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Achieving LDL-C target levels less than 70 mg/dL may provide extra cardiovascular protection in high-risk patients: exploratory analysis of the Standard Versus Intensive Statin Therapy for Patients With Hypercholesterolemia and Diabetic Retinopathy Study

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Treat-to-target statins in high-risk patients

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Abstract

Aims

EMPATHY, a multicenter, randomized, open-label, blinded-endpoint study, assessed the benefits of intensive statin therapy on reducing cardiovascular (CV) events in type 2 diabetic patients with hyperlipidemia and retinopathy in primary prevention in Japan. Intensive therapy (targeting LDL-C <70 mg/dL) was no more effective than standard therapy (LDL-C ≥100 to <120 mg/dL) in the intention-to-treat population. However, after 3 years, intergroup difference in LDL-C was only 27.7 mg/dL, and targeted levels were achieved in <50% of patients. We hypothesized that the intergroup difference in CV events would have been statistically significant if more patients had been successfully treated to target.

Materials and methods

This exploratory post-hoc analysis focused on intergroup data from patients who achieved their target LDL-C levels. A Cox proportional hazards model was used to estimate HRs for incidence of the primary endpoint in patients who achieved target LDL-C levels in each group.

Results

Data were analyzed from 1909 patients (intensive: 703; standard: 1206) who achieved target LDL-C levels. LDL-C at 36 months was 59.7±11.6 mg/dL in the intensive group and 107.1±17.8 mg/dL in the standard group (P< .05). After adjusting for baseline prognostic factors, composite incidence of CV events or deaths associated with CV events was significantly lower in the intensive than the standard group (HR, 0.48; 95% CI, 0.28−0.82; P= .007).

Conclusions

This post-hoc analysis suggests that achieving LDL-C target levels <70 mg/dL may more effectively reduce CV events than achieving target levels ≥100 to <120 mg/dL in patients with hypercholesterolemia and diabetic retinopathy.

KEYWORDS

cardiovascular disease, clinical trial, diabetic retinopathy, dyslipidemia, lipid-lowering therapy

1 INTRODUCTION

Aging populations and modern lifestyles have been increasingly associated with higher levels of dyslipidemia and impairment of glucose metabolism in diseases such as type 2 diabetes around the world. Each of these conditions is a known risk factor for cardiovascular disease (CVD), and the risk of a cardiovascular (CV) event is even higher in patients with both conditions.[1-3] Among patients with diabetes, the CV risk is known to be further increased in patients whose diabetes is complicated by retinopathy; such patients are recognized to be at very high risk for CVD.[4,5]

The EMPATHY study is the first to assess the benefits of intensive statin therapy in type 2 diabetic patients with hyperlipidemia and diabetic retinopathy in a primary prevention setting, and also the first large-scale clinical study to evaluate the effectiveness of the treat-to-target approach. The study compared the benefits of intensive and standard statin therapy on reducing a composite of CV events or deaths from CV events (the primary endpoint). Analysis of the intention-to-treat population showed that lipid-lowering therapy targeting <70 mg/dL of low-density lipoprotein cholesterol (LDL-C) did not have a more beneficial effect on the primary endpoint than therapy targeting ≥100 to <120 mg/dL (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.67−1.07; *P*= .15).[6] These findings appeared to contradict earlier findings that indicate the benefits of lower LDL-C in patients with diabetes.[7-9]

Notably, however, the LDL-C target in the EMPATHY study was achieved by less than half of the patients in either group. In addition, a large percentage of patients on standard therapy in the original study (targeting ≥100 to <120 mg/dL) actually achieved LDL-C levels below the target range (Figure 1). These factors may have contributed to masking the efficacy of the intensive therapy.

To further investigate the efficacy of intensive therapy, we conducted additional exploratory analyses of between-group comparisons. Although previous large-scale clinical studies of statins have included exploratory (post-hoc) analyses stratified by lipid levels achieved, in all cases these subanalyses were for dose comparison studies. More importantly, none of the studies assessed whether the patients achieved prespecified goals for LDL-C levels.[10,11]

We limited our subanalyses to those patients whose LDL-C levels were within the targeted range, in order to better assess the effects of the treat-to-target approach in these patient populations. Our hypothesis was that intensive therapy in patients who achieved their target (LDL-C <70 mg/dL) would be superior to standard therapy (LDL-C target ≥100 to <120 mg/dL) in reducing the incidence of composite CV events.

2 MATERIALS AND METHODS

2.1 Study design

The EMPATHY study was conducted to determine whether intensive lipid-lowering therapy is superior to standard therapy in reducing the incidence of CV events or death from CV events in type 2 diabetic patients with hyperlipidemia and diabetic retinopathy and without a history of CVD.[6,12] The study used a multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) design. It was conducted in Japan in accordance with the Declaration of Helsinki and Japanese ethical guidelines for clinical studies. The protocol was reviewed and approved by the institutional review board of each participating center. The study was registered with the University Hospital Medical Information clinical trials registry (UMIN000003486).

The subanalysis design was based on the results of the primary analysis of the EMPATHY study, in which patients were initially treated to ≥100 to <120 mg/dL (run-in period) and were then randomized (1:1) to intensive therapy targeting LDL-C <70 mg/dL or standard therapy targeting ≥100 to <120 mg/dL (treatment period). The primary endpoint was a composite of the incidence of CV events (cardiac, cerebral, renal, and vascular events) and death from CV events, compared between the two groups.

2.2 Patients

This subanalysis was performed on data collected from patients in the EMPATHY study who achieved mean LDL-C of <70 mg/dL in the intensive therapy group in the original study (the intensive group) and ≥100 to <120 mg/dL in the standard therapy group in the original study (the standard group). The mean LDL-C for each patient was defined as the mean value of measurements obtained at scheduled visits, starting 6 months after randomization to the intensive therapy group or the standard therapy group in the original study and continuing to the final visit for those who developed no events or to the nearest day before onset for those who developed any events.

2.3 Procedures

Analysis included all patients who had at least one scheduled visit during the period starting 6 months after randomization. For reference, in comparison to these mean values, additional analysis was performed on data collected from patients who showed the target LDL-C level at their last visit. The last visit was defined to be the nearest day before onset of an event for patients who developed any events, or the date of the final visit for patients who did not develop any events during the scheduled visits, starting 6 months after randomization to a treatment group.

2.4 Outcomes

In the EMPATHY study, the primary outcome was the composite incidence of CV events, including cardiac, cerebral, renal, and vascular events, or death associated with CV events. The secondary outcomes included death from any cause; individual incidence of the events defined as CV events for the primary endpoint; incidence of stroke; change in laboratory variables related to chronic kidney disease; and safety. Primary and secondary endpoints were adjudicated by an event evaluation committee whose members were unaware of the treatment allocation. In this subanalysis, we analyzed only the primary outcome and safety because of the small number of CV events.

2.5 Statistical analysis

A Cox proportional hazards model was used to estimate HRs and 95% CIs for the incidence of the primary endpoint in patients who achieved target LDL-C levels in the intensive and standard groups. Because this additional analysis was performed in a sub-group of patients, a Cox proportional hazards model was applied, with study group and baseline influencing factors as explanatory variables, to adjust for these factors.

A stepwise method was used with the Cox proportional hazards model in the full analysis set (intention-to-treat [ITT] population) to select influencing factors; the primary endpoint was the objective variable, and prognostic factors were the explanatory variables. In this analysis, fifteen potential prognostic factors were evaluated: gender, age, body mass index (BMI), compliance with lipid-lowering agents (including statins) from enrollment, smoking status (current smoker, past smoker, non-smoker), family history of coronary artery disease, family history of cerebrovascular disease, duration of diabetes, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension,

funduscopic findings at enrollment (simple retinopathy, pre-proliferative retinopathy, proliferative retinopathy), hemoglobin A1c (HbA1c) at informed consent, LDL-C at randomization, and estimated glomerular filtration rate (eGFR) at enrollment (<60, ≥60 mL/min/1.73m^2).

3 RESULTS

3.1 Study patients

Of the 5144 patients randomized to the intensive and standard therapy groups in the EMPATHY study, a total of 1909 patients were included in this subanalysis (703 in the intensive group and 1206 in the standard group). A total of 70 patients (25 in the intensive group and 45 in the standard group) had only one scheduled visit at least 6 months after randomization.

3.2 Baseline characteristics

Some of the demographic characteristics of the patients in both groups at baseline were similar (age, family history of coronary artery disease and/or cerebrovascular disease, the presence of neuropathy and/or nephropathy, the severity of retinopathy, HbA1c levels, and eGFR), while other characteristics differed between the groups (Table 1). In comparison to the standard therapy group, a higher proportion of patients in the intensive therapy group was male (51.9% vs. 43.5%), received no lipid-lowering treatment before study enrollment (54.9% vs. 39.1%), were current smokers (19.3% vs. 16.9%), and had hypertension at enrollment (75.7% vs. 70.6%). Other differences between the two groups included higher mean BMI in the intensive group, and longer duration of diabetes and higher mean LDL-C level at enrollment in the standard group.

The demographic characteristics of the patients who were at their target LDL-C level at the last visit were similar to those who were at their mean target LDL-C level, with the exception of nephropathy (Table S1).

The proportion of patients using atorvastatin, rosuvastatin, or pitavastatin was about the same in the two groups at baseline (48.2% in the intensive group and 53.1% in the standard group), and the proportion using pravastatin, fluvastatin, or simvastatin was 51.2% and 46.7%, respectively. At the end of the study, the proportion of atorvastatin, rosuvastatin, or pitavastatin users remained nearly unchanged in the standard group (50.9%) but had risen to 98.2% in the intensive group. Dose levels at baseline were similar in the intensive and standard groups for all statins. In the intensive group, the dose increased for all statin types over the course of the study. The doses did not change for the standard group (Table S2). It should be noted that the statin dose for "intensive" therapy in Japan is lower than in the U.S. and Europe.

3.3 Laboratory values

The changes in levels of LDL-C, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) in the subanalysis are shown in Figure 2. In the intensive group, the mean level of LDL-C decreased significantly from baseline (93.7±24.0 mg/dL) to the first measurement at 6 months (66.5±13.9 mg/dL) and then remained at this level or lower (59.7±11.6 mg/dL at 36 months) to 60 months after the start of treatment (56.6±16.1 mg/dL). In the standard group, the LDL-C level after 6 months of treatment was slightly higher (109.6±17.3 mg/dL) than the baseline level (107.9±23.5 mg/dL) and remained at or near that level (107.1±17.8 mg/dL at 36 months) throughout the course of the study to 60 months after the start of treatment, when it dropped slightly to near-baseline level (107.5±22.6 mg/dL). TC showed a similar pattern to LDL-C in both groups. TG was slightly higher in the intensive group at baseline, but that gap

diminished somewhat after the start of the study. HDL-C remained substantially unchanged throughout the study in both groups.

