Effect on Fasting Serum Glucose Levels of Adding Ezetimibe to Statins in Patients With Nondiabetic Hypercholesterolemia

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Statin therapy is associated with a slightly increased risk of developing diabetes mellitus and insulin resistance in patients without diabetes. Ezetimibe combined with statins may be considered for high-risk patients who do not achieve optimal low-density lipoprotein cholesterol lowering on statin monotherapy or who are statin intolerant. Changes in fasting serum glucose (FSG) levels during ezetimibe, ezetimibe/statin, and statin treatments were assessed using data pooled from clinical trials in hypercholesterolemic and heterozygous familial hypercholesterolemic patients, who were or were not receiving statin therapy. Study types included first-line trials in statin-naive/wash-out patients and second-line add-on and uptitration studies in patients on stable statin therapy. Similar analyses of FSG changes were performed separately for each study type in patients who were nondiabetic at baseline. Across all study types and treatments, mean FSG increases from baseline were small (0.5 to 3.7 mg/dl with ezetimibe/statin; 0.2 to 4.6 mg/dl with statins) and decreased over time; between-treatment differences (0.3 to 1.4 mg/dl) were nonsignificant for all comparisons. Proportions of patients with elevated FSG ≥126 mg/dl during therapy were low and similar for all treatments in the overall cohort (1.2% to 4.3%). Elevations were highest (3.3% to 25.7%) among patients with baseline factors characteristic of metabolic syndrome and prediabetes, including higher FSG, body mass index, and triglyceride levels, and numerically lower baseline high-density lipoprotein cholesterol; however, these factors were not related to FSG increases. Changes in low-density lipoprotein cholesterol, body mass index, high-density lipoprotein cholesterol, triglycerides, and apolipoprotein B were not significantly correlated with FSG increases. In conclusion, statin therapy was associated with small FSG increases, and the addition of ezetimibe did not further increase FSG levels beyond those of statins when given to patients who are statin naive or those on statin therapy. © 2016 The Authors and Merck Sharp & Dohme Corp. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (Am J Cardiol 2016;118:1812−1820)

Some studies have indicated that statins are associated with an increased risk of developing diabetes mellitus and increased insulin resistance, especially at higher doses of some statins.[1−3] The Food and Drug Administration recently added warnings of increased glycosylated hemoglobin A1c (HbA1c) and fasting serum glucose (FSG) levels to statin labels.[4] However, the risk was said to be small, and the cardiovascular benefits of statins outweigh this small increased risk.[4] The addition of ezetimibe to statins provides low-density lipoprotein cholesterol (LDL-C) reductions greater than statins alone, including more than doubling the statin dose, and provides an incremental reduction in cardiovascular events when added to statin therapy.[5−11] In consideration of the effects of statins on glucose dysregulation, it is important to assess the impact of ezetimibe, both as monotherapy and when combined with statins, on these same issues in a broad population of patients. This analysis assessed changes in FSG levels during ezetimibe,

ezetimibe + simvastatin, and statin treatment using data pooled from randomized clinical studies in patients who are nondiabetic, hypercholesterolemic, and heterozygous familial hypercholesterolemic (HeFH) and were or were not receiving statin therapy at study start.

Methods

Changes in FSG were assessed in first-line short- and long-term studies and second-line add-on and uptitration studies pooled separately in hypercholesterolemic patients without diabetes at baseline. Studies included in the analyses are described in Supplementary Table 1. The first-line (statin naive) analyses included 7 similarly designed studies of up to 12 weeks in duration and 3 long-term studies, including 2 studies in hypercholesterolemic patients (1A and 1B; 26- and 60-week durations, respectively) and 1 in HeFH patients (II; 96 weeks duration). Two studies were included in the second-line add-on analysis with treatment durations up to 8 weeks and 3 studies were included in the second-line uptitration analysis with duration up to 12 weeks.

Treatment comparisons performed were pooled across studies (where applicable). First-line short-term studies were pooled across statin brands and doses, and treatment with ezetimibe 10 mg versus placebo, statins versus placebo, and ezetimibe combined with statins versus statins was compared. For the first-line long-term studies, 2 separate analyses were conducted: one for studies IA and IB pooled across statin doses that compared ezetimibe/all simvastatin versus simvastatin and study II that compared ezetimibe/simvastatin 80 mg versus simvastatin 80 mg. The second-line add-on studies were pooled across statin brand and doses and compared statin versus ezetimibe added to a statin. The second-line uptitration studies compared statin uptitration versus ezetimibe combined with a statin. End points assessed for all studies included change from baseline in mean FSG, proportions of patients with baseline FSG <126 mg/dl who had FSG ≥126 mg/dl during treatment, associations between prespecified baseline covariates and changes in FSG, and correlations between change from baseline in prespecified variables and FSG changes.

