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ORIGINAL ARTICLE

Effective prevention of cardiovascular disease and diabetes-related events with atorvastatin in Japanese elderly patients with type 2 diabetes mellitus: Adjusting for treatment changes using a marginal structural proportional hazards model and a rank-preserving structural failure time model

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Aim: To assess the preventive effect of atorvastatin on cardiovascular disease and on diabetes-related events in elderly type 2 diabetic patients enrolled in the Japanese Elderly Diabetes Intervention Trial (J-EDIT).

Methods: Data were obtained from 1173 patients aged 65–84 years who were enrolled in the J-EDIT. Patients were followed prospectively for 6 years to determine the effects of atorvastatin on serum cholesterol levels, and cardiovascular and diabetes-related events. Because the study protocol allowed atorvastatin to be prescribed according to the clinical needs of each patient, we regarded the J-EDIT data as if they came from a cohort study. We adjusted for clinical characteristics during the study as time-dependent confounders using two methods, inverse-probability-of-treatment (IPT) weighting and *g*-estimation method.

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Results: The total follow-up period was 5310.8 person-years (5.7 years of median follow up), during which 202 patients received atorvastatin treatment. Atorvastatin was associated with moderate reductions in cholesterol levels: 24.2 mg/dL for total cholesterol, 22.9 mg/dL for low-density lipoprotein (LDL) cholesterol and 24.3 mg/dL for non-high-density lipoprotein cholesterol at the first post-treatment year. As a result, the proportion of patients who achieved targeted levels of LDL cholesterol clearly increased after atorvastatin treatment. Eight patients in 476.6 person-years among atorvastatin-treated and 113 untreated patients in 4721.4 person-years had cardiovascular events (the composite end-point of fatal/non-fatal myocardial infarction, angina pectoris, coronary intervention, and fatal/non-fatal cerebrovascular disease); hazard ratio (HR) = 0.48, 95% confidence interval (CI) = 0.19–1.16, $P = 0.10$, and HR = 0.32, 95% CI = 0.05–1.87, $P = 0.21$ from IPT weighting and *g*-estimation method, respectively. Furthermore, seven in 475.0 person-years among atorvastatin-treated and 149 untreated patients in 4682.4 person-years had diabetes-related events (the composite end-point of sudden death, renal failure death, death as a result of hyperglycemia or hypoglycemia, diabetic gangrene and congestive heart failure in addition to cardiovascular event); HR = 0.30, 95% CI = 0.12–0.77, $P = 0.01$, and HR = 0.40, 95% CI = 0.09–0.89, $P = 0.03$ from IPT weighting and *g*-estimation method, respectively. When cardiovascular events were further differentiated into coronary vascular and cerebrovascular events, atorvastatin especially decreased the cerebrovascular risk.

Conclusion: The use of atorvastatin to lower cholesterol levels in elderly Japanese patients with type 2 diabetes mellitus appears to reduce the risk of cardiovascular and diabetes-related events. **Geriatr Gerontol Int 2012; 12 (Suppl. 1): 88–102.**

Keywords: atorvastatin, cardiovascular event, diabetes-related event, time-dependent confounding, type 2 diabetes mellitus.

Introduction

The benefit of cholesterol-lowering with 3-hydroxymethyl-3-methylglutaryl co-enzyme A reductase inhibitors (statins) for the primary and secondary prevention of cardiovascular disease among various patient populations is widely accepted.[1–6] The preventive effect of statins on cardiovascular disease in diabetic patients has also been well documented by previous large controlled clinical trials for both primary[7–9] and secondary prevention.[10,11] In particular, the Collaborative Atorvastatin Diabetes Study (CARDS) prospectively showed in the primary analysis that atorvastatin 10 mg daily reduced cardiovascular events by 37% in type 2 diabetic patients without elevated low-density lipoprotein (LDL) cholesterol levels by further lowering cholesterol levels.[7] Patients in these studies, however, came from relatively young populations and achieved small to moderate reductions in total and LDL cholesterol levels, whether or not they had type 2 diabetes. The evidence for the beneficial effect of statins in elderly populations was shown solely by a limited number of studies[12] and meta-analyses,[3–5] but most studies in the meta-analyses included few or no aged patients. In Japan, the Pravastatin Anti-atherosclerosis Trial in the Elderly (PATE) was the only reported study that showed the beneficial effect of a statin in an elderly population.[13] Furthermore, few studies included elderly type 2 diabetic patients.[14] It therefore remains unclear whether intensive cholesterol-lowering by statins reduces the cardiovascular risk in elderly type 2 diabetic patients.