No changes were noted for either group during the study in blood pressure, HbA1c, creatinine (Cr), or creatine kinase (CK). However, in the intensive group, high-sensitivity C-reactive protein (hsCRP) levels were significantly reduced at all time points except 60 months, and there was a significant difference between the groups in hsCRP (Table S3).

3.4 Efficacy endpoints

Since stepwise variable selection showed that eight factors were statistically related to the primary outcome among the 15 potential prognostic factors, these variables were adjusted: gender; smoking status (current smoker, past smoker, non-smoker); presence or absence of diabetic nephropathy, neuropathy, or hypertension; funduscopic findings at enrollment; HbA1c at informed consent; and eGFR at enrollment (<60, ≥60 mL/min/1.73m^2). Baseline LDL-C was not found to be a prognostic factor. We adjusted for these eight prognostic factors to estimate HRs and 95% CIs for the incidence of CV events (the primary endpoint of the EMPATHY study).

In this subanalysis, a significantly smaller proportion of patients in the intensive group (18/703 patients) experienced CV events or death associated with CV events than in the standard group (56/1206 patients) (HR, 0.48; 95% CI, 0.28−0.82; *P*= .007) (Figure 3, Table S4). This difference between the groups started at approximately 12 months after randomization. These findings remained unchanged even if baseline LDL-C was added as a ninth prognostic factor (data not shown).

In the above subanalysis, we used mean LDL-C values to determine whether each patient achieved the target range. We then repeated our analysis using LDL-C values at the last visit. We

found that the significant difference in the primary endpoint between the intensive group and the standard group was also noted in this analysis (HR, 0.43; 95% CI, 0.27−0.68; *P*< .001) (Figure 4).

3.5 Safety

The safety endpoints examined in this analysis were adverse events (AEs), serious AEs, adverse drug reactions (ADRs), and serious ADRs. There was no significant difference in the incidence rates for each of these endpoints between the two groups. The major AEs were hepatobiliary disorders, renal and urinary disorders, rhabdomyolysis, myopathy, and cancer (Table S5). Overall, the occurrence of these events in the two groups was similar except for renal and urinary disorders, which were more common in the standard group (9.2%) than in the intensive group (5.7%).

4 DISCUSSION

The EMPATHY study assessed the benefits of intensive statin monotherapy for lipid management in type 2 diabetic patients with hypercholesterolemia and diabetic retinopathy in a primary prevention setting. The study also evaluated the appropriateness of the treat-to-target approach in this patient population. Results from the EMPATHY study showed that intensive lipid-lowering therapy targeting <70 mg/dL of LDL-C was no more effective in reducing a composite of incidence of CV events or death from CV events than standard therapy targeting ≥100 to <120 mg/dL (HR, 0.84; 95% CI, 0.67−1.07).[6] However, the ITT method may lead to underestimation of intergroup differences in efficacy in situations where the treatment goals have not been properly achieved. In our study, in particular, less than half of the patients in each group

had LDL-C within their target range, and nearly half in the standard group had LDL-C below the target.

Our planned between-group difference in LDL-C was about 40 mg/dL (< 70 mg/dL for the intensive therapy group vs. about 110 mg/dL for the standard therapy group) in the original study, with a predicted HR of 0.65. However, after 3 years of treatment, the actual LDL-C difference was 27.7 mg/dL (76.5 mg/dL vs. 104.1 mg/dL). We hypothesized that the smaller-than-expected difference may have been due at least in part to the unexpectedly low number of patients who achieved their LDL target. Our exploratory post-hoc analyses were designed to investigate this hypothesis by comparing findings between patients whose LDL-C was within the target range for their group.

The subanalysis involved differences in some prognostic factors between the patient group meeting their target LDL-C levels of <70 mg/dL under intensive therapy and the patient group meeting their LDL-C levels of 100 to 120 mg/dL under standard therapy. We adjusted for eight factors that had been identified as potentially affecting the primary endpoint: gender (male, female), smoking status, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings, baseline HbA1c, and eGFR. We also found some significant intergroup differences for BMI, use of lipid-lowering agents, use of statins, duration of diabetes, and baseline LDL-C level. However, since they did not affect the primary endpoints in this study, we did not adjust for those factors. After adjusting for the eight selected prognostic factors, the results of the analysis showed that the intensive lipid-lowering therapy targeting <70 mg/dL LDL-C significantly reduced the primary endpoint (the composite of incidence of CV events or death from CV events). Due to the low number of events (74), in this analysis we limited the number of factors, using a stepwise method for

adjustment in the analytical model. We did this to avoid potentially non-reproducible and unstable results. For further confirmation, we also performed an analysis with all variables included; similar results were obtained (HR, 0.51; 95% CI, 0.29-0.89, *P*< .05) (Table S6). Safety events occurred at approximately the same rate in the two groups.

We used mean values for LDL-C in patients who achieved their target levels because we thought it was important to ensure that patients were exposed to a specific concentration of LDL-C for a certain period of time. Our results, although exploratory, suggest that achieving a target of <70 mg/dL LDL-C lowers the risk of CV events significantly more than achieving a target of 100 to 120 mg/dL. For reference, we have also provided a summary of our findings for the proportion of patients who achieved their target LDL-C level at the last visit. Results were similar to those based on mean values.

In the main results paper, we performed post-hoc analysis, which involved classifying patient data into four subcategories (mean LDL-C <70, 70 to <100, 100 to <120, and ≥120 mg/dL during the study). That analysis tended to show event prevention at lower LDL-C values in both the intensive and standard therapy groups in the original study[6]; the results of the present subanalysis are consistent with those findings. This fact supports the reliability of our subanalysis. Although exploratory, we believe that these findings could meaningfully impact lipid management in clinical practice for the primary prevention of CV events in type 2 diabetic patients with hyperlipidemia and diabetic retinopathy.

Previous large-scale clinical studies of statins have also used LDL-C levels as a basis for post-hoc subanalyses,[8-11] and usefulness was demonstrated in groups achieving lower target levels. However, all of these subanalyses were in dose-comparison studies, and none assessed whether patients had achieved their target LDL-C levels. To the best of our knowledge, no other

analyses have been reported that show the effect of specified target LDL-C levels using statin monotherapy on the occurrence of CV events or CV-related deaths. Although this is an exploratory analysis, our data are valuable when assessing the importance of the treat-to-target approach in lipid management.

In the ITT analysis for the EMPATHY study, the difference in LDL-C between the two groups was 27.7 mg/dL, and the HR for the primary endpoint was 0.84 (95% CI, 0.67−1.07; *P*= .15).[6] In this subanalysis, LDL-C at 36 months was 59.7 mg/dL in the intensive group and 107.1 mg/dL in the standard group, a difference of 47.4 mg/dL (1.23 mmol/L) between the two groups, and the HR was 0.48 (95% CI, 0.28−0.82; *P*= .007). In this subanalysis, aggressive treatment with the goal of lowering LDL-C to 70 mg/dL was clearly effective in reducing the number of occurrences of the primary endpoint. The actual difference in LDL-C exceeded the planned difference of approximately 40 mg/dL, which meant that the actual HR was also higher than the planned HR of 0.65. The main analysis did not detect a significant difference in primary endpoint occurrence between the two groups. These subanalysis findings indicate that we were unable to obtain significant results from the main analysis because of failure to achieve target LDL-C levels.

No major differences were noted between groups in the incidence of AEs or ADRs. It thus appears unlikely that specific safety concerns will occur when intensive statin monotherapy is used to reduce LDL-C below 70 mg/dL. We found no marked increase in cerebral hemorrhage in the intensive group (2 patients in the intensive group, 1 patient in the standard group), nor any increase in HbA1c associated with statin use in this study.

These study findings are limited because they are derived from an exploratory analysis which included only those patients whose LDL-C was within the target range for their assigned

group: LDL-C <70 mg/dL in the intensive therapy group in the original study and ≥100 to <120 mg/dL in the standard therapy group in the original study. In the EMPATHY study, less than 50% of patients reached their target LDL-C. This can be attributed in part to the fact that over half of the investigators were general practitioners, rather than lipid specialists. Many Japanese physicians who treat hyperlipidemia as part of their routine clinical practice, are not lipid management experts and are concerned about adverse effects such as intracranial hemorrhage from intensive LDL-C lowering. Such concerns may have affected some of the investigators in this study, making them reluctant to prescribe high-dose statin therapy even when the protocol stipulated the aggressive target of 70 mg/dL. Due to the small number of events, secondary endpoints were not assessed (Table S4). In addition, although we detected and adjusted for eight prognostic factors, there may be additional unmeasured factors or confounding factors that should be considered.

In conclusion, the results from this exploratory post-hoc analysis suggest that achievement of LDL-C levels below 70 mg/dL is associated with more effective reduction of CV events than levels of 100 to 120 mg/dL in type 2 diabetic patients with retinopathy and hyperlipidemia who are at high coronary risk.[4,5] There were no major increases in AEs or ADRs when statin monotherapy was used to reduce LDL-C below 70 mg/dL. Our results indicate the importance of targeting LDL-C below 70 mg/dL, and then meeting that target consistently, for the reduction of CV events in this high-risk patient population. However, this analysis was exploratory and must be substantiated in randomized clinical trials. A feasible approach is also needed for achieving these target levels in a clinical setting.

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Conflict of interest

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H.I., I.K., H.D., H.F., S.K., T.Muro., K.Ut., and T.Y. contributed to design, conduct/data collection, and writing the manuscript. M.T. contributed to conduct/data collection, analysis, and writing the manuscript. T.A., J.H., T.I., A.K., M.Ki., T.K., M.Ku., K.No., S.O., Y.Sa., Y.Se., T.S., S.Sh., H.T., S.Y., and N.Y. contributed to writing the manuscript. Y.E. contributed to conduct/data collection. K.H., S.It., S.Su., K.Ue., K.Yok., K.Na., and R.N. contributed to design and writing the manuscript. S.Is., K.K., M.S., Y.T., M.Ya., K.Yos., and M.Yo. contributed to conduct/data collection and writing the manuscript. K.M. contributed to design and conduct/data collection. T.Mura. contributed to design.