The first-line short- and long-term and second-line add-on and uptitration analyses were performed separately for each study type and were generally similar. For both first-line and second-line studies, mean FSG values at baseline, post-baseline, and mean change from baseline were summarized. Mean change from baseline to a given time point for first-line and second-line studies was estimated using a longitudinal data analysis (LDA) model that handled both repeated-measures and missing data.[12] The model included both baseline and post-baseline measurements as response variables and terms for trial, treatment, statin dose (when appropriate), time (categorical variable), and interaction of time by treatment, with a restriction of the same baseline mean across treatment groups (because of randomization). An unstructured covariance matrix was used to model the correlation among repeated measurements. Between-treatment differences were also estimated from the model.

Summary statistics of baseline characteristics (age, gender, race, body mass index [BMI], FSG, LDL-C, triglycerides, high-density lipoprotein cholesterol [HDL-C],

and total cholesterol) for subjects with and without post-baseline FSG values ≥126 mg/dl were provided. The proportion of subjects with baseline FSG values <126 mg/dl who had an FSG value ≥126 mg/dl during treatment was analyzed using adjusted odds ratios, 95% confidence intervals [CIs], and p values. The analysis was performed using the earlier mentioned LDA model to impute missing data within study time frames. Subjects were categorized as having either an elevated FSG measurement (FSG ≥126 mg/dl) or not at each time point after imputations. To estimate the odds ratio, imputed data sets were analyzed by a logistic regression model that included terms for treatment, baseline FSG, and study (when appropriate); the odds ratios for treatment comparisons were combined using Rubin's formula.[13] For the long-term studies that had differing time points, a separate analysis was performed for each study, and therefore, study was not included in the model.

Analysis of the proportion of subjects with FSG ≥126 mg/dl was additionally performed in the subgroups of subjects who had baseline FSG values <100 mg/dl and from 100 to 126 mg/dl. An analysis on the proportion of subjects with baseline FSG <126 mg/dl who had FSG ≥126 mg/dl during the treatment period without imputing the missing data was performed as a sensitivity analysis. Scatter plots of the values for the various baseline characteristics versus maximum FSG values were also produced.

The association between prespecified baseline covariates (study, statin brand, potency, age, gender, race, BMI, and baseline FSG, triglycerides, and HDL-C) and FSG changes was evaluated by univariate analyses using the LDA model with change from baseline as the dependent variable and each covariate as the independent variable. The placebo group was excluded from the covariate analysis as values for potency and statin brand were missing for this treatment. Parameter estimates, 95% CIs, and p values from the model were reported. All covariates with $p < 0.05$ were further explored in a multivariable model using the LDA approach. Associations between post-baseline changes in BMI, LDL-C, apolipoprotein (Apo) B, HDL-C, and triglycerides and FSG changes was evaluated by simple linear regression to provide estimates of slope, intercept, and R-square. Correlation values and the corresponding 95% CIs and p values were provided. Scatterplots were generated to explore the nature (direction) and/or strength of any potential relation with FSG changes for both analyses.

Results

A total of 4,726 subjects were included in the full analysis cohort of pooled, first-line short-term studies. The full analysis cohort of pooled, first-line long-term studies (up to 96 weeks) included 2,041 subjects. A total of 1,295 subjects were included in the full analysis cohort of pooled, second-line uptitration studies, and 2,357 subjects were included in the full analysis cohort of pooled second-line add-on studies. Baseline characteristics were generally similar between the treatment groups in the first-line short- and long-term studies and in the second-line add-on study and uptitration study types with some exceptions (Supplementary Table 2). Mean ages were slightly lower in the first-line long-term study II (46 years) and somewhat higher in the second-line add-on

(61 years) and uptitration (67 years) studies than in the first-line studies IA and IB (56 years). Mean baseline LDL-C was 178 mg/dl in first-line studies but was higher in long-term study II in HeFH patients (318 mg/dl), and lower in second-line add-on (137 mg/dl) and uptitration studies (102 mg/dl). Mean triglyceride levels were somewhat higher in first-line studies (156 mg/dl) than in the second-line add-on (142 mg/dl) and uptitration studies (119 mg/dl). Mean FSG values were (94 mg/dl) for first-line studies but slightly lower for first-line long-term study II (89 mg/dl) and were somewhat higher for second-line add-on and uptitration studies (98 mg/dl).