The Japanese Elderly Diabetes Intervention Trial (J-EDIT) was a randomized, controlled intervention trial for elderly patients with type 2 diabetes in Japan, in which physicians were recommended to use atorvastatin as a first-line or second-line drug for more rigorous control of patients' cholesterol levels. Though patients in the J-EDIT were randomized to either intensive or conventional treatment group, the study protocol allowed physicians to prescribe atorvastatin for the patients based on their clinical status regardless of their treatment group. This introduces at least two analytical complexities in assessing the effect of atorvastatin on disease prevention. First, because each patient's treatment status with atorvastatin changed over the follow-up period, it was necessary to estimate the effect of a time-varying treatment with atorvastatin during the follow-up period rather than the intention-to-treat effect of a randomized intervention. Second, patients who chose to be prescribed atorvastatin were typically those with a worse prognosis for cardiovascular disease, estimating the effect of atorvastatin might require adjustment for post-randomization, time-dependent covariates. If time-dependent covariates independently predict both cardiovascular disease and subsequent

prescription of atorvastatin within strata defined by joint distribution of prior atorvastatin treatments and prior covariates, these are considered time-dependent confounders and require adjustment. In the presence of time-dependent confounders, however, conventional analytic methods, such as stratification, propensity scoring or regression models with time-dependent covariates (e.g. Cox models), can result in biased effect estimates and fail to have causal interpretation with or without time-dependent confounders in the analyses, even if all confounders are measured and model misspecification is absent.[15,16]

We aimed to assess the preventive effect of atorvastatin on cardiovascular disease and on diabetic vascular complications in the J-EDIT data, where time-dependent confounding was suspected, using several analytic methods that allow statistical models to handle atorvastatin treatment as time-varying. In particular, we focused on two novel methods for estimating the effect of time-varying treatments in the presence of time-dependent confounding: inverse-probability-of-treatment (IPT) weighted estimation of marginal structural models[17–19] and *g*-estimation method for fitting structural nested models.[15,20–23]

Methods

Participants and follow up

Details of the J-EDIT have been described elsewhere.[24] Briefly, the J-EDIT was launched in 2001 as a prospective, randomized, controlled intervention trial of Japanese elderly people with type 2 diabetes mellitus for the purpose of determining how to prevent several diabetic complications. Between March 2001 and February 2002, the study enrolled diabetic patients from 39 hospitals in Japan who had met the following eligibility criteria: having type 2 diabetes mellitus; being aged 65–84 years; and having serum glycated hemoglobin A1c (HbA1c) levels of 7.9% or more or 7.4–7.8% with at least one of the comorbidities, including (pre)hypertension (systolic/diastolic blood pressure [BP] more than 130/85 mmHg), obesity (body mass index [BMI] of 25 kg/m^2 or more) or dyslipidemia (total cholesterol of 200 mg/dL or more, or LDL cholesterol of 120 mg/dL or more for patients without a history of ischemic heart disease; total cholesterol of 180 mg/dL or more, or LDL cholesterol of 100 mg/dL or more for patients with ischemic heart disease; high-density lipoprotein [HDL] cholesterol of less than 40 mg/dL; or triglyceride levels of 150 mg/dL or more). Patients were not screened for a history of cardiovascular disease. The study was carried out in compliance with the Declaration of Helsinki, and the study protocol received approval from the ethics committees at all of the enrolled hospitals. Written informed consent was obtained from all participants.