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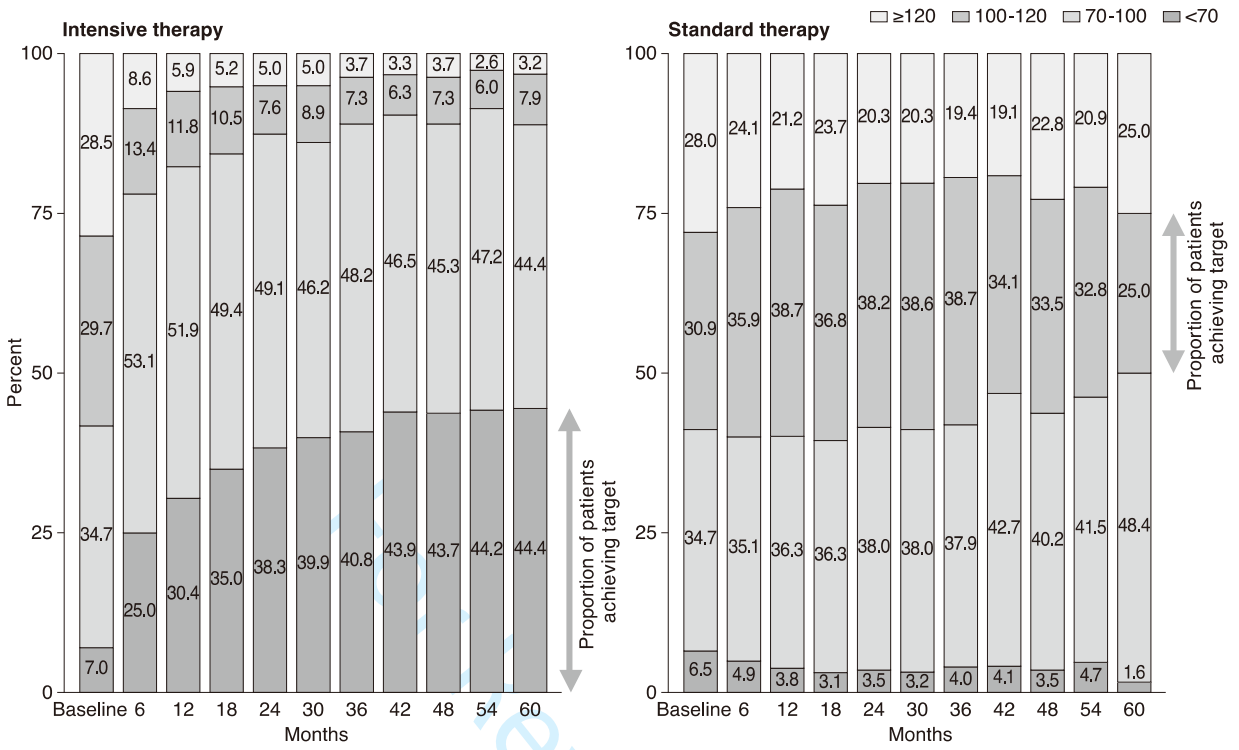

FIGURE 1 Distribution of LDL-C in the Intensive and Standard Therapy Groups in the Original Study

Abbreviations: LDL-C, low-density lipoprotein cholesterol.

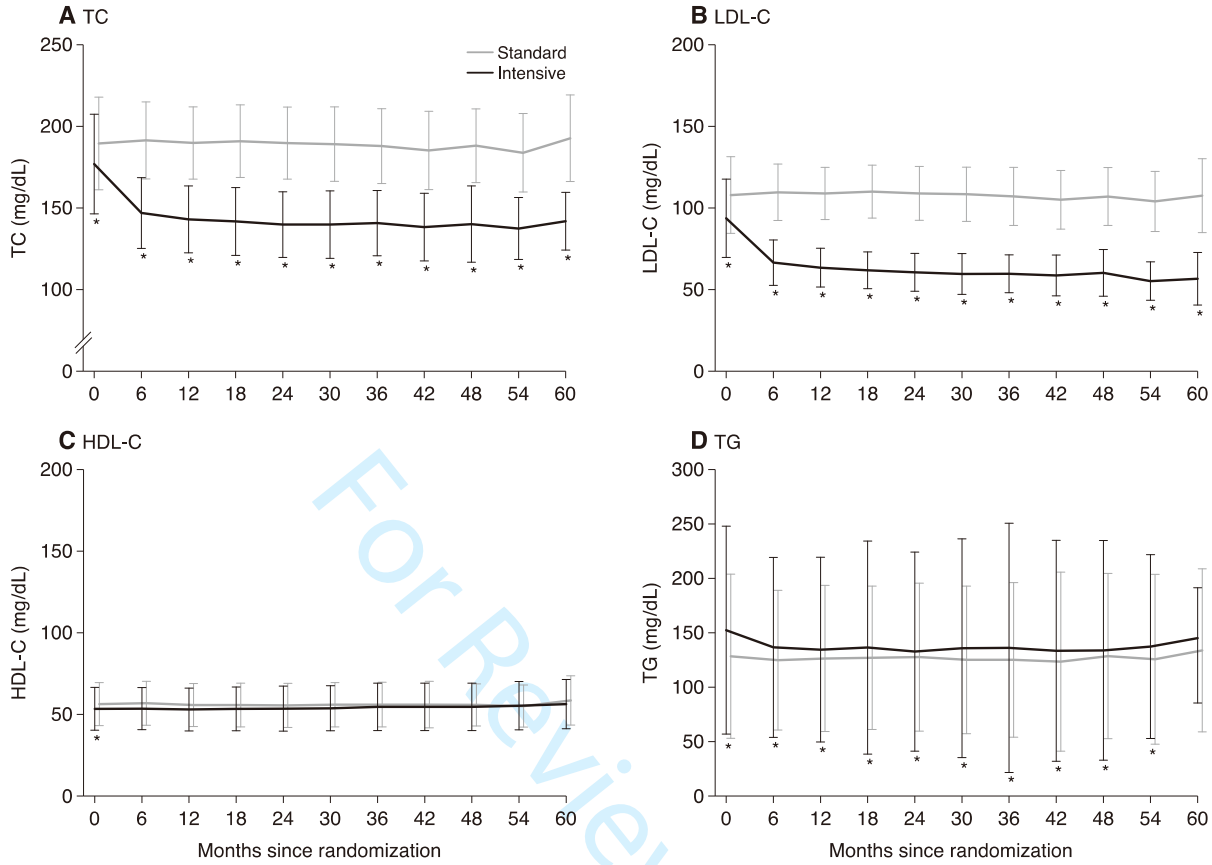

FIGURE 2 Changes in Lipid Parameters Over Time

Data are mean values and SD.

*P< .05, calculated using a mixed model repeated measures (MMRM) approach. The model included group, observation time point, and interaction between group and observation time point as fixed effects.

Abbreviations: TC, indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; SD, standard deviation.

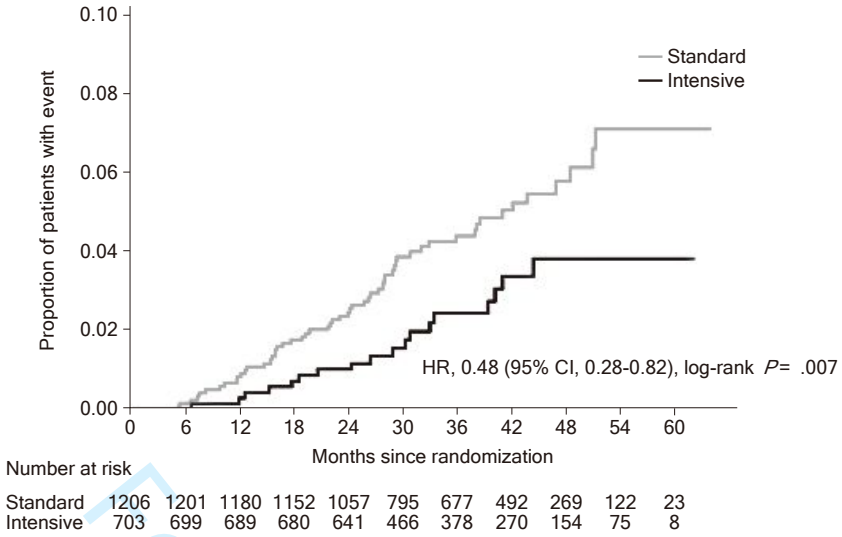

FIGURE 3 Cumulative Event Curve for the Primary Endpoint in the Intensive and Standard Groups (Patients Achieving LDL-C Target, Mean Value)

HR (95% CI) and *P* value were estimated using a stratified Cox proportional hazards model with gender (male, female), smoking status, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings, and baseline hemoglobin A1c (<8.4, ≥8.4%) and estimated glomerular filtration rate (<60, ≥60 [mL/min/1.73m^2]) as covariates.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval.

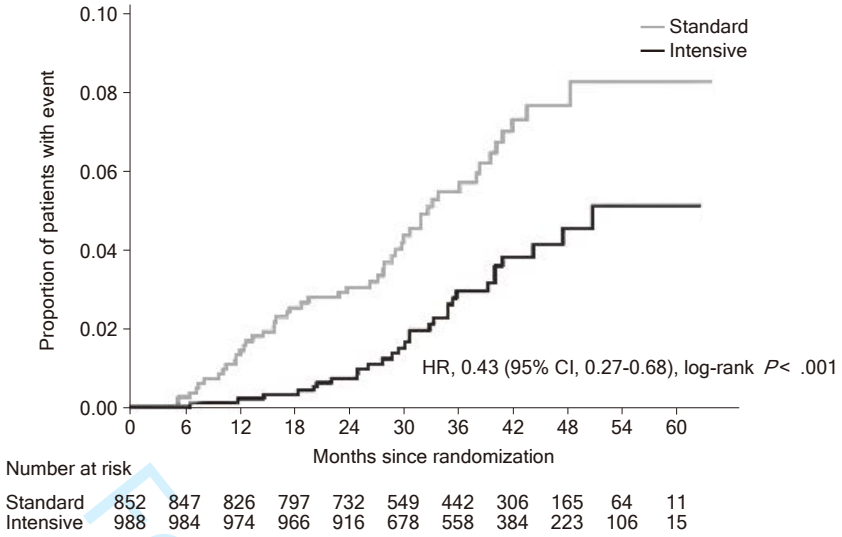

FIGURE 4 Cumulative Event Curve for the Primary Endpoint in the Intensive and Standard Groups (Patients Achieving LDL-C Target at the Last Visit)

HR (95% CI) and *P* value are estimated using a Cox proportional hazards model with gender (male, female), smoking status, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings, and baseline hemoglobin A1c [<8.4, ≥8.4 (NGSP%)] and estimated glomerular filtration rate [< 60, ≥60 (mL/min/1.73m^2)] as covariates.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval.

