endpoints.

Discussion

In this prespecified subgroup analysis of IMPROVE-IT, patients with DM derived significantly greater relative and absolute benefit from E/S as compared to P/S in patients post ACS with LDL-C 50-125 mg/dL relative to patients without DM. This enhanced benefit was driven by reductions of acute ischemic events, including myocardial infarction and ischemic stroke.

It would be incorrect to conclude that patients without diabetes experienced no benefit with the addition of ezetimibe. Although the benefit of adding ezetimibe to simvastatin in patients without DM was modest overall, among non-diabetic patients who were at high risk for cardiovascular events, either on the basis of advanced age or an elevated risk score, significant reductions in cardiovascular events were observed with E/S compared to P/S. Patients without DM who were <75 years or with a low risk score did not exhibit any added benefit with ezetimibe. Lastly, the safety profile of E/S was similar to that of P/S in both patients with and without DM.

As this is the only large cardiovascular outcomes study comparing ezetimibe with placebo on the background of a statin, a comparison of the current results to other similarly designed outcomes studies is not possible. It is notable that the only large placebo-controlled trial of a statin conducted solely in patients with DM[12] was stopped early due to overwhelming

efficacy, with a 37% [17-52%] reduction in major cardiovascular events, was conducted in a primary prevention population, whereas IMPROVE-IT enrolled patients within 10 days of ACS. Moreover, two metanalyses of cholesterol lowering therapy (predominantly statins) did not show a differential benefit of lipid lowering therapy between patients with no DM, type I DM, or type II DM.[6, 18]

The explanation(s) for the findings that patients with DM benefited more than patients without DM is not clear. It is notable that there was a greater incremental reduction in the median time-averaged LDL-C (by 3 mg/dL) in patients with DM with E/S vs. P/S, but there were no similar incremental benefits in triglycerides, HDL-C, or hsCRP, and this difference in LDL-C reduction appears to be too modest to be the sole reason. Furthermore, the odds of achieving the dual targets of LDL-C <70 mg/dL and hsCRP < 2 mg/dL were greater with E/S as compared to P/S among patients *without* DM than in patients with DM. The effect of ezetimibe on other atherogenic lipid particles in patients with DM[8, 9], or the favorable effects of ezetimibe on glucose metabolism, including reductions in fasting plasma glucose, insulin levels, and insulin resistance[8], may also have contributed to the enhanced benefit of E/S in patients with DM in IMPROVE-IT.

Additional possible explanations for the enhanced benefit in patients with DM include inhibition of the heighted levels of platelet aggregation and activation due to ezetimibe[19], a reduction in campesterol cholesterol ratio, which has been linked to regression of atherosclerotic plaques[20], or other pleiotropic effects of ezetimibe to reduce oxidative stress/inflammation[21, 22], smooth muscle proliferation[23] and plaque instability.[24, 25] Greater platelet inhibition has been associated with additional incremental treatment benefit in patients with DM with several[26-28],

but not all[29] potent platelet inhibitors, whereas it is less clear whether the other non-lipid effects of ezetimibe would be particularly of greater benefit in patients with DM.

The enhanced benefit of E/S in patients with DM is consistent with the findings reported present in other high-risk subgroups in IMPROVE-IT, including patients >75 years[30], with prior CABG[31], and with prior stroke[32]. Indeed, each of these high risk features contribute to the TIMI Risk Score for Secondary Prevention and were associated with increased benefit of E/S in IMPROVE-IT[17]; thus these observations in patients with DM are consistent with the hypothesis that patients at highest risk for cardiovascular events have the most to benefit from ezetimibe. This may reflect a greater proportion of "modifiable" events with aggressive lipid-lowering in higher risk patients as compared to low-risk patients.

Several limitations of this analysis deserve consideration. Although this was an analysis of a prespecified subgroup involving 4933 patients from a large clinical trial, it has limited statistical power and was not adjusted for multiple comparisons; hence we cannot exclude a chance finding. Patients enrolled in clinical trials often differ in baseline characteristics and have fewer comorbidities than patients treated in clinical practice, thus limiting the generalizability of the findings. Investigator determined assessment of the presence or absence of DM at randomization was used without a systematic collection of hemoglobin A1c levels, which may have resulted in some misclassification; however, this would be expected to bias toward a null finding. In addition, two sensitivity analyses were performed and were consistent with the main analysis.

Conclusions

In the IMPROVE-IT of 18,144 patients with ACS and LDL-C 50-125 mg/dL, the benefit of adding ezetimibe to statin appeared to be enhanced among patients with DM, with no adverse

effect in safety. These findings support the use of intensive, combination lipid lowering therapy in patients with DM to optimize cardiovascular outcomes, as recommended by the American Association of Clinical Endocrinologists and American College of Endocrinology.[33]

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Table 1. Baseline Characteristics

	Diabetes Absent 13,202 (72.6)	Diabetes Present 4933 (27.4)	P-value
Demographics			
Mean Age (SD), years	63.7 (9.9)	65.3 (9.2)	<0.001
Female	2905 (22.8)	1407 (28.5)	<0.001
White	11359 (86.0)	3837 (77.8)	<0.001
Median Weight, Kg [IQR]	80.0 [70.0, 90.7]	84.8 [74.0, 98.0]	<0.001
Median BMI, Kg/M^2 [IQR]	27.0 [24.5, 30.1]	29.2 [26.1, 33.0]	<0.001
Medical history			
Hyperlipidemia	9504 (72.0)	3647 (73.9)	<0.001
Hypertension	7266 (55.0)	3871 (78.5)	<0.001
Current smoking	4784 (36.2)	1194 (24.2)	<0.001
Myocardial infarction	2541 (19.3)	1265 (25.7)	<0.001
Percutaneous coronary intervention	2360 (17.9)	1202 (24.4)	<0.001
Coronary artery bypass grafting	998 (7.6)	686 (13.9)	<0.001
Congestive heart failure	410 (3.1)	380 (7.7)	<0.001
Peripheral arterial disease	617 (4.7)	388 (7.9)	<0.001
Medications prior to admission			
Aspirin	5011 (38.0)	2643 (53.6)	<0.001
Beta-blocker	4115 (31.2)	2181 (44.2)	<0.001
Statin	3934 (29.8)	2313 (46.9)	<0.001
ACE-I or ARB	4470 (33.9)	2946 (59.8)	<0.001
Medications at randomization			
Aspirin	12827 (97.2)	4765 (96.6)	0.003
Beta-blocker	11517 (87.3)	4274 (86.6)	0.034
ACE-I or ARB	9589 (72.6)	4111 (83.3)	<0.001
At index event			
ST-segment elevation MI	4177 (31.6)	1013 (20.5)	<0.001
Diagnostic angiography	11788 (89.3)	4136 (83.9)	<0.001
Percutaneous coronary intervention	9499 (72.0)	3207 (65.0)	<0.001
Laboratory Values at Admission (Median)			
LDL-C (mg/dL)	97 [81, 112]	89 [74, 103]	<0.001
Prior statin use	81 [70, 93]	78 [66, 89]	<0.001
No prior statin use	105 [91, 116]	100 [84, 113]	<0.001
HDL-C (mg/L)	41 [34, 50]	38 [31, 46]	<0.001
Triglycerides (mg/L)	115 [81, 164]	137 [96, 193]	<0.001
Creatine clearance (ml/min)	84 [66, 106]	86 [64, 111]	0.027
Laboratory Values at Randomization (Median)			
LDL-C (mg/dL)	81 [67, 97]	75 [61, 91]	<0.001
Statin during admission	78 [65, 93]	73 [59, 87]	<0.001
No statin during admission	93 [76, 110]	89 [71, 106]	<0.001
C-reactive protein* (mg/L)	9.5 [3.9, 26.5]	9.7 [4.0, 26.6]	0.740

*C-reactive protein was not routinely collected at admission; values closest to randomization are shown.
ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, IQR = interquartile range, Kg = kilograms, LDL-C = low-density lipoprotein cholesterol, M = meter, MI = myocardial infarction, SD = standard deviation

Table 2. Outcomes Stratified by Age and Diabetes Status

			SIMVA/alone			SIMVA/EZE						
Endpoints	**Age**	**History of diabetes**	**n (%)**		**KM event(%) at 7 yrs**	**n (%)**		**KM event(%) at 7 yrs**	**Hazard Ratio (95%CI)**		**p-value**	**Interaction p-value***
Primary Endpoints	**<75**	**Non-diabetics**	1429	(25.6)	28.82	1460	(25.9)	29.44	1.02	(0.95, 1.10)	0.522	0.011
		Diabetics	749	(36.4)	42.90	658	(32.0)	38.17	0.87	(0.78, 0.96)	0.008	
	>=75	**Non-diabetics**	363	(36.0)	42.94	288	(29.8)	34.46	0.79	(0.68, 0.92)	0.003	0.913
		Diabetics	200	(47.8)	59.94	166	(41.3)	49.86	0.80	(0.65, 0.99)	0.039	
Secondary Endpoints I	**<75**	**Non-diabetics**	1666	(29.8)	33.27	1664	(29.5)	33.12	1.00	(0.94, 1.07)	0.963	0.069
		Diabetics	852	(41.4)	47.81	777	(37.8)	44.53	0.90	(0.81, 0.99)	0.026	
	>=75	**Non-diabetics**	478	(47.4)	53.02	420	(43.4)	48.75	0.88	(0.77, 1.00)	0.049	0.900
		Diabetics	249	(59.6)	69.96	228	(56.7)	63.96	0.86	(0.72, 1.03)	0.105	
Secondary Endpoints II	**<75**	**Non-diabetics**	672	(12.0)	14.09	684	(12.1)	14.26	1.02	(0.92, 1.14)	0.707	0.042
		Diabetics	414	(20.1)	24.17	355	(17.3)	21.95	0.85	(0.74, 0.98)	0.023	
	>=75	**Non-diabetics**	223	(22.1)	27.45	174	(18.0)	21.82	0.79	(0.65, 0.96)	0.019	0.967
		Diabetics	138	(33.0)	42.39	109	(27.1)	34.36	0.78	(0.61, 1.01)	0.059	
Secondary Endpoints III	**<75**	**Non-diabetics**	1513	(27.1)	30.51	1546	(27.4)	31.13	1.03	(0.96, 1.10)	0.489	0.012
		Diabetics	778	(37.8)	44.16	688	(33.4)	39.88	0.87	(0.79, 0.97)	0.009	
	>=75	**Non-diabetics**	371	(36.8)	44.08	306	(31.6)	36.18	0.82	(0.71, 0.96)	0.012	0.993
		Diabetics	206	(49.3)	61.02	176	(43.8)	53.52	0.83	(0.68, 1.02)	0.070	