Eligible patients were randomly assigned to either an intensive treatment group or a conventional treatment group at the central data-coordinating center. The treatment strategy in the intensive treatment group was to achieve the same levels targeted for adult diabetic patients in clinical practice: HbA1c, 6.9% or less; BMI, less than 25 kg/m^2; systolic/diastolic BP, less than 130/80 mmHg; total cholesterol, less than 200 mg/dL for patients without a history of ischemic heart disease and less than 180 mg/dL for patients with a history of ischemic heart disease; LDL cholesterol, less than 120 mg/dL for patients without a history of ischemic heart disease and less than 100 mg/dL for patients with a history of ischemic heart disease; HDL cholesterol, 40 mg/dL or more; and triglyceride levels, less than 150 mg/dL. Target levels were not defined for the conventional treatment group.[24] In the intensive treatment group, the study protocol recommended the use of atorvastatin when control of total cholesterol and LDL cholesterol levels failed.

After randomization, patients were followed up for 6 years. Each year, data on the treatment for diabetes, concomitant use of other drugs, the onset of events, laboratory tests (e.g. HbA1c, blood glucose, total cholesterol, triglycerides, HDL cholesterol, BP, BMI) and occurrence of adverse events were collected by the investigators. Atorvastatin prescription data were also collected annually; 31.2% of prescription data after initiation of atorvastatin (294 of 941 person-visits) were recorded as missing, so we classified all atorvastatin treatment status as on-treatment after initiation (in other words, it was assumed that patients remained on atorvastatin treatment once they were prescribed it). Continuous baseline variables with missing value were imputed by the means among all patients at baseline, and missing dichotomous variables were imputed by the value indicating "absence". When post-randomization variables were missing, they were replaced with information carried forward from the most recent prior observed value.

Although the J-EDIT was designed as a randomized controlled trial (intensive intervention or not intensive intervention), each treatment prescription, such as atorvastatin, was determined by the physicians' practice according to the clinical requirement of each patient. Because it was supposed that there was little or no difference of atorvastatin treatment status between the groups, we regarded this J-EDIT data as observational data as if they came from a cohort study, and analyzed the effect of time-varying atorvastatin treatment for preventing events as defined below.

Clinical measurements and end-points

Laboratory data and diagnoses regarding diabetes and complications were obtained annually from the clinical

charts. After patients fasted overnight, blood samples were taken by venipuncture to assess serum levels of glucose, HbA1c, total cholesterol, HDL cholesterol and triglyceride levels. LDL cholesterol levels were calculated using the Friedewald formula (LDL cholesterol = total cholesterol – HDL cholesterol – [triglyceride/5]), if triglyceride levels were less than or equal to 400 mg/dL; otherwise, data were recorded as missing. Assessments of diabetic nephropathy, diabetic retinopathy and diabetic neuropathy,[25] and information about the previous history of ischemic heart disease and cerebrovascular disease[26] are described elsewhere.

End-points in the J-EDIT were defined as death resulting from atherosclerotic coronary heart disease, sudden and unexpected death, non-fatal myocardial infarction, angina pectoris, arterial peripheral vascular disease, diabetic gangrene, cerebrovascular disease and congestive heart failure, all of which were new-onset diseases. The definition of each end-point in the J-EDIT has been described elsewhere.[24] In the present study, we defined the composite end-points as cardiovascular events (fatal/non-fatal myocardial infarction, angina pectoris, coronary intervention and fatal/non-fatal cerebrovascular disease) and diabetes-related events (sudden death; death as a result of renal failure, hyperglycemia or hypoglycemia, diabetic gangrene, and congestive heart failure; and cardiovascular events). Patients remained in datasets for each event until they experienced a first occurrence of that event, were lost to follow up or were at the end of the follow-up period (6 years after randomization), whichever came first. Safety evaluations were carried out by investigators in each hospital.