TABLE 1 Baseline Demographic Characteristics (Potential Prognostic Factors): for Patients Achieving LDL-C Target in Mean Value

	Intensive group (n=703)	**Standard group (n=1206)**	***P* value [a]**
Male	365 (51.9)	525 (43.5)	*P*c< .001
Age, y†	62.7 (10.8)	63.6 (10.1)	*P*w= .23
Body-mass index, kg/m²‡	26.2 (4.2)	25.5 (4.2)	*P*w< .001
Lipid-lowering agents§			
None	386 (54.9)	472 (39.1)	*P*c< .001
1 drug	316 (45.0)	733 (60.8)	
≥2 drugs	1 (0.1)	1 (0.1)	
Statin§			*P*c< .001
No	428 (60.9)	511 (42.4)	
Yes	275 (39.1)	695 (57.6)	
Smoking ¶	136 (19.3)	204 (16.9)	*P*c= .01
Family history			
Coronary artery disease	86 (12.2)	165 (13.7)	*P*c= .37
Cerebrovascular disease	146 (20.8)	261 (21.6)	*P*c= .65

Duration of diabetes, y	12.3 (8.3)	13.4 (9.1)	*P*w= .02
Diabetic complications			
Neuropathy	217 (30.9)	382 (31.7)	*P*c= .71
Nephropathy	385 (54.8)	614 (50.9)	*P*c= .10
Hypertension	532 (75.7)	852 (70.6)	*P*c= .02
Funduscopy††			
Simple retinopathy	454 (64.6)	785 (65.1)	*P*c= .99
Preproliferative retinopathy	141 (20.1)	243 (20.1)	
Proliferative retinopathy	103 (14.7)	170 (14.1)	
Other‡‡	3 (0.4)	5 (0.4)	
HbA1c, %†	7.71 (1.20)	7.71 (1.19)	*P*w= .91
LDL-C, mg/dL§§	93.7 (24.0)	107.9 (23.5)	*P*w< .001
eGFR, mL/min/1.73m^2	75.1 (21.7)	74.6 (19.6)	*P*w= .81

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Data are mean (SD) or n (%).

[a] *P*w, Wilcoxon rank sum test; *P*c, Chi-square test without Yates' correction.

† Values were obtained at the time of consent.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Values were obtained at provisional enrollment.

¶ Not including past smokers.

†† Diagnosed by ophthalmologists based on the modified Davis classification.

‡‡ Includes 5 patients who had a history of laser therapy but no funduscopic findings at enrollment. The remaining 3 patients were found to be retinopathy-negative after enrollment.

§§ Values were calculated using the Friedewald equation; LDL-C = total cholesterol (TC) - [high-density lipoprotein cholesterol (HDL-C) + triglyceride (TG)/5].

Supporting Information

Achieving LDL-C target levels less than 70mg/dL may provide extra cardiovascular protection in high-risk patients: exploratory analysis of the Standard Versus Intensive Statin Therapy for Patients With Hypercholesterolemia and Diabetic Retinopathy Study

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Supplementary Tables

TABLE S1 Baseline Demographic Characteristics (Potential Prognostic Factors): for Patients Achieving LDL-C Target at the Last Visit

	Intensive group (n=988)	Standard group (n=852)	*P* value [a]
Male	487 (49.3)	381 (44.7)	*P*c= .05
Age, y[†]	62.7 (10.6)	63.8 (10.1)	*P*w= .04
Body-mass index, kg/m^{2}[‡]	26.0 (4.1)	25.5 (4.2)	*P*w= .008
Lipid-lowering agent[§]			
None	509 (51.5)	325 (38.1)	*P*c< .001
1 drug	477 (48.3)	526 (61.7)	
≥2 drugs	2 (0.2)	1 (0.1)	
Statin[§]			*P*c< .001
No	561 (56.8)	348 (40.8)	
Yes	427 (43.2)	504 (59.2)	
Smoking[¶]	199 (20.1)	150 (17.6)	*P*c= .29
Family history			
Coronary artery disease	126 (12.8)	104 (12.2)	*P*c= .72
Cerebrovascular disease	198 (20.0)	186 (21.8)	*P*c= .35
Duration of diabetes, y	12.5 (8.3)	13.2 (9.2)	*P*w= .23
Diabetic complications			
Neuropathy	303 (30.7)	273 (32.0)	*P*c= .53
Nephropathy	543 (55.0)	426 (50.0)	*P*c= .03
Hypertension	727 (73.6)	615 (72.2)	*P*c= .50
Funduscopy[††]			
Simple retinopathy	659 (66.7)	568 (66.7)	*P*c= .50
Preproliferative retinopathy	186 (18.8)	177 (20.8)	
Proliferative retinopathy	137 (13.9)	101 (11.9)	
Other[‡‡]	4 (0.4)	3 (0.4)	
HbA1c, %[†]	7.8 (1.2)	7.7 (1.2)	*P*w= .07
LDL-C, mg/dL[§§]	98.5 (24.5)	107.8 (24.7)	*P*w< .001
eGFR, mL/min/1.73m^{2}	74.9 (20.7)	75.0 (19.1)	*P*w= .82

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SD, standard deviation.
Data are mean (SD) or n (%).
[a] *P*w, Wilcoxon rank sum test; *P*c, Chi-square test without Yates' correction.
[†] Values were obtained at the time of consent.
[‡] The body-mass index is the weight in kilograms divided by the square of the height in meters.
[§] Values were obtained at provisional enrollment.
[¶] Not including past smokers.
[††] Diagnosed by ophthalmologists based on the modified Davis classification.
[‡‡] Includes 5 patients who had a history of laser therapy but no funduscopic findings at enrollment. The remaining 2 patients were found to be retinopathy-negative after enrollment.
[§§] Values were calculated using the Friedewald equation; LDL-C = total cholesterol (TC) - [high-density lipoprotein cholesterol (HDL-C) + triglyceride (TG)/5].

TABLE S2 Mean Dose by Statin Type at Baseline and Last Visit

Statin type	Intensive group (n=703)		Standard group (n=1206)	
	Baseline	Last visit	Baseline	Last visit
Pravastatin	7.6	8.9	7.7	7.7
Fluvastatin	22.3	-	20.8	20.2
Simvastatin	5.3	5.0	5.1	5.0
Atorvastatin	8.2	13.2	7.9	7.5
Rosuvastatin	2.6	6.4	2.6	3.3
Pitavastatin	1.3	2.4	1.4	1.5

Data are mg.

TABLE S3 Non-lipid Parameters Over Time

Parameters		Intensive group (n=703)	Standard group (n=1204)	*P* value
Systolic blood pressure, mmHg	Baseline†	136.3±16.9 (696)	134.0±15.9 (1196)	
	Month 6	134.0±17.1 (697)	134.0±15.8 (1197)	-
	Month 12	132.5±15.4 (667)	134.4±16.4 (1158)	-
	Month 18	133.4±15.3 (657)	134.5±16.1 (1102)	-
	Month 24	132.5±15.8 (652)	135.0±16.4 (1078)	-
	Month 30	132.8±16.5 (458)	135.0±16.3 (792)	-
	Month 36	133.9±15.9 (368)	134.4±16.8 (686)	-
	Month 42	133.3±15.0 (272)	134.4±17.3 (513)	-
	Month 48	133.3±15.0 (163)	135.2±16.4 (289)	-
	Month 54	133.6±15.2 (76)	134.6±17.5 (156)	-
	Month 60	142.2±24.5 (16)	134.6±17.0 (46)	-
Diastolic blood pressure, mmHg	Baseline†	76.0±12.2 (696)	73.8±10.9 (1196)	
	Month 6	74.7±12.0 (697)	73.5±10.9 (1197)	-
	Month 12	73.9±11.1 (667)	73.7±11.1 (1158)	-
	Month 18	73.2±11.3 (657)	73.7±11.0 (1102)	-
	Month 24	72.8±11.0 (652)	73.6±11.0 (1078)	-
	Month 30	72.3±11.3 (458)	72.8±11.3 (792)	-
	Month 36	72.7±11.9 (368)	72.5±11.1 (686)	-
	Month 42	72.7±11.0 (272)	72.5±11.7 (513)	-
	Month 48	72.3±11.3 (163)	71.4±10.4 (289)	-
	Month 54	72.6±11.7 (76)	70.5±9.8 (156)	-
	Month 60	73.9±13.9 (16)	71.8±13.6 (46)	-
HbA1c, %	Baseline†	7.5±1.2 (696)	7.5±1.2 (1190)	
	Month 6	7.5±1.2 (693)	7.5±1.2 (1193)	-
	Month 12	7.5±1.1 (674)	7.4±1.1 (1160)	-
	Month 18	7.4±1.2 (661)	7.4±1.2 (1103)	-
	Month 24	7.4±1.1 (651)	7.4±1.2 (1093)	-
	Month 30	7.5±1.2 (458)	7.4±1.2 (785)	-
	Month 36	7.4±1.1 (373)	7.4±1.1 (690)	-
	Month 42	7.4±1.2 (276)	7.3±1.0 (508)	-
	Month 48	7.4±1.1 (163)	7.3±1.0 (278)	-
	Month 54	7.4±1.3 (76)	7.3±1.3 (148)	-
	Month 60	7.1±0.8 (13)	7.1±1.1 (44)	-
Cr, mg/dL	Baseline†	0.8±0.3 (701)	0.7±0.2 (1198)	
	Month 6	0.8±0.3 (685)	0.8±0.2 (1175)	-
	Month 12	0.8±0.3 (662)	0.8±0.3 (1138)	-
	Month 18	0.8±0.3 (640)	0.8±0.3 (1086)	-
	Month 24	0.8±0.3 (639)	0.8±0.3 (1066)	-
	Month 30	0.8±0.3 (449)	0.8±0.3 (773)	-
	Month 36	0.8±0.3 (365)	0.8±0.3 (675)	-
	Month 42	0.9±0.4 (267)	0.8±0.3 (477)	-
	Month 48	0.9±0.4 (158)	0.8±0.3 (273)	-
	Month 54	0.9±0.5 (71)	0.8±0.3 (141)	-
	Month 60	1.5±2.1 (10)	0.8±0.4 (40)	-

TABLE S3 Non-lipid Parameters Over Time (Continued)