			SIMVA/alone			SIMVA/EZE							
Endpoints	**Age**	**History of diabetes**	**n (%)**		**KM event(%) at 7 yrs**	**n (%)**		**KM event(%) at 7 yrs**	**Hazard Ratio (95%CI)**		**p-value**	**Interaction p-value***
Tertiary Endpoints	**<75**	**Non-diabetics**	802	(14.3)	16.83	820	(14.5)	17.18	1.02	(0.93, 1.13)	0.639	0.003
		Diabetics	492	(23.9)	28.98	397	(19.3)	24.15	0.79	(0.69, 0.90)	0.001	
	>=75	**Non-diabetics**	268	(26.6)	31.63	205	(21.2)	25.39	0.77	(0.64, 0.92)	0.004	0.856
		Diabetics	168	(40.2)	50.97	129	(32.1)	39.93	0.75	(0.60, 0.95)	0.016	

Primary endpoints: Cardiovascular death, non-fatal myocardial infarction, unstable angina, coronary revascularization at least 30 days post –randomization, or non-fatal stroke.
Secondary endpoints I: All death, non-fatal myocardial infarction, unstable angina, coronary revascularization at least 30 days post –randomization, or non-fatal stroke.
Secondary endpoints II: Coronary heart disease death, non-fatal myocardial infarction, urgent coronary revascularization at least 30 days post-randomization
Secondary endpoints III: Cardiovascular death, non-fatal myocardial infarction, unstable angina, all arterial revascularization (coronary and non-coronary) at least 30 days post –randomization, or non-fatal stroke.
Tertiary endpoints: Coronary heart disease death, unstable angina requiring hospitalization, non-fatal myocardial infarction, and non-fatal ischemic stroke.
*Interaction effect of treatment arm and history of diabetes using Cox proportional hazards regression modeling

Table 3. Safety Outcomes

	Simvastatin	Ezetimibe/Simvastatin	P-value	P-Interaction
ALT and/or AST > 3x ULN				0.36
(N=432)	150 (2.3)	153 (2.3)	0.91	
Diabetes absent	58 (2.3)	71 (2.9)	0.25	
Diabetes present				
Cholecystectomy				0.94
(N=267)	90 (1.4)	89 (1.3)	0.94	
Diabetes absent	44 (1.8)	44 (1.8)	>0.99	
Diabetes present				
Gall-bladder adverse event				0.76
(N=603)	215 (3.3)	186 (2.8)	0.14	
Diabetes absent	106 (4.3)	96 (3.9)	0.52	
Diabetes present				
Rhabdomyolysis				0.69
(N=31)	7 (0.1)	6 (0.1)	0.79	
Diabetes absent	11 (0.4)	7 (0.3)	0.48	
Diabetes present				
Rhabdomyolysis, myopathy, or elevated creatine				0.64
phosphokinase >5x ULN	38 (0.6)	37 (0.6)	0.91	
(N=111)	20 (0.8)	16 (0.7)	0.62	
Diabetes absent				
Diabetes present				
Hemorrhagic stroke				0.092
(N=102)	33 (0.5)	36 (0.5)	0.81	
Diabetes absent	10 (0.4)	23 (0.9)	0.023	
Diabetes present				
Cancer				0.96
(N=1480)	543 (8.2)	551 (8.3)	0.83	
Diabetes absent	189 (7.6)	197 (8.0)	0.63	
Diabetes present				