Statistical analyses

Descriptive statistics of baseline characteristics were calculated in atorvastatin-treated and untreated patients separately. To compare the time-dependent variables when atorvastatin was initiated with those of patients who did not initiate the drug, we summarized the following data during the follow-up period: updated values at the time atorvastatin was initiated, and across the non-initiating period for all patients (i.e. by the time of initiation for those who initiated atorvastatin and across all periods for those who didn't receive atorvastatin). Their association with the initiation of atorvastatin was also seen by estimating the rate ratio from standard univariate (time-independent or time-dependent) Cox models regarding time-to-initiate atorvastatin as the outcome. The rate of initiating atorvastatin treatment was also compared between randomized treatment groups, so we could verify that the clinical use of atorvastatin was similar between the groups.

We then assessed the effects of atorvastatin on total, LDL and non-HDL cholesterol control, and on prevention of events. Descriptive statistics of these cholesterol levels were calculated in each year for subgroups defined by time-to-initiate atorvastatin. Whether targeted values for LDL cholesterol (less than 120 mg/dL for patients without a history of ischemic heart disease or less than 100 mg/dL for patients with it) were achieved was also summarized by a previous history of ischemic heart disease. To estimate the effect on cholesterol control, weighted generalized estimating equation (GEE) regression analyses were carried out.[27,28] We fitted linear and logistic models with an independent working covariance to the means of cholesterol levels and to the probability of LDL cholesterol target achievement, respectively, each conditional on atorvastatin at that time and baseline covariates. Our models allowed intercepts to vary over the follow-up years and over the treatment period. The GEE compared the data on cholesterol levels during the treatment period among atorvastatin initiators with data across the non-initiating period for all patients, and the weighting provided the estimates with causal interpretation. Weights in the GEE were calculated as in the Cox models described later.

To assess the effect of atorvastatin for the prevention of events, we estimated hazard ratios (HR) of atorvastatin treatment compared with no atorvastatin use for each event by fitting five statistical models, all of which handled atorvastatin treatment as time-varying. Three of them were conventional regression methods that merely modeled the association between observed event hazards and observed time-varying atorvastatin treatment status. The last two models were structural modeling approaches that modeled counterfactual outcomes, that is, event hazards that would have been observed, possibly contrary to fact, under a specific regime of atorvastatin treatment during the follow-up period.[16] The parameter representing HR in structural models compared the event hazard had all patients been treated with atorvastatin with the event hazard had no patients been treated with atorvastatin at each time.

At first, we fitted a Cox (proportional hazards) model that treated atorvastatin as a time-dependent variable, and adjusted for baseline covariates (Model 1: baseline-adjusted Cox model). Baseline covariates included sex, age, HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, systolic BP, diastolic BP, BMI, diabetic retinopathy, diabetic nephropathy, current smoking status, and history of ischemic heart disease and cerebrovascular disease. Model 2 was the same as Model 1, except that we adjusted for variables for which target levels had been set in the intensive treatment group (HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, systolic BP, diastolic BP and BMI) as time-dependent. We called this Model 2 the time-dependent-adjusted Cox model. We also fitted a pooled logistic regression model (Model 3) that treated each person-month as a repeated observation and included variables in the same manner as Model 2 by

updating variables in the next observation within a patient, allowing time-dependent intercepts as a restricted cubic spline function of the months after follow-up with five knots at the 5th, 25th, 50th, 75th and 95th percentiles. Our pooled logistic regression model (Model 3) was mathematically almost equivalent to the time-dependent-adjusted Cox model (Model 2) because of a sufficiently short interval (i.e. 1 month) for each observation.[29]

In the absence of time-dependent confounders, one common statistical approach to estimate the treatment effect on a time-to-event outcome has been Cox models that treat an atorvastatin treatment as time-dependent, such as Model 1 or Model 2; however, it was plausible that atorvastatin treatment was initiated more often among patients with worse prognoses during the follow-up period (known as confounding-by-indication) and atorvastatin affects such prognostic factors, such as serum cholesterol levels. In fact, it is known that when (i) there exist time-varying risk factors for an outcome that also predict subsequent treatments (i.e. there is time-dependent confounding) and (ii) the treatment history predicts subsequent levels of these risk factors, then the estimates of effects from conventional statistical procedures, such as Cox models, including time-varying treatments, are biased and have no causal interpretation whether or not one adjusts for these time-dependent confounders.[15,16] In our example, Model 1 did not adjust for covariates during follow up and would suffer from a time-dependent confounding bias, whereas Model 2 would underestimate treatment effects as a result of adjustments for earlier treatment effects and selection bias would also occur.