CK, IU/L	Baseline†	123.4±83.4 (658)	122.0±98.7 (1124)	
	Month 6	121.1±78.6 (636)	128.8±120.6 (1103)	-
	Month 12	132.0±169.4 (643)	127.9±105.4 (1084)	-
	Month 18	122.2±77.2 (623)	121.9±82.3 (1037)	-
	Month 24	122.2±89.3 (622)	126.4±108.9 (1040)	-
	Month 30	118.7±84.4 (438)	128.6±103.6 (741)	-
	Month 36	119.0±83.9 (354)	127.0±129.5 (651)	-
	Month 42	115.4±67.4 (259)	118.8±80.0 (455)	-
	Month 48	114.2±57.8 (151)	118.7±82.3 (261)	-
	Month 54	111.8±76.3 (66)	117.5±81.4 (135)	-
	Month 60	118.3±118.1 (10)	109.1±58.0 (36)	-
log hsCRP	Baseline†	6.4±1.2 (698)	6.2±1.2 (1197)	
	Month 12	6.2±1.2 (657)	6.2±1.2 (1133)	< .001
	Month 24	6.1±1.2 (627)	6.3±1.3 (1045)	< .001
	Month 36	6.1±1.3 (353)	6.2±1.2 (655)	< .001
	Month 48	6.0±1.3 (148)	6.3±1.2 (254)	= .001
	Month 60	6.3±1.8 (9)	6.4±1.0 (35)	.18

Abbreviations: HbA1c, hemoglobin A1c; Cr, serum creatinine; CK, creatine kinase; hsCRP, high-sensitivity C-reactive protein; SD, standard deviation.
Data are Mean±SD (n).
† Baseline: At the time of enrollment except for HbA1c, which was measured at the time of consent
P value of hsCRP was calculated using a mixed-effects model repeated measures (MMRM) approach. The model included group, observation time point, and interaction between group and observation time point as fixed effects.

TABLE S4 Events for Primary and Secondary Endpoints

	Intensive group (n=703)	Standard group (n=1206)
Primary endpoint	18	56
Secondary endpoint		
All deaths	8	12
Cardiac events	8	22
Cerebral events	5	13
Renal events	6	22
Vascular events	0	2
Stroke	7	13
Cerebral infarction	5	12
Cerebral hemorrhage	2	1
Subarachnoid hemorrhage	0	0

Cardiac events: myocardial infarction, unstable angina requiring unscheduled hospitalization, or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting).
Cerebral events: cerebral infarction or cerebral revascularization.
Renal events: initiation of chronic dialysis, increase in serum creatinine level by at least 2-fold (and >1.5 mg/dL).
Vascular events: aortic disease or peripheral artery disease (aortic dissection, mesenteric artery thrombosis, severe lower limb ischemia [ulceration], revascularization, or finger/lower limb amputation caused by arteriosclerosis obliterans.

TABLE S5 Adverse Events and Key Safety Data

		Intensive group		Standard group		*P* value
		n of events	n of patients (%)	n of events	n of patients (%)	
Adverse events	Total	2067	534 (76.0)	4264	942 (78.2)	.26
	Serious	189	127 (18.1)	440	261 (21.7)	.06
Adverse drug reactions	Total	72	52 (7.4)	104	82 (6.8)	.64
	Serious	7	7 (1.0)	12	10 (0.8)	.80
Major adverse events						
Hepatobiliary disorders	Total	18	18 (2.6)	26	25 (2.1)	.52
	Serious	4	4 (0.6)	8	8 (0.7)	1.00
Renal and urinary disorders	Total	45	40 (5.7)	126	111 (9.2)	.006
	Serious	3	3 (0.4)	10	10 (0.8)	.39
Rhabdomyolysis	Total	1	1 (0.1)	1	1 (0.1)	1.00
	Serious	1	1 (0.1)	0	0 (0)	.37
Myopathy	Total	0	0 (0)	0	0 (0)	–
	Serious	0	0 (0)	0	0 (0)	–
Cancer[†]	Total	39	34 (4.8)	63	55 (4.6)	.82
	Serious	27	22 (3.1)	48	41 (3.4)	.79

P value was calculated using the Fisher Exact Test.
[†] Including neoplasms benign, malignant, and unspecified including cysts and polyps.

TABLE S6 Intergroup Analysis of Primary Endpoint in Patients Who Achieved Target LDL-C (including all covariates)

	HR	95%CI		*P* value
		Lower limit	Upper limit	
Patients who achieved target LDL-C (mean) †	0.51	0.29	0.89	.018

Abbreviations: HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval; HbA1c, hemoglobin A1c.
HR (95% CI) and *P* value were estimated using a stratified Cox proportional hazards model with gender (male, female), age, body mass index, adherence to lipid-lowering agent (including statins), smoking status, family history of coronary artery disease, family history of cerebrovascular disease, duration of type 2 diabetes mellitus, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings, HbA1c (<8.4, ≥8.4) at the time of consent, baseline LDL-C, and estimated glomerular filtration rate (<60, ≥60 [mL/min/1.73m^2]) as covariates.
† LDL-C <70mg/dL in the intensive group (n=703) and LDL-C ≥100 to <120mg/dL in the standard group (n=1206).

Table for referees only

Intergroup Analysis of Primary Endpoint in Patients Who Achieved Target LDL-C (Including all covariates)

	HR	95%CI		P-value
		Lower limit	Upper limit	
Patients who achieved target LDL-C (mean)†	0.51	0.29	0.89	.018
Patients who achieved target LDL-C (last)‡	0.43	0.27	0.70	.001
Patients who achieved target LDL-C (mean)§	0.52	0.31	0.87	.012
Patients who achieved target LDL-C (last)¶	0.62	0.40	0.95	.027
Patients who archived target LDL-C (month 12)††	0.78	0.44	1.39	.391
Patients who achieved target LDL-C (Landmark analysis, month 12)††	0.80	0.44	1.42	.438

Abbreviations: HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval, HbA1c; hemoglobin A1c.

HR (95% CI) and P value were estimated using a stratified Cox proportional hazards model with gender (male, female), age, body mass index, adherence to lipid-lowering agent (including statins), smoking status, family history of coronary artery disease, family history of cerebrovascular disease, duration of diabetes, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings, HbA1c (<8.4, ≥8.4) at the time of consent, baseline

LDL-C, and estimated glomerular filtration rate (<60, ≥60 [mL/min/1.73m^2]) as covariates.

†LDL-C <70mg/dL in the intensive group (n=703) and LDL-C ≥100 to <120mg/dL in the standard group (n=1206).

‡LDL-C <70mg/dL in the intensive group (n=988) and LDL-C ≥100 to <120mg/dL in the standard group (n=852).

§LDL-C <70 mg/dL in the intensive group (n=703) and LDL-C <120 mg/dL in the standard group (n=2094).

¶LDL-C <70 mg/dL in the intensive group (n=988) and LDL-C <120 mg/dL in the standard group (n=1962).

††LDL-C <70 mg/dL in the intensive group (n=666) and LDL-C <120 mg/dL in the standard group (n=1742).

Article Type: Original Article

Title:

Achieving LDL-C target levels less than 70 mg/dL may provide extra cardiovascular protection in high-risk patients: exploratory analysis of the Standard Versus Intensive Statin Therapy for Patients With Hypercholesterolemia and Diabetic Retinopathy Study

Running title:

Treat-to-target statins in high-risk patients

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Abstract

Aims

EMPATHY, a multicenter, randomized, open-label, blinded-endpoint study, assessed the benefits of intensive statin therapy on reducing cardiovascular (CV) events in type 2 diabetic patients with hyperlipidemia and ~~diabetic~~ retinopathy in ~~a~~ primary prevention ~~setting~~ in Japan. Intensive therapy (targeting ~~low-density lipoprotein cholesterol [~~LDL-C~~]~~ <70 mg/dL) was no more effective than standard therapy (LDL-C ≥100 to <120 mg/dL) in the intention-to-treat population. However, after 3 years, ~~the~~ intergroup difference in LDL-C was only 27.~~6~~7 mg/dL, and targeted levels were achieved in ~~less than~~ <50% of patients. We hypothesized that the intergroup difference in CV events would have been statistically significant if more patients had been successfully treated to target.

Materials and methods

This exploratory post-hoc analysis focused on intergroup data from patients who achieved their target LDL-C levels. A Cox proportional hazards model was used to estimate HRs for incidence of the primary endpoint in patients who achieved target LDL-C levels in each group.

Results

Data were analyzed from 1909 patients (intensive: 703; standard: 1206) who achieved target LDL-C levels ~~were analyzed~~. LDL-C at 36 months was 59.7±11.6 mg/dL in the intensive group and 107.1±17.8 mg/dL in the standard group (P< .05). After adjusting for baseline prognostic factors, ~~the~~ composite incidence of CV events or deaths associated with CV events was

significantly lower ~~with~~in the intensive ~~therapy~~ than the standard ~~therapy~~group (HR, 0.48; 95% CI, 0.28−0.82; *P*= .007).

Conclusions

~~Achieving~~This post-hoc analysis suggests that achieving LDL-C target levels <70 mg/dL may more effectively reduce CV events than achieving target levels ≥100 to <120 mg/dL in patients with hypercholesterolemia and diabetic retinopathy.

KEYWORDS

cardiovascular disease, clinical trial, diabetic retinopathy, ~~dyslipidaemia~~dyslipidemia, lipid-lowering therapy

1 INTRODUCTION

Aging populations and modern lifestyles have been increasingly associated with higher levels of dyslipidemia and impairment of glucose metabolism in diseases such as type 2 diabetes around the world. Each of these conditions is a known risk factor for cardiovascular disease (CVD), and the risk of a cardiovascular (CV) event is even higher in patients with both conditions.[1-3] Among patients with diabetes, the CV risk is known to be further increased in patients whose diabetes is complicated by retinopathy; such patients are recognized to be at very high risk for CVD.[4,5]

The EMPATHY study is the first to assess the benefits of intensive statin therapy in type 2 diabetic patients with hyperlipidemia and diabetic retinopathy in a primary prevention setting, and also the first large-scale clinical study to evaluate the effectiveness of the treat-to-target approach. The study compared the benefits of intensive and standard statin therapy on reducing a composite of CV events or deaths from CV events (the primary endpoint). Analysis of the intention-to-treat population showed that lipid-lowering therapy targeting <70 mg/dL of low-density lipoprotein cholesterol (LDL-C) did not have a more beneficial effect on the primary endpoint than therapy targeting ≥100 to <120 mg/dL (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.67−1.07; *P*= .15).[6] These findings appeared to contradict earlier findings that indicate the benefits of lower LDL-C in patients with diabetes.[7-9]

Notably, however, the LDL-C target in the EMPATHY study was achieved by less than half of the patients in either group. In addition, a large percentage of patients on standard therapy in the original study (targeting ≥100 to <120 mg/dL) actually achieved LDL-C levels below the target range (Figure 1). These factors may have contributed to masking the efficacy of the intensive therapy.