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal

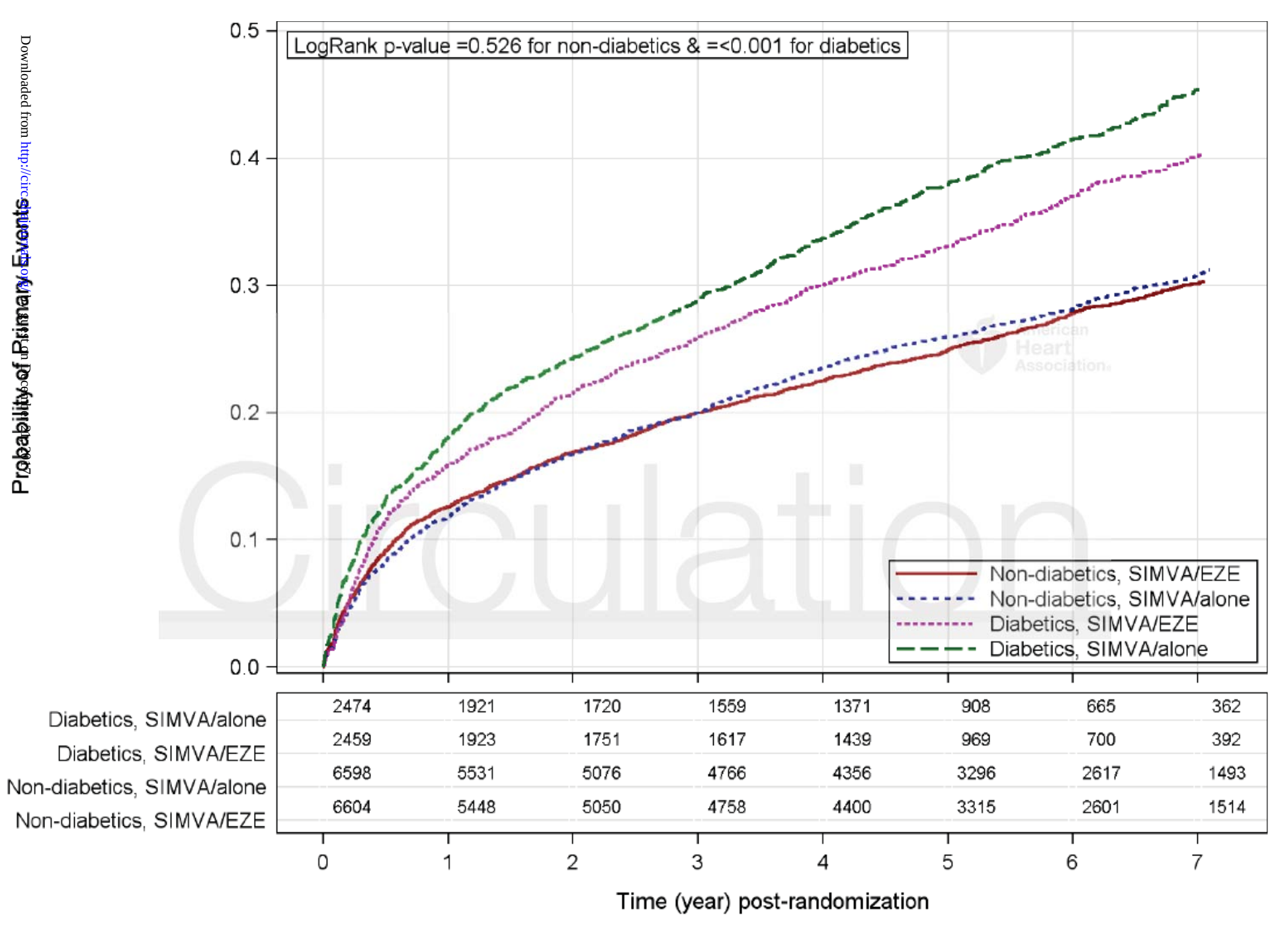
Figure Legends

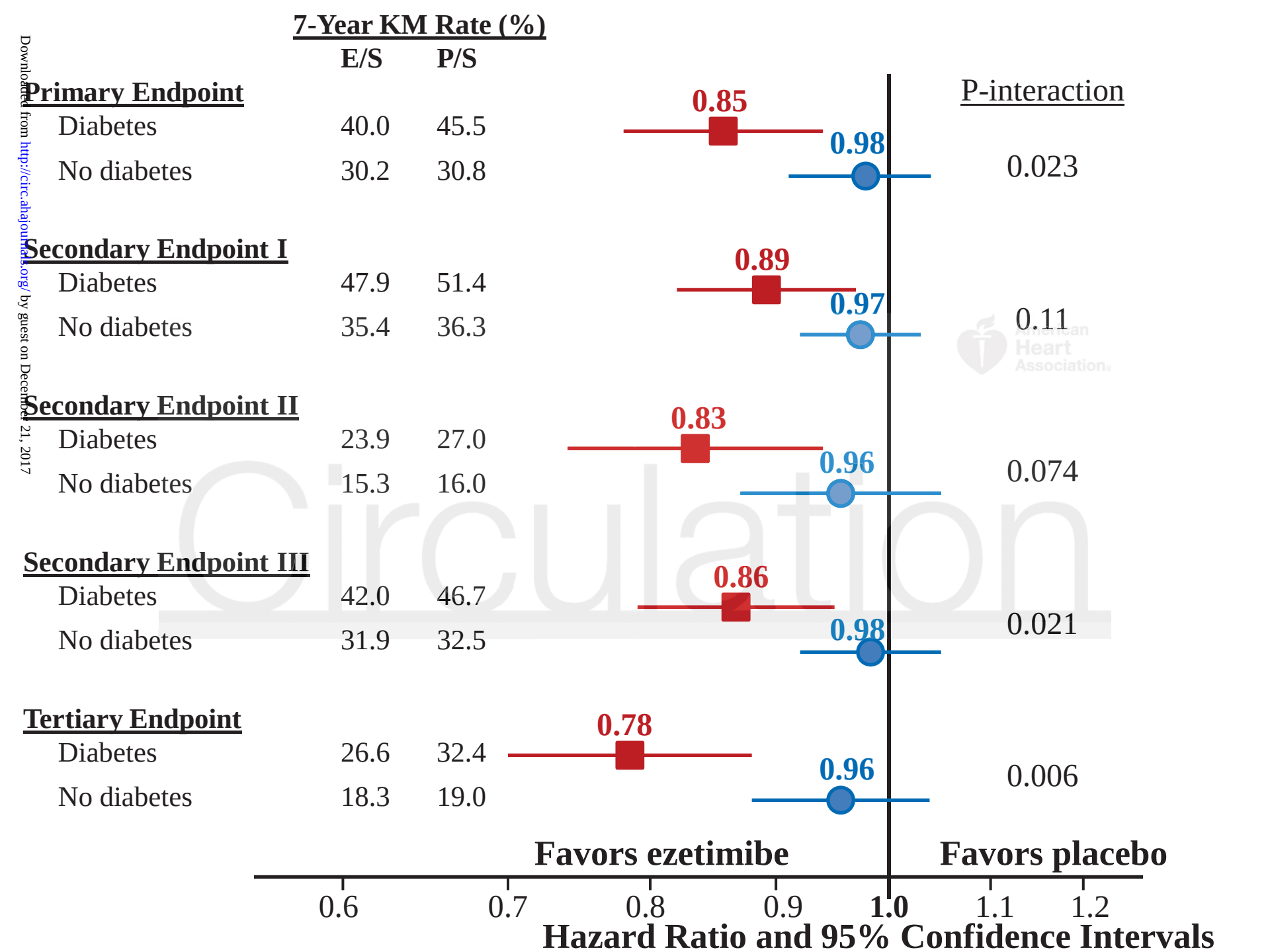
Figure 1. Kaplan-Meier curves for the primary efficacy endpoint. Shown are the cumulative event rates for the primary composite endpoint of cardiovascular death, major coronary event (nonfatal myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization occurring ≥ 30 days post randomization), or nonfatal stroke in the intention-to-treat population during the overall study period (i.e., from randomization to the first occurrence of a primary endpoint event or last contact with the patient).

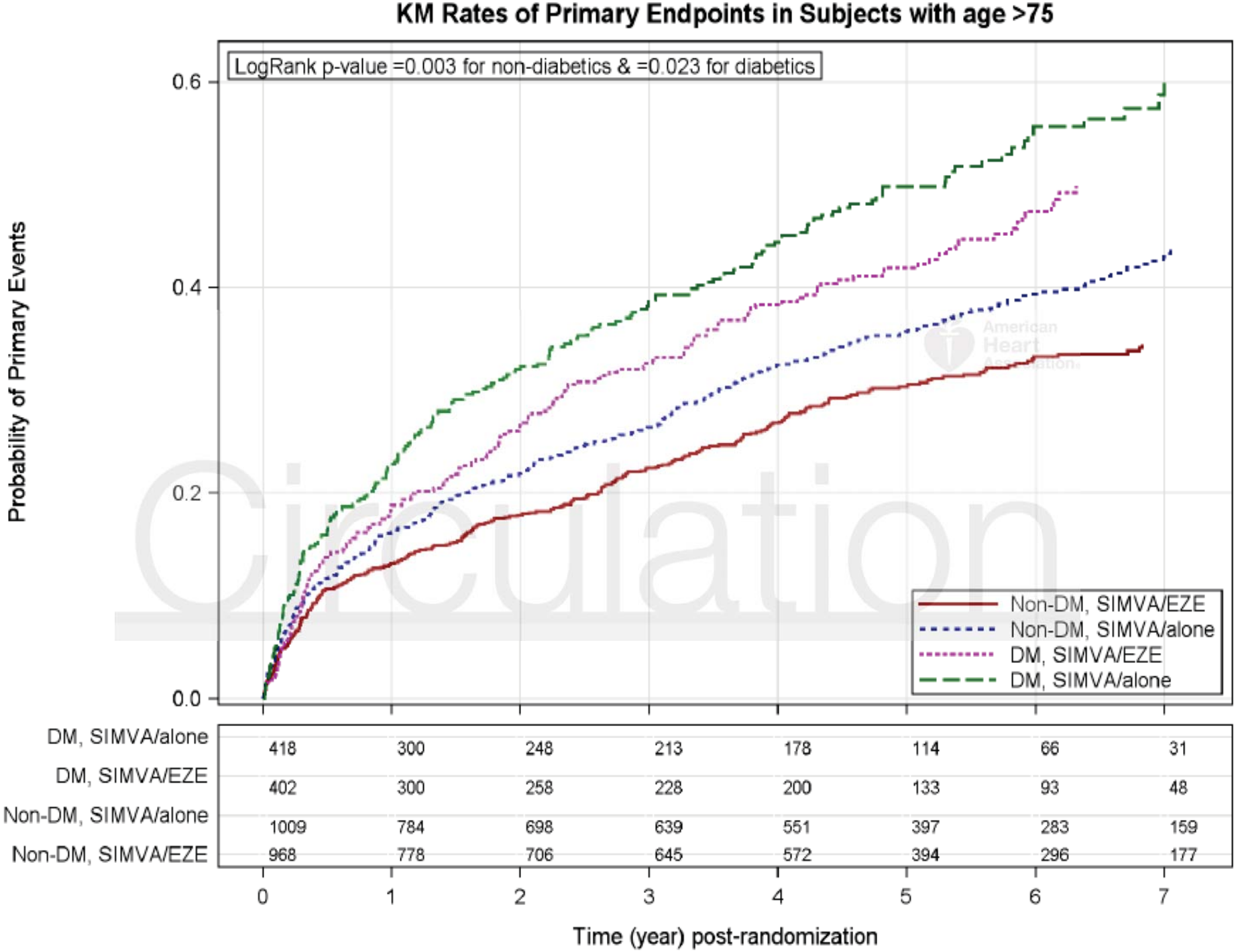
Figure 2. Composite efficacy outcomes stratified by treatment and diabetic status. Hazard ratios and 95% confidence intervals are shown for the comparison of ezetimibe/simvastatin (E/S) vs placebo/simvastatin (P/S) in patients with diabetes (red) and without diabetes (blue).

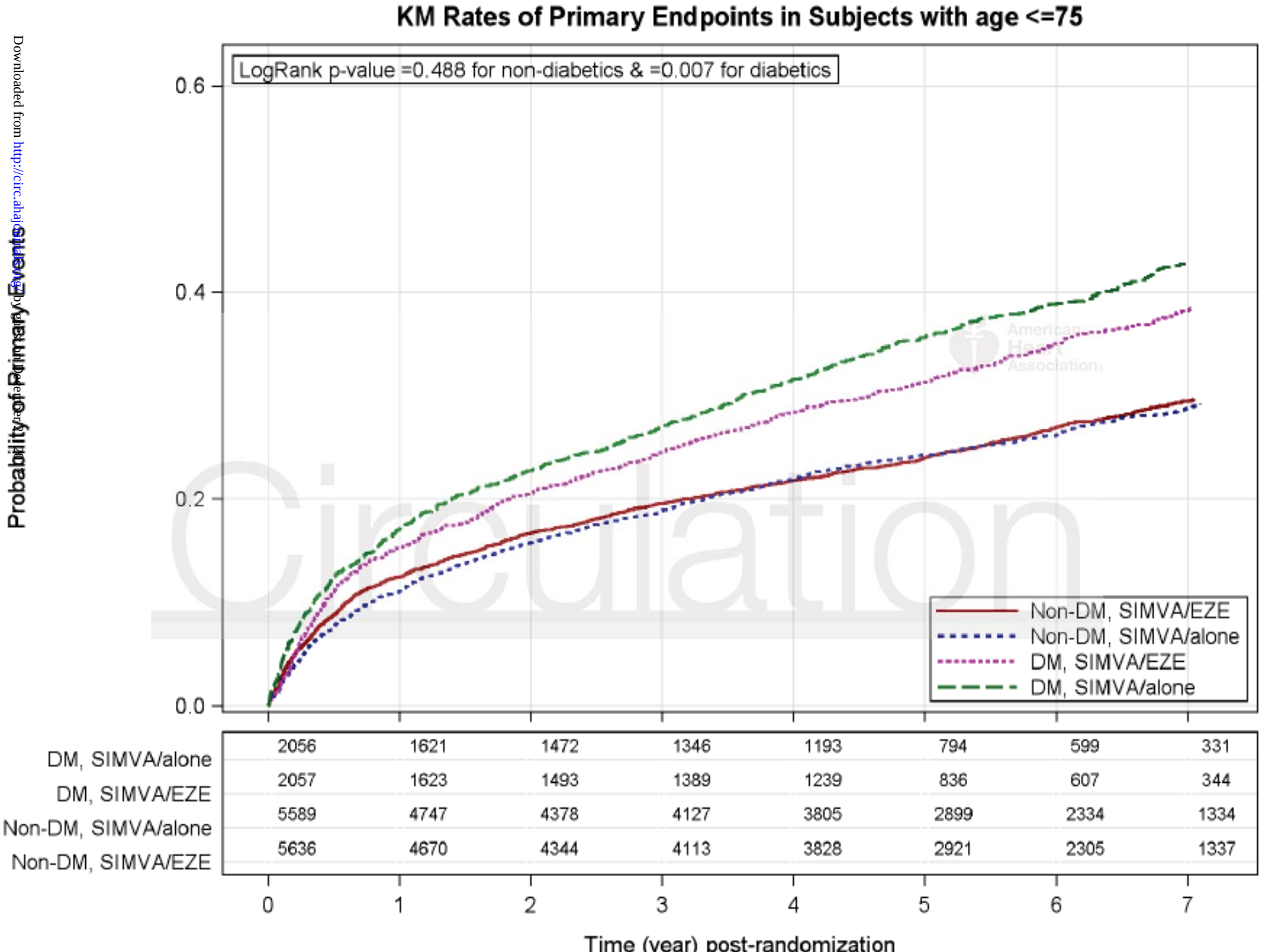
Figure 3. Kaplan-Meier curves for the primary efficacy endpoint stratified by age and diabetes status. Shown are the cumulative event rates for the primary composite endpoint in patients age 75 or greater (Panel A), stratified by diabetes status. Similar curves for patients under age 75 are shown in Panel B.