Mean FSG changes from baseline were overall small for all study types and treatments. The mean FSG values at post-treatment time points were similar for statin and ezetimibe/statin groups. In the first-line studies, the range in FSG levels for post-treatment time points was 96 to 97 mg/dl in both the short-term studies and the long-term studies IA + IB and 90 to 93 mg/dl for the long-term study II. Post-treatment FSG levels in the second-line studies were 98 mg/dl for add-on and 99 mg/dl for uptitration study types. In the first-line short-term studies, changes from baseline in ezetimibe monotherapy were very small and comparable with placebo (0.5 to 0.6 mg/dl for both) during 12 weeks. For the pooled statin and ezetimibe + statin treatment groups, a statistically significant increase from baseline in mean FSG was observed by week 2 that continued to increase through week 8 and then decreased at week 12 (Figure 1). The maximum increase over the 12-week period occurred at week 8 and was 2.0 mg/dl (95% CI 1.4, 2.5) for the pooled statin and 1.7 mg/dl (95% CI 1.1, 2.2) for the ezetimibe + pooled statin treatment groups. At week 12, the pooled statin group showed a significantly higher increase from baseline compared with placebo, with a difference in FSG of 1.4 mg/dl (95% CI 0.3, 2.5, $p = 0.011$). No other treatment group comparisons (ezetimibe vs placebo and ezetimibe/statin vs statins) were statistically significantly different (Figure 1).

By week 12 in the first-line, long-term studies, the simvastatin and ezetimibe/simvastatin treatment groups in pooled studies 1A and IB and the simvastatin 80 mg and ezetimibe/simvastatin 80 mg groups in study II had statistically significant changes from baseline in FSG ($p < 0.05$) with no statistically significant differences between treatment groups in either analysis (Figure 1). The change in FSG increased over time for the simvastatin and ezetimibe/simvastatin treatment groups through week 36 (maximum increase: 4.6 mg/dl; 95% CI 3.5, 5.8 and 3.7 mg/dl; 95% CI 2.6, 4.7, respectively) and then decreased at week 60. The change in FSG increased over time for the simvastatin 80 mg and ezetimibe/simvastatin 80-mg treatment groups through week 84 (maximum increase: 3.6 mg/dl; 95% CI 2.6, 4.7 and 3.7 mg/dl; 95% CI 2.7, 4.8, respectively) and then decreased at week 96 (Figure 1).

Increases from baseline in FSG were small in the add-on studies for the statin (0.2 mg/dl; 95% CI −0.6, 1.0) compared with ezetimibe + statin groups (0.5 mg/dl; 95% CI −0.1, 1.1; $p > 0.05$) and slightly higher for the ezetimibe + statin group (1.4 mg/dl; 95% CI 0.6, 2.3) compared with the statin dose-doubling group (1.1 mg/dl; 95% CI 0.3, 2.0) in the uptitration studies ($p < 0.05$;
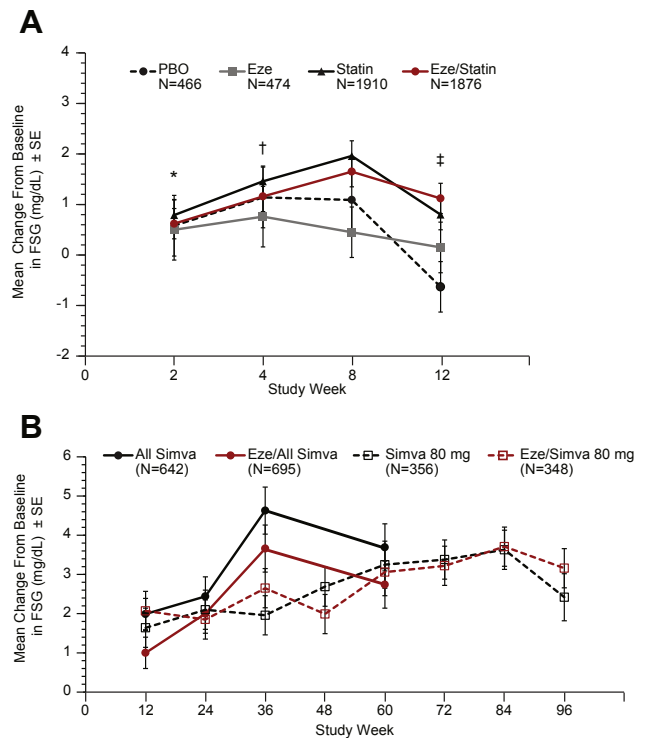