To further investigate the efficacy of intensive therapy, we conducted additional exploratory analyses of between-group comparisons. Although previous large-scale clinical studies of statins have included exploratory (post-hoc) analyses stratified by lipid levels achieved, in all cases these subanalyses were for dose comparison studies. More importantly, none of the studies assessed whether the patients achieved prespecified goals for LDL-C levels.[10,11]

We limited our subanalyses to those patients whose LDL-C levels were within the targeted range, in order to better assess the effects of the treat-to-target approach in these patient populations. Our hypothesis was that intensive therapy in patients who achieved their target (LDL-C <70 mg/dL) would be superior to standard therapy (LDL-C target ≥100 to <120 mg/dL) in reducing the incidence of composite CV events.

2 MATERIALS AND METHODS

2.1 Study design

The EMPATHY study was conducted to determine whether intensive lipid-lowering therapy is superior to standard therapy in reducing the incidence of CV events or death from CV events in type 2 diabetic patients with hyperlipidemia and diabetic retinopathy and without a history of CVD.[6,12] The study used a multicenter, prospective, randomized, open-label, blinded endpoint (PROBE) design. It was conducted in Japan in accordance with the Declaration of Helsinki and Japanese ethical guidelines for clinical studies. The protocol was reviewed and approved by the institutional review board of each participating center. The study was registered with the University Hospital Medical Information clinical trials registry (UMIN000003486).

The subanalysis design was based on the results of the primary analysis of the EMPATHY study, in which patients were initially treated to ≥100 to <120 mg/dL (run-in period) and were then randomized (1:1) to intensive therapy targeting LDL-C <70 mg/dL or standard therapy targeting ≥100 to <120 mg/dL (treatment period). The primary endpoint was a composite of the incidence of CV events (cardiac, cerebral, renal, and vascular events) and death from CV events, compared between the two groups.

2.2 Patients

This subanalysis was performed on data collected from patients in the EMPATHY study who achieved mean LDL-C of <70 mg/dL in the intensive therapy group in the original study (the intensive group) and ≥100 to <120 mg/dL in the standard therapy group in the original study (the standard group). The mean LDL-C for each patient was defined as the mean value of measurements obtained at scheduled visits, starting 6 months after randomization to the intensive therapy group or the standard therapy group in the original study and continuing to the final visit for those who developed no events or to the nearest day before onset for those who developed any events.

2.3 Procedures

Analysis included all patients who had at least one scheduled visit during the period starting 6 months after randomization. For reference, in comparison to these mean values, additional analysis was performed on data collected from patients who showed the target LDL-C level at their last visit. The last visit was defined to be the nearest day before onset of an event for patients who developed any events, or the date of the final visit for patients who did not develop any events during the scheduled visits, starting 6 months after randomization to a treatment group.

2.4 Outcomes

In the EMPATHY study, the primary outcome was the composite incidence of CV events, including cardiac, cerebral, renal, and vascular events, or death associated with CV events. The secondary outcomes included death from any cause; individual incidence of the events defined as CV events for the primary endpoint; incidence of stroke; change in laboratory variables related to chronic kidney disease; and safety. Primary and secondary endpoints were adjudicated by an event evaluation committee whose members were unaware of the treatment allocation. In this subanalysis, we analyzed only the primary outcome and safety because of the small number of CV events.

2.5 Statistical analysis

A Cox proportional hazards model was used to estimate HRs and 95% CIs for the incidence of the primary endpoint in patients who achieved target LDL-C levels in the intensive ~~therapy~~ and standard ~~therapy~~ groups. Because this additional analysis was performed in a sub-group of patients, ~~the HRs were estimated after adjusting for~~ a Cox proportional hazards model was applied, with study group and baseline ~~prognostic~~influencing factors as explanatory variables, to adjust for these factors.

A stepwise method was used with the Cox proportional hazards model in the full analysis set (intention-to-treat [ITT] population) to select influencing factors; the primary endpoint was the objective variable, and prognostic factors were the explanatory variables. In this analysis, fifteen potential prognostic factors were evaluated: gender, age, body mass index (BMI), compliance with lipid-lowering agents (including statins) from enrollment, smoking status (current smoker, past smoker, non-smoker), family history of coronary artery disease, family history of cerebrovascular disease, duration of diabetes, presence or absence of diabetic

nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings at enrollment (simple retinopathy, pre-proliferative retinopathy, proliferative retinopathy), hemoglobin A1c (HbA1c) at informed consent, LDL-C at randomization, and estimated glomerular filtration rate (eGFR) at enrollment (<60, ≥60 mL/min/1.73m^2).

3 RESULTS

3.1 Study patients

Of the 5144 patients randomized to the intensive and standard therapy groups in the EMPATHY study, a total of 1909 patients were included in this subanalysis (703 in the intensive group and 1206 in the standard group). A total of 70 patients (25 in the intensive group and 45 in the standard group) had only one scheduled visit at least 6 months after randomization.

3.2 Baseline characteristics

Some of the demographic characteristics of the patients in both groups at baseline were similar (age, family history of coronary artery disease and/or cerebrovascular disease, the presence of neuropathy and/or nephropathy, the severity of retinopathy, HbA1c levels, and eGFR), while other characteristics differed between the groups (Table 1). In comparison to the standard therapy group, a higher proportion of patients in the intensive therapy group was male (51.9% vs. 43.5%), received no lipid-lowering treatment before study enrollment (54.9% vs. 39.1%), were current smokers (19.3% vs. 16.9%), and had hypertension at enrollment (75.7% vs. 70.6%). Other differences between the two groups included higher mean BMI in the intensive ~~therapy~~ group, and longer duration of diabetes and higher mean LDL-C level at enrollment in the standard ~~therapy~~ group.

The demographic characteristics of the patients who were at their target LDL-C level at the last visit were similar to those who were at their mean target LDL-C level, with the exception of nephropathy (Table S1).

The proportion of patients using atorvastatin, rosuvastatin, or pitavastatin was about the same in the two groups at baseline (48.~~5%~~ 2% in the intensive group and 53.~~2~~1% in the standard group), and the proportion using pravastatin, fluvastatin, or simvastatin was 51.~~5~~2% and 46.~~8~~7%, respectively. At the end of the study, the proportion of atorvastatin, rosuvastatin, or pitavastatin users remained nearly unchanged in the standard group (~~51.0~~50.9%) but had risen to 98.2% in the intensive group. Dose levels at baseline were similar in the intensive and standard ~~therapy~~ groups for all statins. In the intensive group, the dose increased for all statin types over the course of the study. The doses did not change for the standard group (Table S2). It should be noted that the statin dose for "intensive" therapy in Japan is lower than in the U.S. and Europe.

3.3 Laboratory values

The changes in levels of LDL-C, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) in the subanalysis are shown in Figure 2. In the intensive ~~therapy~~ group, the mean level of LDL-C decreased significantly from baseline (93.7±24.0 mg/dL) to the first measurement at 6 months (66.5±13.9 mg/dL) and then remained at this level or lower (59.7±11.6 mg/dL at 36 months) to 60 months after the start of treatment (56.6±16.1 mg/dL). In the standard ~~therapy~~ group, the LDL-C level after 6 months of treatment was slightly higher (109.6±17.3 mg/dL) than the baseline level (107.9±23.5 mg/dL) and remained at or near that level (107.1±17.8 mg/dL at 36 months) throughout the course of the study to 60 months after the start of treatment, when it dropped slightly to near-baseline level (107.5±22.6 mg/dL). TC showed a similar pattern to LDL-C in both groups. TG was slightly

higher in the intensive group at baseline, but that gap diminished somewhat after the start of the study. HDL-C remained substantially unchanged throughout the study in both groups.

No changes were noted for either group during the study in blood pressure, HbA1c, creatinine (Cr), or creatine kinase (CK). However, in the intensive ~~therapy~~ group, high-sensitivity C-reactive protein (hsCRP) levels were significantly reduced at all time points except 60 months, and there was a significant difference between the groups in hsCRP (Table S3).

3.4 Efficacy endpoints

Since stepwise variable selection showed that eight factors were statistically related to the primary outcome among the 15 potential prognostic factors, these variables were adjusted: gender; smoking status (current smoker, past smoker, non-smoker); presence or absence of diabetic nephropathy, neuropathy, or hypertension; funduscopic findings at enrollment; HbA1c at informed consent; and eGFR at enrollment (<60, ≥60 mL/min/1.73m^2). Baseline LDL-C was not found to be a prognostic factor. We adjusted for these eight prognostic factors to estimate HRs and 95% CIs for the incidence of CV events (the primary endpoint of the EMPATHY study).

In this subanalysis, a significantly smaller proportion of patients in the intensive group (18/703 patients) experienced CV events or death associated with CV events than in the standard group (56/1206 patients) (HR, 0.48; 95% CI, 0.28−0.82; *P*= .007) (Figure 3, Table S4). This difference between the groups started at approximately 12 months after randomization. These findings remained unchanged even if baseline LDL-C was added as a ninth prognostic factor (data not shown).

In the above subanalysis, we used mean LDL-C values to determine whether each patient achieved the target range. We then repeated our analysis using LDL-C values at the last visit. We

found that the significant difference in the primary endpoint between the intensive group and the standard group was also noted in this analysis (HR, 0.43; 95% CI, 0.27−0.68; *P*< .001) (Figure 4).

3.5 Safety

The safety endpoints examined in this analysis were adverse events (AEs), serious AEs, adverse drug reactions (ADRs), and serious ADRs. There was no significant difference in the incidence rates for each of these endpoints between the two groups. The major AEs were hepatobiliary disorders, renal and urinary disorders, rhabdomyolysis, myopathy, and cancer (Table S5). Overall, the occurrence of these events in the two groups was similar except for renal and urinary disorders, which were more common in the standard ~~therapy~~ group (9.2%) than in the intensive ~~therapy~~ group (5.7%).