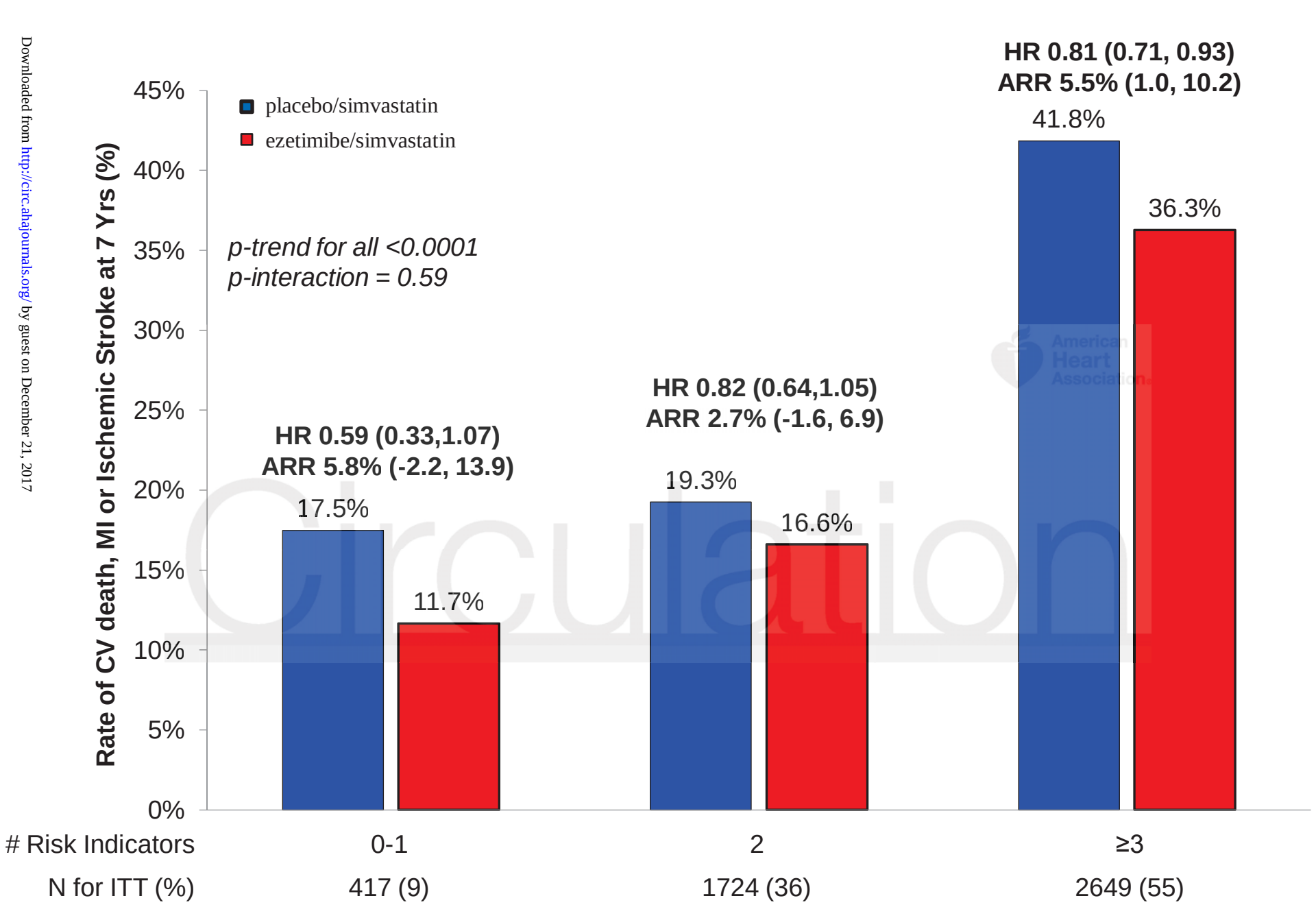
Figure 4. Efficacy of ezetimibe stratified by diabetic status and TIMI Risk Score for Secondary Prevention. Cumulative event rates of the composite of cardiovascular death, myocardial infarction, or ischemic stroke in patients at low (0-1 risk indicators), intermediate (2) and high (≥ 3) risk are shown for placebo/ezetimibe (black) and ezetimibe/simvastatin (grey) in patients with diabetes mellitus (Panel A) and without diabetes mellitus (Panel B).

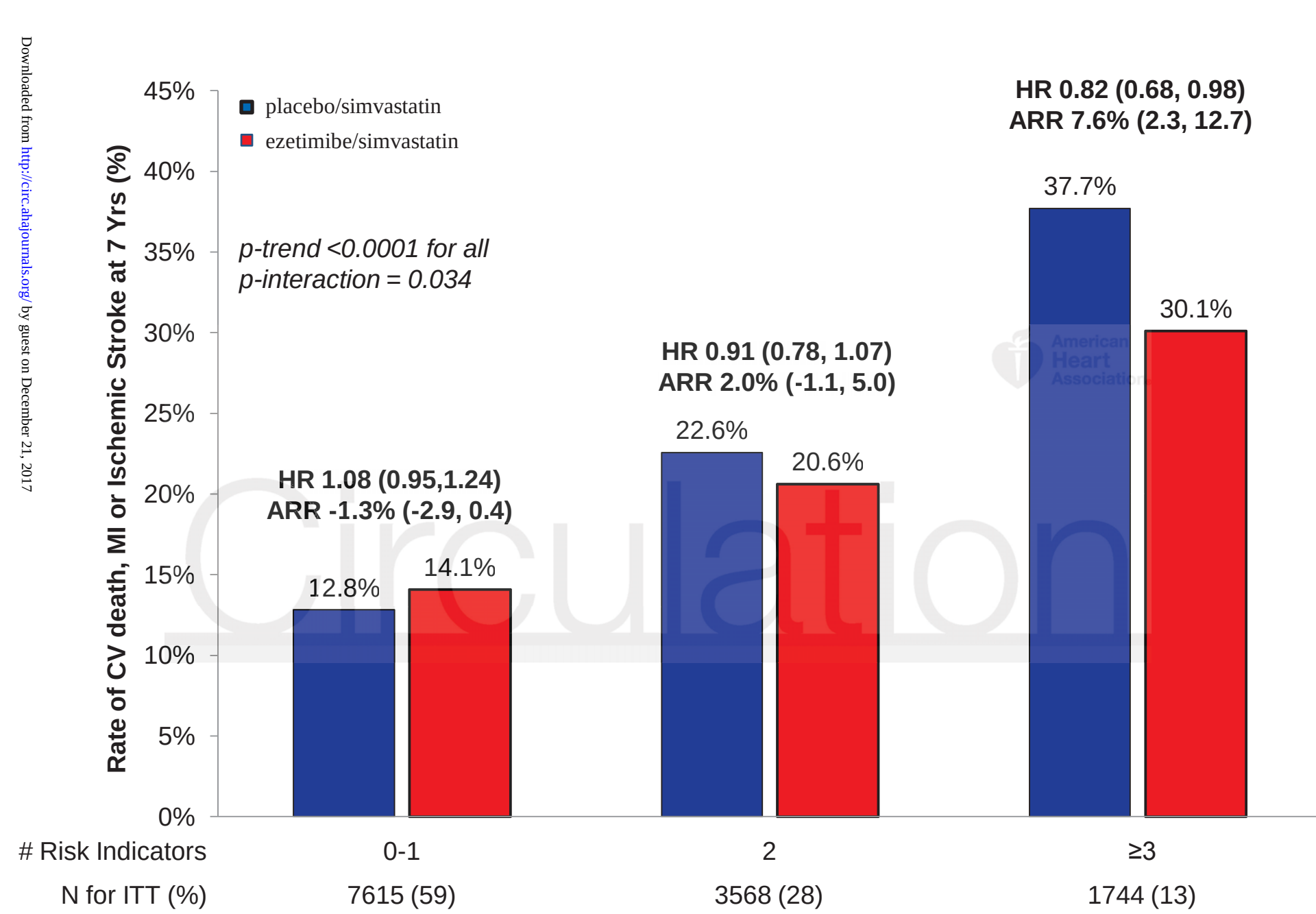












Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With vs. Without Diabetes: Results from IMPROVE-IT