One of the solutions to this problem is to use an IPT weighted Cox model (Model 4), adjusting baseline covariates with time-varying weights. In this method, we adjusted for time-dependent covariates by using them to calculate the weights rather than by adding them to the regression model as explanatory variables.[17–19] We estimated weights by fitting pooled logistic models to the conditional probability of initiating atorvastatin at each visit given the history of covariates. Similar weights were calculated to correct outcome-related censoring, and were multiplied by IPT weights. Our IPT weighted Cox model (Model 4) is regarded as a marginal structural Cox model.[17] Further explanation and how we implemented the IPT weighting method are provided in the Appendix.

As another approach to dealing with time-dependent confounding, we used the rank-preserving structural failure time (RPSFT) model (Model 5) that related each patient's counterfactual failure time (time-to-event variable) to his/her observed data. This RPSFT model is one of the simplest forms of structural nested failure time models,[22,23] under which the ranks of the patients' failure times are preserved across all treatment regimes. In other words, the RPSFT models assume that if an event would occur in patient 1 before patient 2, had they both been treated under one regime, the event also would occur in patient 1 before patient 2 had they both been treated under other regimes.[23] To fit structural nested models, we usually use a technique named "*g*-estimation". Our *g*-estimates (estimated values of parameters in the RPSFT models from *g*-estimation) were based on a pooled logistic regression model for the probability of initiating atorvastatin as used in the process fitting Model 4, assuming underlying counterfactual hazards are constant (see Appendix).

For the safety evaluation, we visually examined the free-form reports from study investigators. To evaluate adverse effects of atorvastatin on blood glucose control, because statins are reported to slightly increase the risk of diabetes,[30–32] HbA1c data during the follow-up period were analyzed similar to how we summarized cholesterol levels and carried out the IPT weighted GEE analysis.

To deal with within-patient correlations, all standard errors for the parameters in the pooled logistic regression models were obtained by the robust estimators with sandwich formula.[27] The alpha level below which *P*-values were considered to be statistically significant was arbitrarily chosen at 0.05, so all interval estimates of parameters were presented with a 95% confidence level. All analyses were carried out with SAS version 9.2 (Cary, NC, USA).

Results

Patients and events during the follow-up period

The J-EDIT included 1173 patients who had met the eligibility criteria. The total follow-up period was 5310.8 person-years and the median follow up was 5.7 years. During the follow-up period, 202 patients received atorvastatin treatment. The atorvastatin-treated and untreated periods were approximately 520 person-years and approximately 4900 person-years for each subevent, respectively. Table 1 summarizes the numbers of observed subevents in each period. Patients who had experienced two or more subevents of the composite event were censored at the first occurrence of the subevent, regardless of their atorvastatin treatment status. Despite the balance at baseline between the randomized groups, there were no differences for event hazards between the groups (cardiovascular events: 63 among 2517.5 person-years in the intensive treatment group, 58 among 2553.5 person-years in the conventional treatment group, log–rank $P = 0.61$; diabetes-related events: 80 among 2493.5 person-years in the intensive treatment group, 76 among 2537.7 person-years in conventional treatment group, log–rank $P = 0.68$).

Table 1 Subevents during the follow-up period

	Atorvastatin-treated patients (about 520 person-years for each subevent)	Atorvastatin-untreated patients (about 4900 person-years for each subevent)
Fatal myocardial infarction	1	11
Non-fatal myocardial infarction	2	15
Angina pectoris	5	16
Coronary intervention	0	18
Fatal cerebrovascular disease	0	6
Non-fatal cerebrovascular disease	1	62
Sudden death	0	13
Renal failure and death	1	2
Death due to hyperglycemia or hypoglycemia	0	1
Diabetic gangrene	0	12
Congestive heart failure	1	14

Each subevent listed might have occurred in more than one patient, making the number of composite events less than the total number of subevents.