Figure 1. Changes in FSG over time in first-line statin-naive cohorts. Error bars represent SE. *(A)* Short-term studies. *p <0.05 at week 2 for statin and ezetimibe 10 mg (Eze) + statin groups, and †p <0.05 from weeks 2 to 4 for statin group for within-treatment group FSG increases. ‡p <0.05 for within-treatment group decrease in FSG from week 8 to 12 for placebo (PBO) and statin. Statin = simvastatin (10, 20, 40, or 80 mg), lovastatin (10, 20, or 40 mg), pravastatin (10, 20, or 40 mg), and atorvastatin (10, 20, 40, or 80 mg). *(B)* Long-term studies with the All Simva, Eze/Simva, Simva 80 mg, and Eze/Simva 80 mg treatment groups. All Simva = simvastatin (10, 20, 40, or 80 mg), Eze/Simva = Eze 10 mg/Simva (10, 20, 40, or 80 mg).

Figure 2). These changes were similar relative to those observed in first-line studies at 12 weeks in the statin (0.8 mg/dl; 95% CI 0.3, 1.3) versus ezetimibe/statin group (1.1 mg/dl; 95% CI 0.6, 1.6). There were no significant differences in mean FSG changes between treatment groups (Figure 2).

Among subgroups of patients in first-line and second-line studies with post-baseline FSG <126 and ≥126 mg/dl, baseline characteristics were generally similar with some numerical differences, including higher baseline BMI, FSG, triglyceride levels, and lower HDL-C levels in subjects with post-baseline FSG ≥126 mg/dl compared with subjects with post-baseline FSG <126 mg/dl (Table 1). Proportions of patients with FSG ≥126 mg/dl were overall low and were highest in the group with baseline FSG ≥100 to ≤126 mg/dl for all treatments in all the first-line short-term (Figure 3), first-line long-term (Figure 3), and second-line add-on and uptitration studies (Figure 3). There were no significant treatment differences between any of the treatment groups in any of the analyses. Overall, elevated FSG ≥126 mg/dl did not appear to be related to increasing age, higher baseline BMI, FSG, and triglyceride levels and lower HDL-C levels,
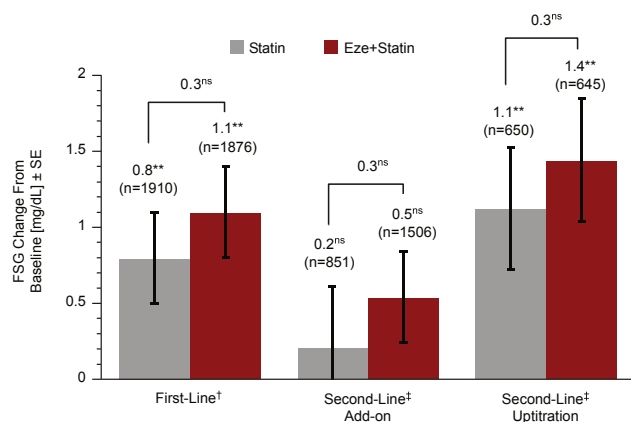
Figure 2. Changes from baseline in FSG in first- and second-line studies. The error bars represent SE. **p <0.05; ns at the 0.05 alpha level (p >0.05). "†," First-line short-term studies: ezetimibe 10 mg (Eze) + statin versus statins as described in Figure 1 during 12 weeks. "‡,"Second-line add-on studies: Eze versus placebo for 8 weeks added to on-going statin = atorvastatin (10, 20, 40, or 80 mg), cerivastatin (0.2, 0.3, 0.4, or 0.8 mg), fluvastatin (10, 20, 40, or 80 mg; 1 patient received 160 mg), lovastatin (10, 20, 40, or 80 mg), pravastatin (10, 20, 40, or 80 mg), and simvastatin (10, 20, 40, or 80 mg). "‡,"Second-line uptitration studies: Eze 10 mg versus doubling the statin dose during 6 to 8 weeks. ns = not statistically significant; Ongoing statin = atorvastatin (10, 20, or 40 mg), then uptitrated to atorvastatin (20, 40, or 80 mg).

although there was a trend toward increasing FSG in patients with higher FSG at baseline (Supplementary Figure 1).