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on behalf of the IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators

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SUPPLEMENTARY MATERIAL

Supplementary Appendix: Table of Contents

Table S1: Baseline Characteristics by Diabetes Status and Treatment Group

	Diabetes Absent 13,202 (72.6%)			**Diabetes Present** 4933 (27.4%)		
	Simvastatin N=6598	**Ezetimibe/Simva** N=6604	P	**Simvastatin** N=2474	**Ezetimibe/Simva** N=2459	P
Demographics						
Mean Age (SD)	63.7 (9.9)	63.7 (9.9)	0.76	65.3 (9.3)	65.3 (9.1)	0.71
Female	1473 (22.3)	1532 (23.2)	0.23	716 (28.9)	691 (28.1)	0.51
White	5682 (86.1)	5677 (86.0)	0.80	1938 (78.3)	1899 (77.2)	0.35
Median Weight, kg [IQR]	80.0 [70.0, 91.0]	80.0 [70.0, 90.3]	0.50	84.5 [74.0, 97.7]	85.0 [74.0, 98.0]	0.62
Median BMI [IQR]	27.0 [24.5, 30.1]	27.1 [24.6, 30.0]	0.76	29.2 [26.2, 33.1]	29.2 [26.0, 32.9]	0.81
Medical history						
Hyperlipidemia	4742 (71.9)	4762 (72.1)	0.76	1845 (74.6)	1802 (73.3)	0.30
Hypertension	3631 (55.0)	3635 (55.0)	0.99	1926 (77.8)	1945 (79.1)	0.29
Current smoking	2437 (36.9)	2347 (35.6)	0.099	598 (24.2)	596 (24.2)	0.96
Myocardial infarction	1243 (18.9)	1298 (19.7)	0.24	638 (25.8)	627 (25.6)	0.85
PCI	1180 (17.9)	1180 (17.9)	0.97	616 (24.9)	586 (23.9)	0.39
CABG	489 (7.4)	509 (7.7)	0.52	353 (14.3)	333 (13.5)	0.46
Congestive heart failure	192 (2.9)	218 (3.3)	0.20	179 (7.2)	201 (8.2)	0.22
Peripheral arterial disease	329 (5.0)	288 (4.4)	0.088	189 (7.6)	199 (8.1)	0.55
Medications prior to admission						
Aspirin	2522 (38.3)	2489 (37.7)	0.52	1333 (53.9)	1310 (53.3)	0.68
Beta-blocker	2041 (31.0)	2074 (31.4)	0.56	1102 (44.6)	1079 (43.9)	0.63
Statin	1939 (29.4)	1995 (30.2)	0.31	1172 (47.4)	1140 (46.4)	0.47
ACE-I or ARB	2202 (33.4)	2268 (34.4)	0.24	1474 (59.6)	1472 (59.9)	0.85
Medications at randomization						
Aspirin	6412 (97.2)	6415 (97.2)	0.68	2382 (96.3)	2383 (96.9)	0.24
Beta-blocker	5746 (87.1)	5771 (87.4)	0.44	2133 (86.2)	2141 (87.1)	0.52
ACE-I or ARB	4834 (73.3)	4755 (72.0)	0.10	2044 (82.6)	2067 (84.1)	0.18

	Diabetes Absent 13,202 (72.6%)			**Diabetes Present** 4933 (27.4%)		
	Simvastatin N=6598	**Ezetimibe/Simva** N=6604	P	**Simvastatin** N=6598	**Ezetimibe/Simva** N=6604	P
At index event						
ST-segment elevation MI	2089 (31.7)	2088 (31.6)	0.95	517 (20.9)	496 (20.2)	0.53
Diagnostic angiography	5581 (89.1)	5907 (89.5)	0.51	2055 (83.1)	2081 (84.6)	0.15
PCI	4739 (71.8)	4760 (72.1)	0.74	1582 (64.0)	1625 (66.1)	0.12
Laboratory Values at Qualifying Event						
LDL-C (mg/dL)	97 [81, 112]	97 [81, 112]	0.55	88 [73, 103]	89 [74, 103]	0.37
Prior statin use	81 [69, 93]	81 [70, 92]	0.82	78 [66, 89]	78 [67, 89]	0.47
No prior statin use	105 [91, 116]	105 [91, 116]	0.79	101 [84, 113]	100 [85, 113]	0.74
HDL-C (mg/dL)	41 [34, 50]	41 [34, 50]	0.71	38 [31, 46]	38 [31, 46]	0.15
Triglycerides (mg/dL)	115 [81, 163]	115 [81, 164]	0.96	138 [96, 192]	135 [95, 193]	0.87
C-reactive protein (mg/L)	5.0 [2.0, 15.0]	5.0 [2.0, 17.7]	0.68	6.0 [2.3, 21.0]	5.4 [2.0, 21.0]	0.47
Laboratory Values at Randomization						
LDL-C (mg/dL)	81 [67, 98]	81 [66, 96]	0.20	75 [60, 92]	75 [61, 91]	0.92
Statin use during admit	78 [65, 93]	78 [64, 92]	0.46	73 [59, 88]	72 [59, 87]	0.42
No statin use during admit	94 [76, 111]	92 [76, 109]	0.15	87 [69, 104]	90 [73, 108]	0.024
C-reactive protein* (mg/L)	9.6 [4.0, 26.7]	9.5 [3.8, 26.2]	0.60	9.4 [4.0, 25.4]	9.9 [4.0, 27.5]	0.13

*Values shown are those closest to randomization

ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, HDL-C = high-density lipoprotein cholesterol, IQR = interquartile range, Kg = kilograms, LDL-C = low-density lipoprotein cholesterol, M = meter, MI = myocardial infarction, SD = standard deviation

Table S2 – Patient adherence to study drug among those at risk for the primary endpoint, stratified by diabetes status

Year End	No Diabetes Mellitus (N, %)	Diabetes Mellitus (n, %)
1	9161 (83.7)	3118 (81.6)
2	7839 (77.7)	2597 (75.3)
3	6924 (72.9)	2246 (71.1)
4	6037 (69.0)	1891 (67.6)
5	4364 (66.2)	1208 (64.7)
6	3340 (64.2)	827 (60.9)
7	1842 (61.4)	444 (59.0)

Table S3 – Efficacy Outcomes

		SIMVA/alone		SIMVA/EZE				
Endpoints[1]	History of diabetes	n (%)	KM event(%) at 7 yrs	n (%)	KM event(%) at 7 yrs	Hazard Ratio (95%CI)	p-value	Interaction p-value[2]
Primary Endpoints	**Non-diabetics**	1792 (27.2)	30.84	1748 (26.5)	30.16	0.98 (0.91, 1.04)	0.471	0.023
	Diabetics	949 (38.4)	45.50	824 (33.5)	40.04	0.85 (0.78, 0.94)	0.001	
Secondary Endpoints I	**Non-diabetics**	2144 (32.5)	36.26	2084 (31.6)	35.40	0.97 (0.92, 1.03)	0.378	0.109
	Diabetics	1101 (44.5)	51.42	1005 (40.9)	47.86	0.89 (0.82, 0.97)	0.009	
Secondary Endpoints II	**Non-diabetics**	895 (13.6)	15.98	858 (13.0)	15.31	0.96 (0.87, 1.05)	0.396	0.074
	Diabetics	552 (22.3)	26.98	464 (18.9)	23.89	0.83 (0.74, 0.94)	0.004	
Secondary Endpoints III	**Non-diabetics**	1884 (28.6)	32.45	1852 (28.0)	31.86	0.98 (0.92, 1.05)	0.640	0.021
	Diabetics	984 (39.8)	46.72	864 (35.1)	42.04	0.86 (0.79, 0.95)	0.002	
Tertiary Endpoints	**Non-diabetics**	1070 (16.2)	18.97	1025 (15.5)	18.33	0.96 (0.88, 1.04)	0.322	0.006
	Diabetics	660 (26.7)	32.39	526 (21.4)	26.63	0.78 (0.70, 0.88)	0.000	

[1] Primary endpoints: CV death, non-fatal MI, Unstable angina, Coronary revascularization (PCI or CABG) at least 30 days post-randomization, or non-fatal stroke.
[1] Secondary endpoints I: All death, non-fatal MI, Unstable angina, Coronary revascularization (PCI or CABG) at least 30 days post-randomization, or non-fatal stroke.
[1] Secondary endpoints II: CHD death, non-fatal MI, Urgent coronary revascularization (PCI or CABG) at least 30 days post-randomization.
[1] Secondary endpoints III: CV death, non-fatal MI, Unstable angina, All revascularization (both coronary and non-coronary) at least 30 days post-randomization, or non-fatal stroke.
[1] Tertiary Endpoints: composite of CHD death, UA required hospitalization, MI, and Ischemic Stroke.
[2] Interaction effect of treatment arm and history of diabetes using Cox PH regression modeling.