4 DISCUSSION

The EMPATHY study assessed the benefits of intensive statin monotherapy for lipid management in type 2 diabetic patients with hypercholesterolemia and diabetic retinopathy in a primary prevention setting. The study also evaluated the appropriateness of the treat-to-target approach in this patient population. Results from the EMPATHY study showed that intensive lipid-lowering therapy targeting <70 mg/dL of LDL-C was no more effective in reducing a composite of incidence of CV events or death from CV events than standard therapy targeting ≥100 to <120 mg/dL~~.~~ (HR, 0.84; 95% CI, 0.67−1.07).[6] However, the ITT method may lead to underestimation of intergroup differences in efficacy in situations where the treatment goals have not been properly achieved. In our study, in particular, less than half of the patients in each group had LDL-C within their target range, and nearly half in the standard group had LDL-C below the

target. ~~Consequently, we undertook exploratory analyses to compare findings between patients in each group whose LDL-C was within the target range for their group.~~

~~There were~~Our planned between-group difference in LDL-C was about 40 mg/dL (< 70 mg/dL for the intensive therapy group vs. about 110 mg/dL for the standard therapy group) in the original study, with a predicted HR of 0.65. However, after 3 years of treatment, the actual LDL-C difference was 27.7 mg/dL (76.5 mg/dL vs. 104.1 mg/dL). We hypothesized that the smaller-than-expected difference may have been due at least in part to the unexpectedly low number of patients who achieved their LDL target. Our exploratory post-hoc analyses were designed to investigate this hypothesis by comparing findings between patients whose LDL-C was within the target range for their group.

The subanalysis involved differences in some prognostic factors between the patient group meeting their target LDL-C levels of <70 mg/dL under intensive therapy and the patient group meeting their LDL-C levels of 100 to 120 mg/dL under standard therapy. ~~In the subanalysis, we~~We adjusted for eight factors that had been identified as potentially affecting the primary endpoint: gender (male, female), smoking status, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings, baseline HbA1c, and eGFR. We also found some significant intergroup differences for BMI, use of lipid-lowering agents, use of statins, duration of diabetes, and baseline LDL-C level. However, since they did not affect the primary endpoints in this study, we did not adjust for those factors. After adjusting for the eight selected prognostic factors, the results of the analysis showed that the intensive lipid-lowering therapy targeting <70 mg/dL LDL-C significantly reduced the primary endpoint (the composite of incidence of CV events or death from CV events). Due to the low number of events (74), in this analysis we limited the

number of factors, using a stepwise method for adjustment in the analytical model. We did this to avoid potentially non-reproducible and unstable results. For further confirmation, we also performed an analysis with all variables included; similar results were obtained (HR, 0.51; 95% CI, 0.29-0.89, *P*< .05) (Table S6). Safety events occurred at approximately the same rate in the two groups.

We used mean values for LDL-C in patients who achieved their target levels because we thought it was important to ensure that patients were exposed to a specific concentration of LDL-C for a certain period of time. Our results, although exploratory, suggest that achieving a target of <70 mg/dL LDL-C lowers the risk of CV events significantly more than achieving a target of 100 to 120 mg/dL. For reference, we have also provided a summary of our findings for the proportion of patients who achieved their target LDL-C level at the last visit. Results were similar to those based on mean values.

In the main results paper, we performed post-hoc analysis, which involved classifying patient data into four subcategories (mean LDL-C <70, 70 to <100, 100 to <120, and ≥120 mg/dL during the study). That analysis tended to show event prevention at lower LDL-C values in both the intensive and standard ~~groups~~[6]therapy groups in the original study[6]; the results of the present subanalysis are consistent with those findings. This fact supports the reliability of our subanalysis. Although exploratory, we believe that these findings could meaningfully impact lipid management in clinical practice for the primary prevention of CV events in type 2 diabetic patients with hyperlipidemia and diabetic retinopathy.

Previous large-scale clinical studies of statins have also used LDL-C levels as a basis for post-hoc subanalyses,[8-11] and usefulness was demonstrated in groups achieving lower target levels. However, all of these subanalyses were in dose-comparison studies, and none assessed

whether patients had achieved their target LDL-C levels. To the best of our knowledge, no other analyses have been reported that show the effect of specified target LDL-C levels using statin monotherapy on the occurrence of CV events or CV-related deaths. Although this is an exploratory analysis, our data are valuable when assessing the importance of the treat-to-target approach in lipid management.

In the ITT analysis for the EMPATHY study, the difference in LDL-C between the two groups was 27.~~6~~7 mg/dL, and the HR for the primary endpoint was 0.84 (95% CI, 0.67−1.07; *P*= .15).[6] In this subanalysis, LDL-C at 36 months was 59.7 mg/dL in the intensive group and 107.1 mg/dL in the standard group, a difference of 47.4 mg/dL (1.23 mmol/L) between the two groups, and the HR was 0.48 (95% CI, 0.28−0.82; *P*= .007). In this subanalysis, aggressive treatment with the goal of lowering LDL-C to 70 mg/dL was clearly effective in reducing the number of occurrences of the primary endpoint. The actual difference in LDL-C exceeded the planned difference of approximately 40 mg/dL, which meant that the actual HR was also higher than the planned HR of 0.65. The main analysis did not detect a significant difference in primary endpoint occurrence between the two groups. These subanalysis findings indicate that we were unable to obtain significant results from the main analysis because of failure to achieve target LDL-C levels.

No major differences were noted between groups in the incidence of AEs or ADRs. It thus appears unlikely that specific safety concerns will occur when intensive statin monotherapy is used to reduce LDL-C below 70 mg/dL. We found no marked increase in cerebral hemorrhage in the intensive group (2 patients in the intensive group, 1 patient in the standard group), nor any increase in HbA1c associated with statin use in this study.

These study findings are limited because they are derived from an exploratory analysis which included only those patients whose LDL-C was within the target range for their assigned group: LDL-C <70 mg/dL in the intensive ~~group and ≥100 to <120 mg/dL in the standard group.~~therapy group in the original study and ≥100 to <120 mg/dL in the standard therapy group in the original study. In the EMPATHY study, less than 50% of patients reached their target LDL-C. This can be attributed in part to the fact that over half of the investigators were general practitioners, rather than lipid specialists. Many Japanese physicians who treat hyperlipidemia as part of their routine clinical practice, are not lipid management experts and are concerned about adverse effects such as intracranial hemorrhage from intensive LDL-C lowering. Such concerns may have affected some of the investigators in this study, making them reluctant to prescribe high-dose statin therapy even when the protocol stipulated the aggressive target of 70 mg/dL. Due to the small number of events, secondary endpoints were not assessed (Table S4). In addition, although we detected and adjusted for eight prognostic factors, there may be additional unmeasured factors or confounding factors that should be considered.

In conclusion, the results from this exploratory post-hoc analysis suggest that achievement of LDL-C levels below 70 mg/dL is associated with more effective reduction of CV events than levels of 100 to 120 mg/dL in type 2 diabetic patients with retinopathy and hyperlipidemia who are at high coronary risk.[4,5] There were no major increases in AEs or ADRs when statin monotherapy was used to reduce LDL-C below 70 mg/dL. Our results indicate the importance of targeting LDL-C below 70 mg/dL, and then meeting that target consistently, for the reduction of CV events in this high-risk patient population. However, this analysis was exploratory and must be substantiated in randomized clinical trials. A feasible approach is also needed for achieving these target levels in a clinical setting.

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Conflict of interest

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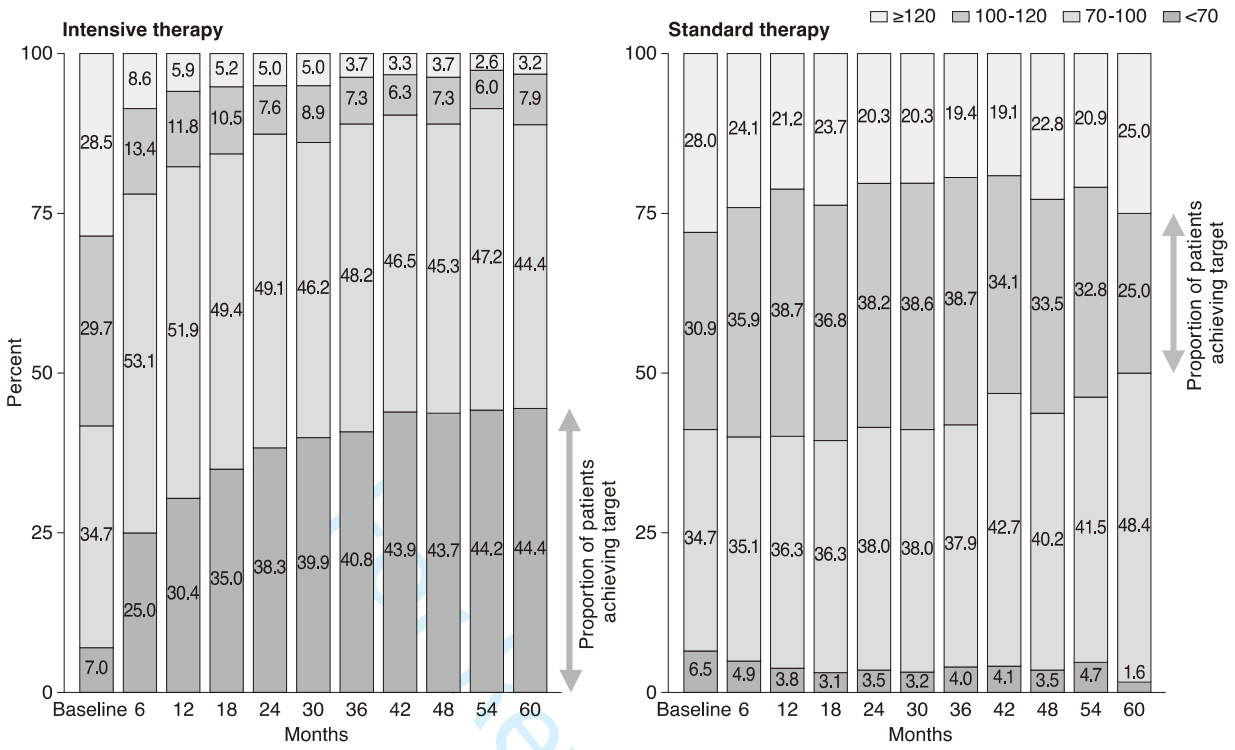

FIGURE 1 Distribution of LDL-C in the Intensive ~~Therapy~~ and ~~the~~ Standard Therapy Groups in the Original Study

Abbreviations: LDL-C,- low-density lipoprotein cholesterol.