Of several baseline factors explored, increasing age, BMI, and baseline FSG, HDL-C, and triglycerides were associated with very small but statistically significant percent changes from baseline in FSG in univariate analyses for all first-line and second-line uptitration studies (Supplementary Table 3). In second-line add-on studies, only BMI was significant. Additional significant factors identified included race, Apo B, and treatment in long-term studies 1A and 1B, and gender and Apo B in long-term study II. Because of the very small effect sizes, these factors were not considered to be clinically meaningful. In multivariate analysis, age, BMI, and baseline FSG, HDL-C, and triglycerides remained significant factors for the short-term first-line studies, whereas in the first-line long-term studies (IA, IB, and II), all variables (including Apo B) with the exception of HDL-C and triglycerides remained statistically significant; race was additionally significant in long-term studies 1A and 1B. In the second-line add-on studies, only baseline BMI was associated with a significant decrease in FSG, and thus, multivariate analysis was not further pursued. In the second-line uptitration studies, age, BMI, and baseline FSG and triglycerides remained statistically significant when assessed in a multivariable model. Age and baseline BMI, FSG, triglycerides, and HDL-C did not appear to be related to changes from baseline in FSG in the first-line and second-line studies (Supplementary Figure 2) consistent with the very small size effects seen in univariate analyses. Correlation analysis at the final data points for the first-line long-term and second-line study analyses showed that the magnitude of associations was small (Supplementary Table 4), indicating no evidence of

clinically meaningful relations between changes in FSG and changes in LDL-C, BMI, HDL-C, triglycerides, and Apo B. Correlational analyses were not conducted for the first-line short-term studies.

Discussion

The results of these analyses suggest that the addition of ezetimibe therapy does not further increase FSG levels beyond those observed with statin monotherapy for up to 96 weeks of treatment in patients who were statin naive or on statin therapy at baseline. Both statin monotherapy and ezetimibe/statin combination therapy were associated with small, statistically significant increases in FSG levels from baseline that decreased over time. However, no significant effect was observed with ezetimibe monotherapy, and FSG elevations ≥126 mg/dl were overall infrequent in all treatment groups. Baseline factors characteristic of subjects with the metabolic syndrome or prediabetes, including numerically higher baseline BMI, baseline FSG and triglyceride levels, and numerically lower baseline HDL-C levels, were observed in patients with baseline FSG ≥126 mg/dl versus those with FSG <126 mg/dl; however, these factors were not related to increased changes from baseline in FSG. Changes from baseline in LDL-C, BMI, HDL-C, triglycerides, and Apo B were not related to changes in FSG.

The results of the present study agree with previous reports of the effects of ezetimibe as monotherapy and combined with statin therapy on glucose metabolism. For example, a significant reduction in insulin resistance and/or fatty liver was reported for ezetimibe as monotherapy or in combination with pravastatin in small clinical trials.[14–16] In a recent study including 120 Japanese patients with hypercholesterolemia at moderate to high risk for CVD, 12 weeks of treatment with ezetimibe combined with statins conferred a significant decrease in HbA1c levels (−0.3% from baseline, p <0.05) and fasting serum insulin levels, although there was no significant difference in glucose levels between treatments.[17] Moutzouri et al[18] also reported no significant changes from baseline nor significant differences between groups in FSG, HbA1c, or homeostatic model assessment β-cell function in a study comparing simvastatin 40 mg, rosuvastatin 10 mg, and ezetimibe 10 mg/simvastatin 10 mg. Limited data suggest that ezetimibe monotherapy does not result in dysregulation of glucose metabolism. In Japanese subjects with type 2 diabetes mellitus, there were no significant differences between ezetimibe and placebo in changes from baseline in HbA1c, fasting plasma glucose, or glycoalbumin over 24 weeks of treatment,[19] consistent with the first-line, long-term results shown in the present analysis. Taken together, these results strengthen and confirm that ezetimibe treatment does not result in dysregulation of glucose metabolism, either as monotherapy or when added to a statin.

Although statins have been associated with a slight increase in the incidence of diabetes, the overall benefit of statins on CVD risk and mortality outweighs this risk.[1–3] Moreover, the development of diabetes has been shown to be more limited in those predisposed to a higher diabetes risk.[20,21] In the present study, numerically higher baseline

Table 1
Baseline characteristics of subjects with fasting plasma glucose <126 mg/dL at baseline in subgroups with post-baseline fasting plasma glucose <126 or ≥126 mg/dL