Table S4 – Other Efficacy Endpoints by Treatment Group and Diabetes Status

		SIMVA/alone			SIMVA/EZE						
	History of diabetes	n (%)		KM event(%) at 7 yrs	n (%)		KM event(%) at 7 yrs	p-value	Hazard Ratio (95%CI)		Interaction p-value[1]
CV Death	**Non-diabetics**	302	(4.6)	5.29	312	(4.7)	5.28	0.696	1.03 (0.88, 1.21)		0.570
	Diabetics	235	(9.5)	11.15	225	(9.2)	11.68	0.687	0.96 (0.80, 1.16)		
MI	**Non-diabetics**	706	(10.7)	12.73	660	(10.0)	11.99	0.211	0.93 (0.84, 1.04)		0.028
	Diabetics	412	(16.7)	20.81	317	(12.9)	16.41	0.000	0.76 (0.66, 0.88)		
Hosp. for Unstable Angina	**Non-diabetics**	94	(1.4)	1.64	100	(1.5)	1.80	0.658	1.07 (0.80, 1.41)		0.941
	Diabetics	54	(2.2)	2.74	56	(2.3)	2.81	0.821	1.04 (0.72, 1.52)		
CHD Death	**Non-diabetics**	247	(3.7)	4.32	248	(3.8)	4.23	0.973	1.00 (0.84, 1.20)		0.450
	Diabetics	213	(8.6)	10.07	192	(7.8)	10.07	0.327	0.91 (0.75, 1.10)		
Stroke	**Non-diabetics**	216	(3.3)	3.99	201	(3.0)	3.79	0.472	0.93 (0.77, 1.13)		0.151
	Diabetics	129	(5.2)	7.14	95	(3.9)	5.25	0.020	0.73 (0.56, 0.95)		
Ischemic Stroke	**Non-diabetics**	180	(2.7)	3.35	164	(2.5)	3.24	0.399	0.91 (0.74, 1.13)		0.031
	Diabetics	117	(4.7)	6.48	72	(2.9)	3.94	0.001	0.61 (0.46, 0.82)		
Any Death	**Non-diabetics**	759	(11.5)	12.93	746	(11.3)	12.57	0.740	0.98 (0.89, 1.09)		0.842
	Diabetics	471	(19.0)	21.79	469	(19.1)	23.46	1.000	1.00 (0.88, 1.14)		

CVDeath/MI/Stroke	**Non-diabetics**	1060	(16.1)	17.99	1019	(15.4)	17.16	0.310	0.96	(0.88,	1.04)	0.016
	Diabetics	643	(26.0)	29.88	525	(21.4)	25.31	0.000	0.80	(0.71,	0.90)	
PCI/CABG 30days-post	**Non-diabetics**	1224	(18.6)	21.45	1173	(17.8)	20.59	0.326	0.96	(0.89,	1.04)	0.514
	Diabetics	569	(23.0)	29.07	517	(21.0)	25.38	0.148	0.92	(0.81,	1.03)	
Urgent PCI/CABG 30days-post	**Non-diabetics**	409	(6.2)	7.50	346	(5.2)	6.44	0.020	0.84	(0.73,	0.97)	0.395
	Diabetics	217	(8.8)	11.84	164	(6.7)	8.63	0.007	0.76	(0.62,	0.93)	

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[1] Interaction p-value between treatment arm and diabetes status.

Table S5 – Sensitivity Analysis of Efficacy Endpoints Using a Broader Definition* of Pre-existing Diabetes Mellitus

		SIMVA/alone		SIMVA/EZE				
Endpoints	Diabetes status	n (%)	KM event(%) at 7 yrs	n (%)	KM event(%) at 7 yrs	Hazard Ratio (95%CI)	p-value	Interaction p-value*
Primary Endpoints	**Non-diabetics**	1660 (27.0)	30.65	1633 (26.7)	30.27	0.99 (0.92, 1.06)	0.778	0.006
	Diabetics	985 (37.5)	44.07	855 (32.2)	38.50	0.84 (0.77, 0.93)	0.000	
Secondary Endpoints I	**Non-diabetics**	1989 (32.4)	36.10	1945 (31.8)	35.46	0.98 (0.92, 1.05)	0.610	0.036
	Diabetics	1148 (43.7)	49.96	1044 (39.3)	46.34	0.88 (0.81, 0.96)	0.003	
Secondary Endpoints II	**Non-diabetics**	822 (13.4)	15.72	812 (13.3)	15.61	0.99 (0.90, 1.10)	0.911	0.005
	Diabetics	581 (22.1)	26.61	472 (17.8)	22.29	0.79 (0.70, 0.90)	0.000	
Secondary Endpoints III	**Non-diabetics**	1746 (28.4)	32.20	1729 (28.3)	31.96	1.00 (0.93, 1.07)	0.959	0.006
	Diabetics	1022 (38.9)	45.40	898 (33.8)	40.55	0.85 (0.78, 0.93)	0.001	
Tertiary Endpoints	**Non-diabetics**	992 (16.2)	18.81	967 (15.8)	18.56	0.98 (0.90, 1.07)	0.648	<0.001
	Diabetics	690 (26.2)	31.84	540 (20.3)	25.28	0.76 (0.68, 0.85)	0.000	

*Diabetes mellitus identified by the investigator at time of admission, or first glucose after randomization $\geq$ 126 mg/dL (fasting) or 200 mg/dL (non-fasting).

Primary endpoints: Cardiovascular (CV) death, non-fatal myocardial infarction (MI), unstable angina (UA), coronary revascularization $\geq$30 days post-randomization, or stroke.
Secondary endpoints I: All death, MI, UA, coronary revascularization $\geq$30 days post-randomization, or stroke.
Secondary endpoints II: Coronary heart disease (CHD) death, MI, urgent coronary revascularization $\geq$30 days post-randomization.

Secondary endpoints III: CV death, MI, UA, all revascularization (both coronary and non-coronary) ≥30 days post-randomization, or stroke.
Tertiary Endpoints: CHD death, UA, MI, and ischemic stroke.
*Interaction effect of treatment arm and history of diabetes using Cox proportional hazards regression modeling

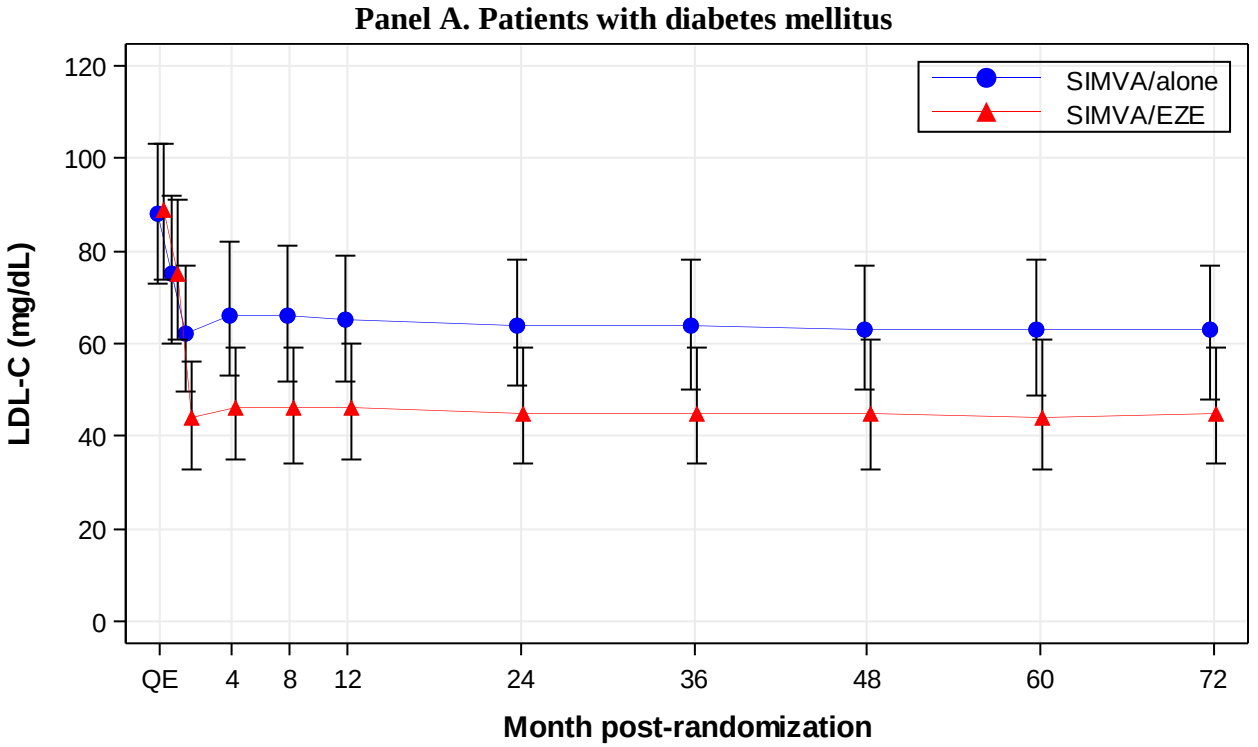
Table S6 – On-treatment Sensitivity Analysis of Efficacy Endpoints

Within 30 days of stopping study drug in subjects who were on treatment								
		SIMVA/alone		SIMVA/EZE				
Endpoints	History of diabetes	n (%)	KM event(%) at 7 yrs	n (%)	KM event(%) at 7 yrs	Hazard Ratio (95%CI)	p-value	Interaction p-value*
Primary Endpoints	**Non-diabetics**	1383 (21.5)	29.33	1332 (20.6)	27.64	0.96 (0.89, 1.03)	0.281	0.067
	Diabetics	696 (28.9)	41.27	600 (25.1)	36.32	0.85 (0.76, 0.95)	0.003	
Secondary Endpoints I	**Non-diabetics**	1445 (22.4)	30.65	1380 (21.3)	28.74	0.95 (0.88, 1.02)	0.182	0.144
	Diabetics	728 (30.2)	43.16	640 (26.8)	39.27	0.86 (0.78, 0.96)	0.007	
Secondary Endpoints II	**Non-diabetics**	625 (9.7)	14.07	595 (9.2)	12.94	0.95 (0.85, 1.06)	0.341	0.042
	Diabetics	368 (15.3)	22.59	291 (12.2)	18.90	0.78 (0.67, 0.91)	0.001	
Secondary Endpoints III	**Non-diabetics**	1461 (22.7)	31.07	1411 (21.8)	29.21	0.96 (0.89, 1.04)	0.311	0.069
	Diabetics	728 (30.2)	42.50	636 (26.6)	38.70	0.86 (0.77, 0.95)	0.004	
Tertiary Endpoints	**Non-diabetics**	770 (11.9)	17.28	727 (11.2)	15.97	0.94 (0.85, 1.04)	0.219	0.015
	Diabetics	445 (18.5)	27.40	345 (14.5)	22.46	0.76 (0.66, 0.87)	0.000	