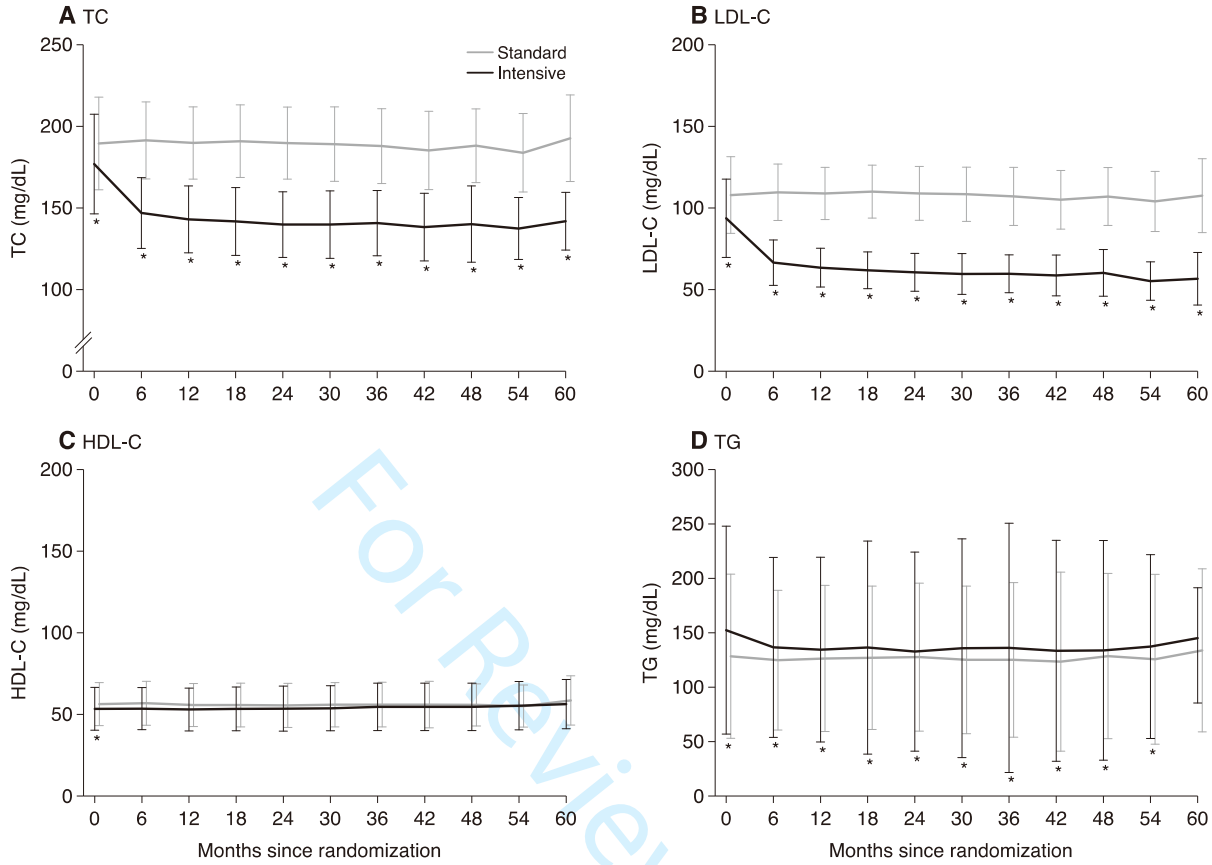

FIGURE 2 Changes in Lipid Parameters Over Time

Data are mean values and SD.

*P< .05, calculated using a mixed model repeated measures (MMRM) approach. The model included group, observation time point, and interaction between group and observation time point as fixed effects.

Abbreviations: TC, indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; SD, standard deviation.

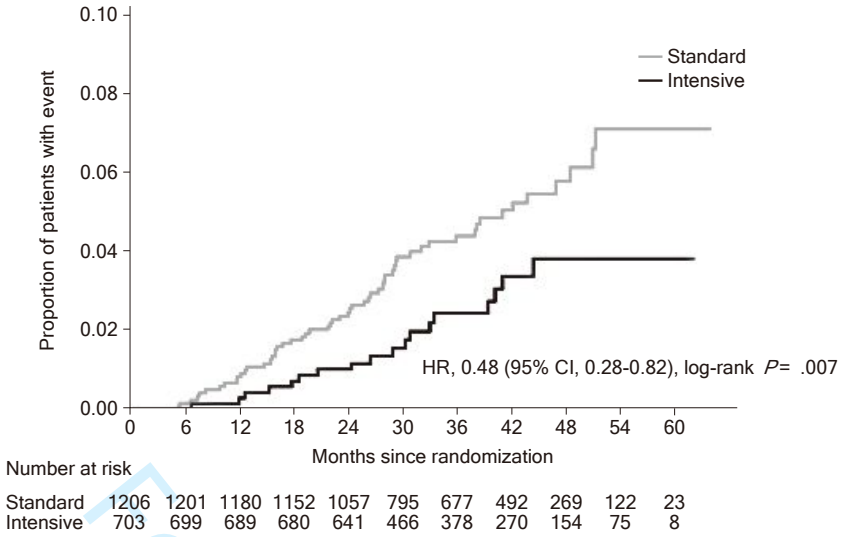

FIGURE 3 Cumulative Event Curve for the Primary Endpoint in the Intensive and ~~the~~ Standard ~~Therapy~~ Groups (Patients Achieving LDL-C Target ~~in,~~ Mean Value)

HR (95% CI) and *P* value were estimated using a stratified Cox proportional hazards model with gender (male, female), smoking status, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings, and baseline hemoglobin A1c (<8.4, ≥8.4%) and estimated glomerular filtration rate (<60, ≥60 [mL/min/1.73m^2]) as covariates.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval.

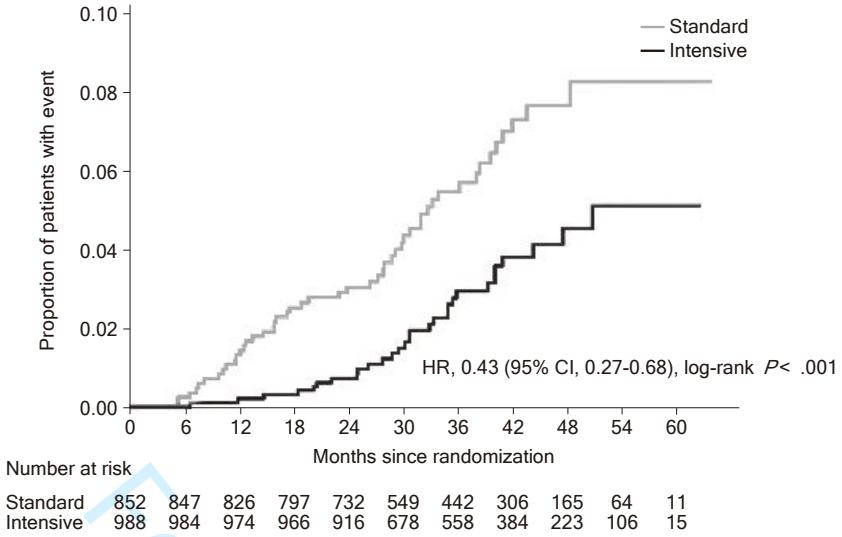

FIGURE 4 Cumulative Event Curve for the Primary Endpoint in the Intensive and Standard Groups (Patients Achieving LDL-C Target at the Last Visit)

HR (95% CI) and *P* value are estimated using a Cox proportional hazards model with gender (male, female), smoking status, presence or absence of diabetic nephropathy, presence or absence of diabetic neuropathy, presence or absence of hypertension, funduscopic findings, and baseline hemoglobin A1c [<8.4, ≥8.4 (NGSP%)] and estimated glomerular filtration rate [< 60, ≥60 (mL/min/1.73m^2)] as covariates.

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval.

TABLE 1 Baseline Demographic Characteristics (Potential Prognostic Factors): for Patients Achieving LDL-C Target in Mean Value

	Intensive ~~therapy~~group (n=703)	**Standard ~~therapy~~group (n=1206)**	***P* value [a]**
Male	365 (51.9)	525 (43.5)	*P*c< .001
Age, y†	62.7 (10.8)	63.6 (10.1)	*P*w= .23
Body-mass index, kg/m²‡	26.2 (4.2)	25.5 (4.2)	*P*w< .001
Lipid-lowering agents§			
None	386 (54.9)	472 (39.1)	*P*c< .001
1 drug	316 (45.0)	733 (60.8)	
≥2 drugs	1 (0.1)	1 (0.1)	
Statin§			*P*c< .001
No	428 (60.9)	511 (42.4)	
Yes	275 (39.1)	695 (57.6)	
Smoking ¶	136 (19.3)	204 (16.9)	*P*c= .01
Family history			
Coronary artery disease	86 (12.2)	165 (13.7)	*P*c= .37

Cerebrovascular disease	146 (20.8)	261 (21.6)	*P*c= .65
Duration of diabetes, y	12.3 (8.3)	13.4 (9.1)	*P*w= .02
Diabetic complications			
Neuropathy	217 (30.9)	382 (31.7)	*P*c= .71
Nephropathy	385 (54.8)	614 (50.9)	*P*c= .10
Hypertension	532 (75.7)	852 (70.6)	*P*c= .02
Funduscopy††			
Simple retinopathy	454 (64.6)	785 (65.1)	*P*c= .99
Preproliferative retinopathy	141 (20.1)	243 (20.1)	
Proliferative retinopathy	103 (14.7)	170 (14.1)	
Other‡‡	3 (0.4)	5 (0.4)	
HbA1c, %†	7.71 (1.20)	7.71 (1.19)	*P*w= .91
LDL-C, mg/dL§§	93.7 (24.0)	107.9 (23.5)	*P*w< .001
eGFR, mL/min/1.73m^2	75.1 (21.7)	74.6 (19.6)	*P*w= .81

Abbreviations: LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Data are mean (SD) or n (%).

[a] *P*w, Wilcoxon rank sum test; *P*c, Chi-square test without Yates' correction.

† Values were obtained at the time of consent.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Values were obtained at provisional enrollment.

¶ Not including past smokers.

†† Diagnosed by ophthalmologists based on the modified Davis classification.

‡‡ Includes 5 patients who had a history of laser therapy but no funduscopic findings at enrollment. The remaining 3 patients were found to be retinopathy-negative after enrollment.

§§ Values were calculated using the Friedewald equation; LDL-C = total cholesterol (TC) - [high-density lipoprotein cholesterol (HDL-C) + triglyceride (TG)/5].