	Post baseline FSG level [mg/dL]	Treatment Groups	Number of subjects	Mean BMI, kg/m² ± SD	Mean FSG, mg/dL ± SD	Mean LDL-C, mg/dL ± SD	Median TG, mg/dL ± SD	Mean HDL-C, mg/dL ± SD
1st-line short-term studies								
All Studies	<126	PBO	425	28 ± 5	93 ± 10	178 ± 23	151 ± 75	52 ± 13
		Eze	430	28 ± 6	94 ± 9	179 ± 22	154 ± 84	52 ± 13
		Statin*	1722	28 ± 5	93 ± 10	179 ± 23	157 ± 77	51 ± 12
		Eze+Statin*	1690	28 ± 5	94 ± 93	178 ± 23	157 ± 83	52 ± 13
	≥126	PBO	7	30 ± 3	105 ± 10	179 ± 14	168 ± 43	48 ± 8
		Eze	8	31 ± 4	103 ± 13	172 ± 17	188 ± 86	46 ± 5
		Statin*	47	31 ± 5	109 ± 13	176 ± 26	165 ± 107	49 ± 11
		Eze+Statin*	46	32 ± 6	109 ± 11	176 ± 17	185 ± 81	48 ± 10
1st-line long-term studies								
Study 1A	<126	All Simva†	208	28 ± 5	93 ± 10	176 ± 25	167 ± 90	49 ± 11
		Eze +All Simva†	277	28 ± 5	93 ± 10	176 ± 27	161 ± 88	52 ± 12
	≥126	All Simva†	7	30 ± 5	113 ± 15	180 ± 34	208 ± 63	45 ± 14
		Eze +All Simva†	5	29 ± 5	115 ± 8	171 ± 18	263 ± 69	42 ± 10
Study 1B	<126	All Simva†	406	28 ± 5	92 ± 11	180 ± 25	151 ± 74	51 ± 12
		Eze +All Simva†	392	28 ± 6	92 ± 11	177 ± 25	148 ± 80	53 ± 13
	≥126	All Simva†	10	31 ± 8	106 ± 12	180 ± 31	195 ± 84	53 ± 13
		Eze +All Simva†	7	32 ± 5	114 ± 6	170 ± 27	240 ± 111	44 ± 11
Study II	<126	Simva 80	339	27 ± 4	89 ± 9	319 ± 67	158 ± 100	47 ± 12
		Eze + Simva 80	332	27 ± 4	88 ± 8	318 ± 64	154 ± 90	47 ± 11
	≥126	Simva 80	15	28 ± 5	98 ± 13	302 ± 51	192 ± 112	48 ± 13
		Eze + Simva 80	15	35 ± 6	99 ± 14	322 ± 69	194 ± 176	37 ± 8
2nd-line studies								
All Add-on studies	<126	All Statin‡	779	29 ± 5	96 ± 10	139 ± 37	156 ± 75	51 ± 12
		Eze +All Statin‡	1365	29 ± 6	97 ± 10	136 ± 34	160 ± 73	49 ± 12
	≥126	All Statin‡	14	35 ± 8	104 ± 16	134 ± 52	47 ± 14	145 ± 53
		Eze +All Statin‡	24	31 ± 6	112 ± 20	130 ± 32	42 ± 8	160 ± 83
All Uptitration studies	<126	Eze +All Statin§	613	29 ± 5	97 ± 11	102 ± 21	130 ± 53	53 ± 13
		Eze +All Statin§	604	29 ± 4	97 ± 11	103 ± 27	131 ± 55	53 ± 13
	≥126	All Statin§	12	29 ± 4	108 ± 9	96 ± 14	146 ± 71	43 ± 10
		Eze +All Statin§	23	32 ± 6	112 ± 10	97 ± 19	133 ± 54	51 ± 12

BMI = body mass index; Eze = ezetimibe 10 mg; FSG = fasting serum glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PBO = placebo; SD = standard deviation; Simva = simvastatin; TC = total cholesterol; TG = triglycerides.

Note: Only subjects with baseline FSG <126 mg/dL are included in this summary table.

* Simvastatin (10, 20, 40, or 80 mg), lovastatin (10, 20, or 40 mg), pravastatin (10, 20, or 40 mg), atorvastatin (10, 20, 40, or 80 mg).

† Simvastatin (10, 20, 40, or 80 mg).

‡ Ongoing atorvastatin (10, 20, 40, 80 mg), cerivastatin (0.2, 0.3, 0.4, 0.8 mg), fluvastatin (10, 20, 40, 80 mg; 1 patient received 160 mg), lovastatin (10, 20, 40, 80 mg), pravastatin (10, 20, 40, 80 mg), and simvastatin (10, 20, 40, 80 mg).

§ Ongoing atorvastatin (10, 20, or 40 mg), then uptitrated to atorvastatin (20, 40, or 80 mg).