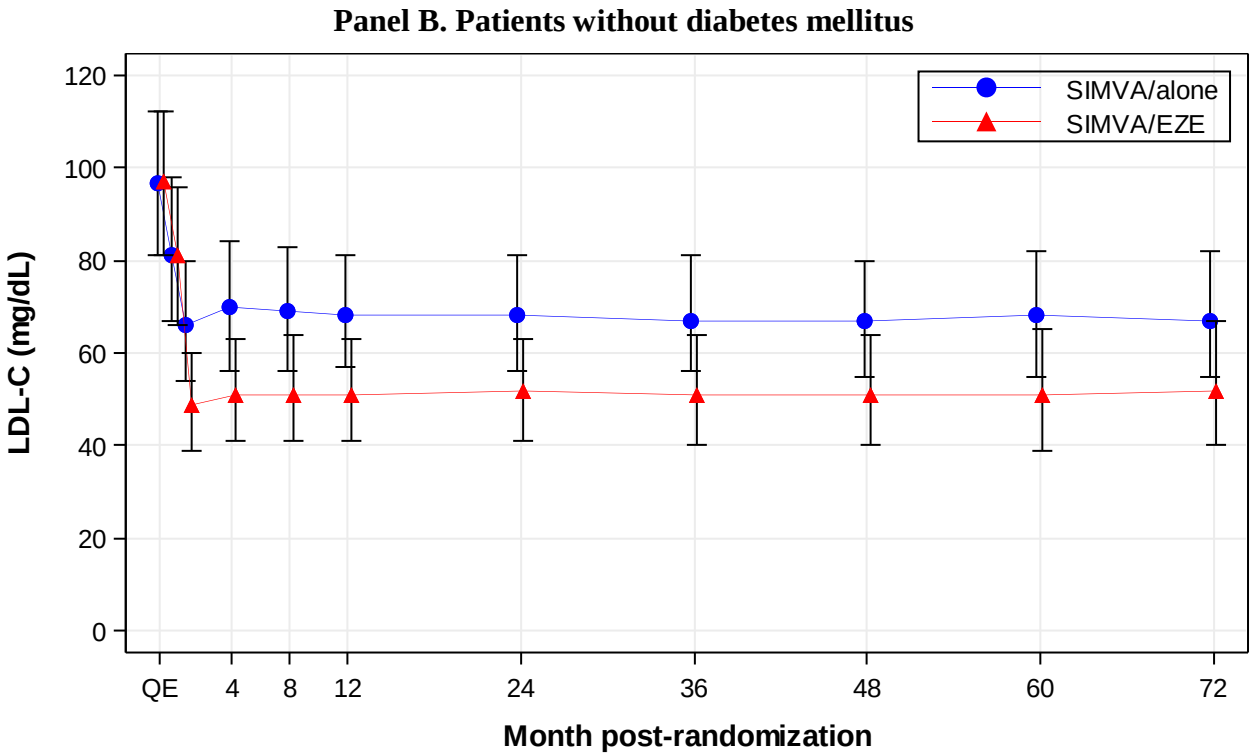
See footnote to Table S3 for explanation of endpoints.

*Interaction effect of treatment arm and history of diabetes using Cox proportional hazards regression modeling

Figure S1



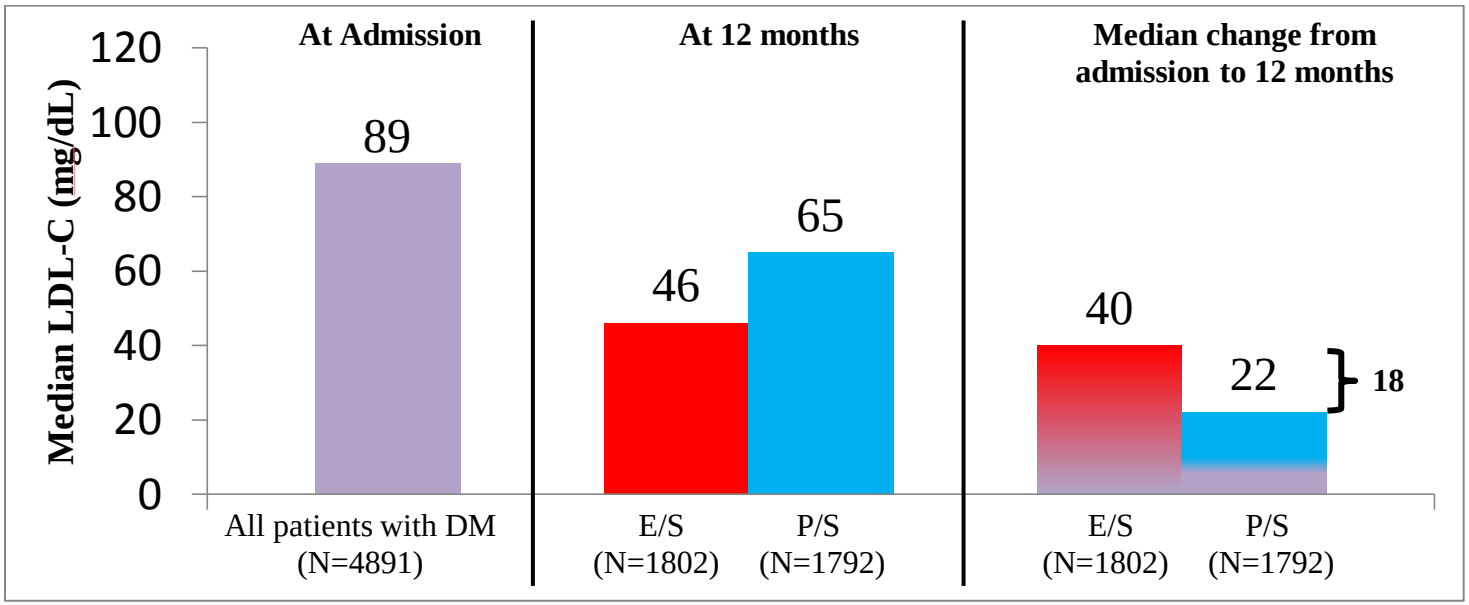
LDL-C over time. In Panel A, the median LDL-C (dark circle) and interquartile range (bars) are shown for patients with diabetes from prior to the time of the qualifying event (QE) though 72 months for placebo/simvastatin (solid line) and ezetimibe/simvastatin (dashed line). Panel B shows similar data among patients without diabetes.



LDL-C over time. In Panel A, the median LDL-C (dark circle) and interquartile range (bars) are shown for patients with diabetes from prior to the time of the qualifying event (QE) though 72 months for placebo/simvastatin (solid line) and ezetimibe/simvastatin (dashed line). Panel B shows similar data among patients without diabetes.

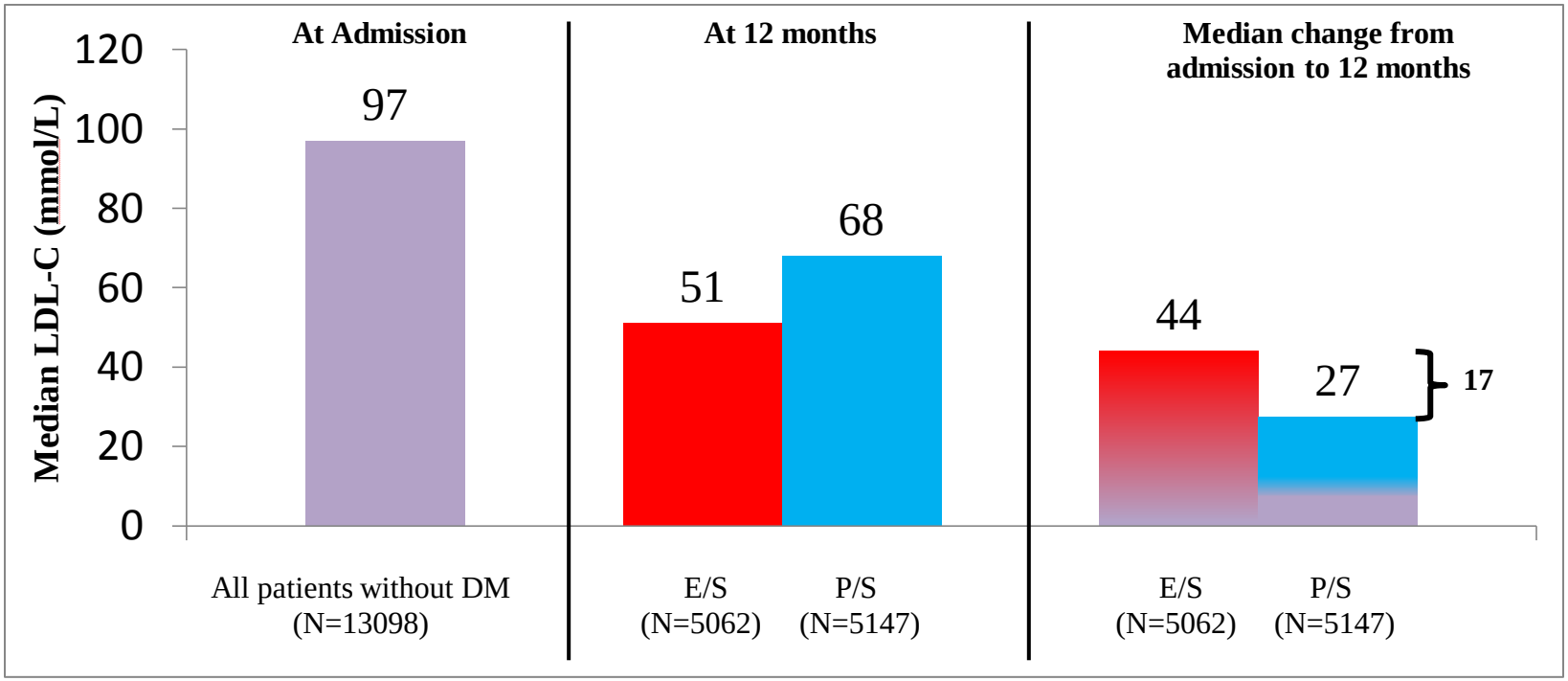
Figure S2 – Change in median LDL-C between admission and 12 months by diabetic status and treatment group

A. Median LDL-C at admission and 12 months in patients with diabetes mellitus



Change in median LDL-C between admission and 12 months by diabetic status and treatment group. Results in patients with diabetes are shown in Panel A and results in patients without diabetes are shown in Panel B. There was no significant effect modification by diabetes status on the treatment difference in LDL-C reduction from admission to 12 months ($P_{interaction}$ 0.12).

B. Median LDL-C at admission and 12 months in patients without diabetes mellitus



Change in median LDL-C between admission and 12 months by diabetic status and treatment group. Results in patients with diabetes are shown in Panel A and results in patients without diabetes are shown in Panel B. There was no significant effect modification by diabetes status on the treatment difference in LDL-C reduction from admission to 12 months ($P_{interaction}$ 0.12).

Figure S3. Efficacy composite endpoints by treatment group stratified by age and diabetes status

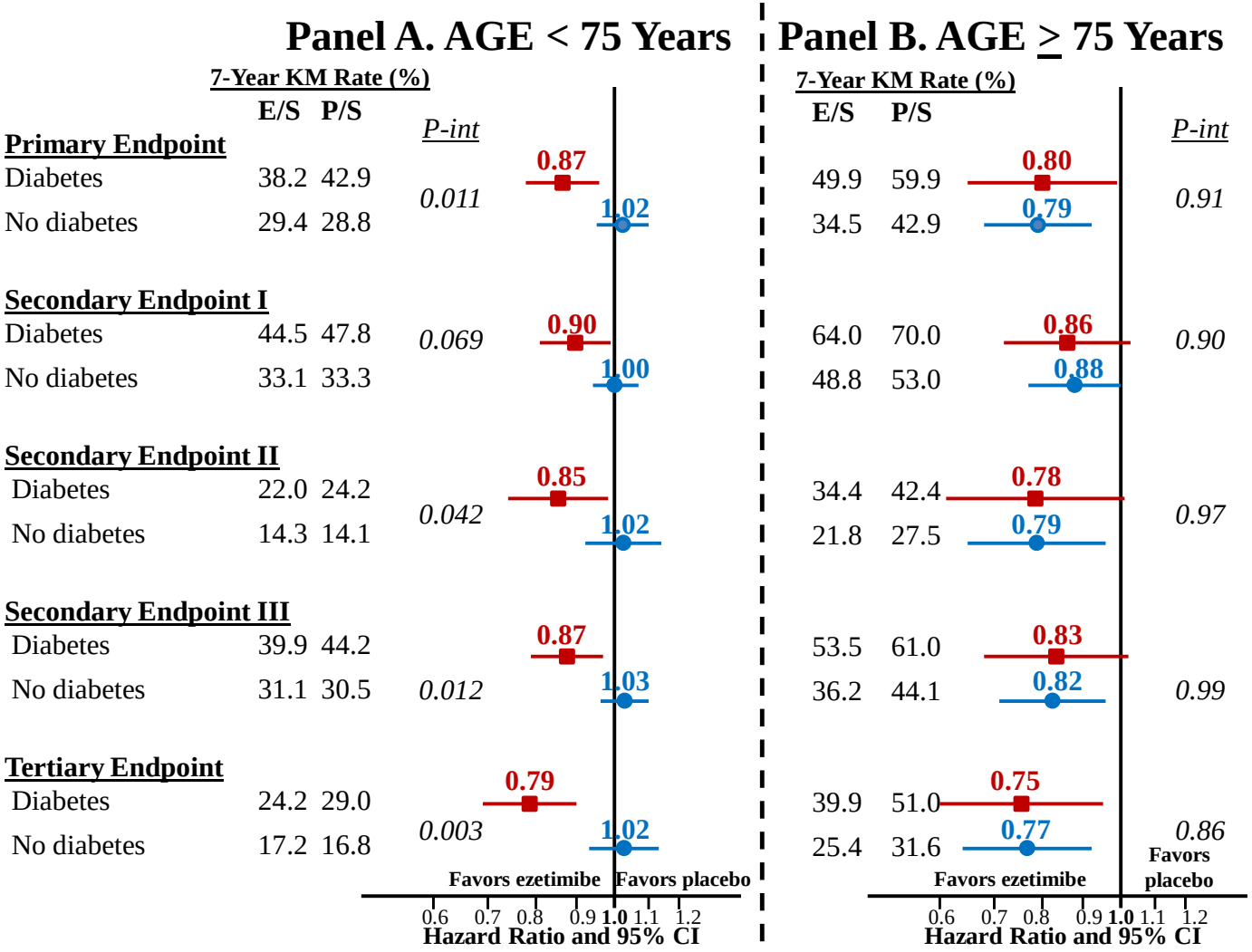
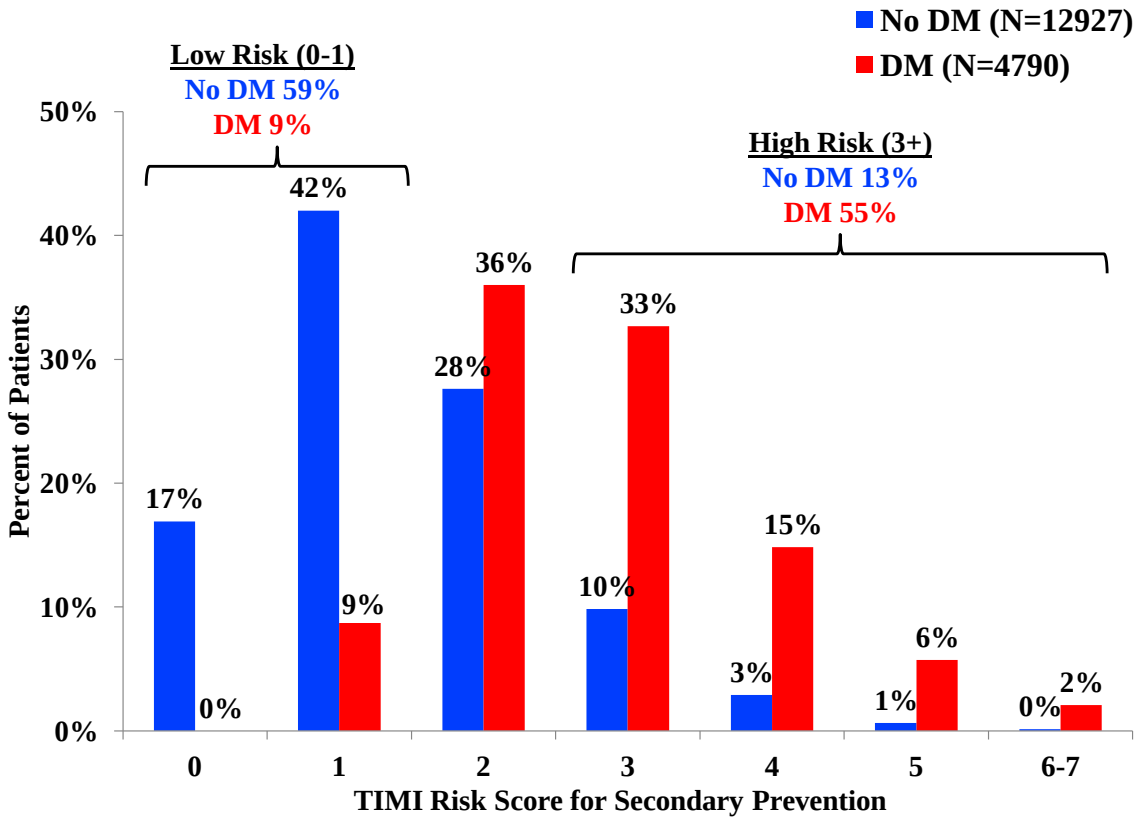


Figure S4. Risk distribution of patients with vs without diabetes mellitus



Risk distribution of patients with vs without diabetes mellitus. Patients with diabetes mellitus (red) were at higher risk (mean score 2.8) compared to patients without diabetes mellitus (blue, mean score 1.4), as categorized by the TIMI Risk Score for Secondary Prevention.[1, 2] Note: The score could not be calculated in 427 patients (2.4%) due to missing data.

1. Bohula EA, Bonaca MP, Braunwald E, Aylward PE, Corbalan R, De Ferrari GM, et al. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. *Circulation*. 2016;134:304-313
2. Bohula EA, Morrow DA, Giugliano RP, Blazing MA, He P, Park JG, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. *Journal of the American College of Cardiology*. 2017;69:911-921