BMI, baseline FSG, and triglyceride levels and numerically lower baseline HDL-C levels were observed in patients with post-baseline FSG ≥126 mg/dl versus those with FSG <126 mg/dl. Although these baseline factors are generally characteristic of subjects with the metabolic syndrome or prediabetes, none were shown to be related to increased changes from baseline in FSG in this study. Conversely, a trial that compared high-dose atorvastatin with placebo demonstrated that baseline FSG level and features of the metabolic syndrome were predictive of new-onset type 2 diabetes.[21] A later analysis showed that the incidence of new-onset diabetes increased with atorvastatin 80 mg/day compared with low-dose statin therapy in patients with higher numbers of baseline diabetes risk factors (FSG >100 mg/dl, triglycerides >150 mg/dl, BMI >30 kg/m², history of hypertension).[22] Preiss et al[1] showed that the incidence of new-onset diabetes mellitus and CVD events at moderate- and high-dose statins were similar across subgroups of age and baseline HDL-C, BMI, and FSG. A meta-regression analysis demonstrated that age was associated with the risk of incident diabetes with stronger statin-attributable risk found in studies with elderly patients.[3] Statin use resulted in significant FSG increases in patients with (7 mg/dl) and without diabetes (2 mg/dl), although this increase in FSG was not related to age.[23] Of note, these other trials assessed statins and not ezetimibe, making comparison between this and the other trials difficult. However, additional study is needed to illuminate the baseline factors that may play a role in new-onset diabetes during treatment for dyslipidemia.

Studies have shown that statin use has been associated with small increases in FSG, which may vary depending on
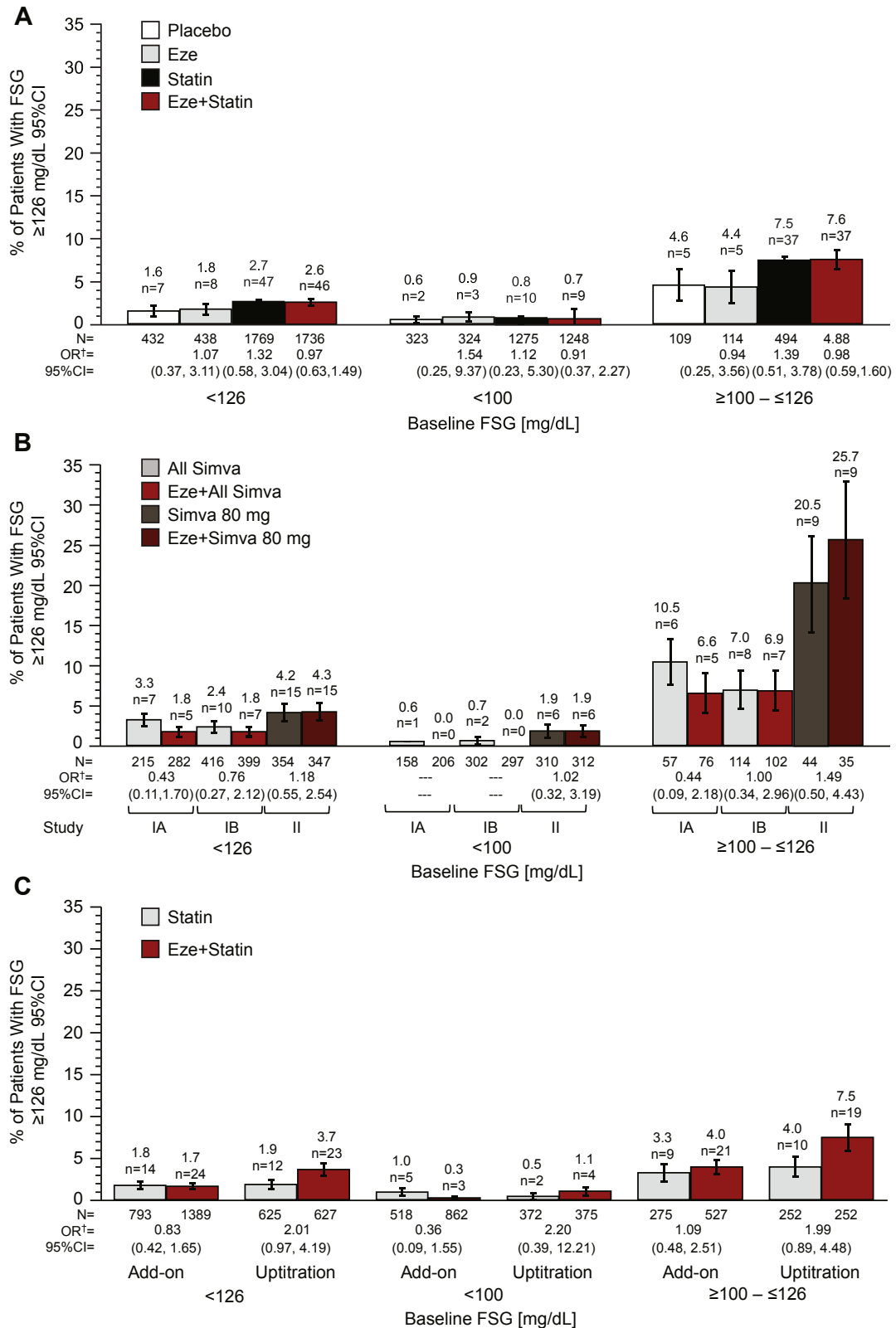
Figure 3. Proportion of subjects with FSG $\geq$126 mg/dl with baseline FSG <126, <100, and $\geq$100 to $\leq$126 mg/dl. Error bars represent 95% CIs. "†," Odds ratios (ORs) for treatment comparisons based on logistic regression adjusted for treatment, study, and baseline FSG; all comparisons are p >0.05 in the overall (<126 mg/dl), <100, and $\geq$100 to $\leq$126 mg/dl subgroups. *(A)* First-line short-term studies: ezetimibe 10 mg (Eze); placebo and statin as described in Figure 1. ORs for Eze versus placebo, statin versus placebo, and Eze + statin versus statin treatment comparisons. *(B)* First-line long-term studies: all simvastatin (Simva) and Eze + Simva as described in Figure 1, Simva 80 mg and Eze/Simva 80 mg. *(C)* Second-line studies. Add-on: Eze or placebo added to ongoing statins and uptitration: Eze + statin versus doubling the ongoing statin dose, both as described in Figure 2.

the statin (i.e., lipophilicity, potency).[24,25] The underlying cause of statin-induced glucose dysregulation is unclear, although several potential mechanisms have been proposed, including LDL-C lowering.[1,24−30] This is supported by Mendelian genetics, suggesting that new-onset diabetes is related partly to inhibition of HMG CoA reductase and is inversely associated with LDL-C levels.[31,32] However, in our analysis, LDL-C reduction was not related to increased FSG, consistent with a previous study showing that the magnitude of LDL-C reduction by various statins and doses did not influence the development of diabetes.[25] It should be noted that bile acid−binding resins that reduce LDL-C also lower FSG and HbA1c.[33] Moreover, recent genetic analyses suggest that inhibition of HMG CoA reductase, the target of statin therapy, is partly related to increased glycemic burden, whereas the LDL-C lowering and CVD risk reduction effects of NPC1L1 are not.[34] These findings support our results, which demonstrated that ezetimibe did not increase FSG levels more than statins alone.[35] Consistent with this, there was no increase in the incidence of new-onset diabetes with ezetimibe/simvastatin compared with simvastatin in the recently reported Improved Reduction of Outcomes: Vytorin Efficacy International Trial.[6,36]

Our study has some limitations. This was a post hoc analysis of pooled clinical trial data, and thus, the results are considered to be hypothesis generating. The analyses were conducted across doses; therefore, the effects of the statin intensity included in the trials were not evaluated. In the present study, FSG data were assessed; however, patient information including the diagnoses of diabetes, changes in weight and HBA1c levels, and the initiation of glucose-lowering medications during the trial were not consistently available to evaluate new-onset diabetes mellitus. Nonetheless, FSG is an important marker of type 2 diabetes mellitus recommended for screening of patients with CVD.[3] Although our study did not demonstrate a statistically significant effect of adding ezetimibe on FSG levels, it is possible that because of small sample sizes, there may have been inadequate power in some treatment groups to detect additional effects. Additionally, it was unclear as to what role baseline factors may have played in new-onset diabetes during treatment for dyslipidemia. It was also not feasible to evaluate glycemic effects in patients with diabetes in our analysis because of incomplete anti-diabetic medication histories. Although one of our studies included HeFH patients who have been shown to have a lower incidence of insulin resistance or diabetes than the general population and a low rate of new-onset diabetes with statin therapy, which could have affected the results of the analyses,[37,38] the results were generally similar across all study types, suggesting that HeFH is not associated with increased FSG.

In conclusion, these data suggest that statin therapy is associated with small increases in FSG and that addition of ezetimibe therapy does not further increase FSG levels beyond those observed with statin therapy up to 60 weeks in subjects with hypercholesterolemia or up to 96 weeks of treatment in subjects with heterozygous familial hypercholesterolemia, when co-administered in patients who are statin naive or those on stable statin therapy.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.08.071.

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