Characteristics of patients

Table 2 provides the baseline characteristics of atorvastatin-treated patients and atorvastatin-untreated patients, and the characteristics at the time of initiating the drug of atorvastatin-treated patients and the characteristics of the non-initiating period across all patients. Table 2 also shows a significantly greater rate of atorvastatin being initiated among women and patients who had higher total cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides, BMI and who had previously been prescribed statins (other than atorvastatin) at baseline; and higher total cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides and BMI when atorvastatin was initially given. Transition of atorvastatin treatment status by the randomized groups is shown in Figure 1, which shows that the proportion of atorvastatin prescription had increased yearly irrespective of the treatment group (log–rank *P*-value for time-to-initiation of atorvastatin between the groups is 0.35).

Change in total, LDL and non-HDL cholesterol levels

Mean values of total, LDL and non-HDL cholesterol levels by subgroup defined by time-to-initiate atorvastatin (Table 3) show that atorvastatin seemed to be associated with a moderate reduction in these cholesterol levels. Among the 161 patients who had been treated with atorvastatin after 1 year of follow up, the means (standard deviations) of difference between the first post-treatment and last pretreatment values were –24.2 mg/dL (37.5 mg/dL) for total cholesterol, –22.9 mg/dL (34.5 mg/dL) for LDL cholesterol and –24.3 mg/dL (37.4 mg/dL) for non-HDL cholesterol. As a result, proportions of achieving targeted levels for LDL cholesterol clearly increased after atorvastatin treatment both in the context of primary and secondary prevention for cardiovascular disease as shown in Table 4. IPT weighted GEE analyses for all patients yielded the estimates that each cholesterol value in the atorvastatin-treated period became lower than the values in the atorvastatin-untreated period by 8–10 mg/dL, after adjusting for covariates at baseline and on starting atorvastatin treatment: total cholesterol by 7.9 mg/dL (95% confidence interval [CI] was 2.9–12.9 mg/dL, $P < 0.01$); LDL cholesterol by 10.2 mg/dL (5.5–14.9 mg/dL, $P < 0.01$); and non-HDL cholesterol by 9.8 mg/dL (4.9–14.7 mg/dL, $P < 0.01$). Similarly, target levels of LDL cholesterol were significantly well achieved by atorvastatin (an IPT weighted GEE estimate: odds ratio = 2.75, 95% CI = 1.85–4.10, $P < 0.01$).

Event occurrence

Table 5 shows the hazard ratios for each event with 95% CI of atorvastatin treatment compared with no atorvastatin treatment estimated from five statistical models. Observed numbers of events were as follows: for cardiovascular event, eight in 476.6 person-years (16.8 per 1000 person-years) among atorvastatin-treated patients and 113 in 4721.4 person-years (23.9 per 1000 person-years) among untreated patients; for diabetes-related events, seven in 475.0 person-years (14.7 per 1000 person-years) among atorvastatin-treated patients and 149 in 4682.4 person-years (31.8 per 1000 person-years) among untreated patients. Note that fewer events in the atorvastatin-treated period could be observed for a broader definition of composite endpoints (i.e. a diabetes-related event relative to a cardiovascular event). A broader definition could have censored patients with event occurrence before they started

Table 2 Patients' characteristics and atorvastatin status

	Atorvastatin-treated patients ($n = 202$)	Atorvastatin-untreated patients ($n = 971$)	Non-initiating period of all patient[†]	Rate ratio[‡] for initiating atorvastatin (95% CI)
Baseline				
Sex (male), *n* (%)	61 (30.2)	482 (49.6)		0.49 (0.36–0.66)
Age, mean (SD)	71.4 (4.7)	71.9 (4.6)		0.84 (0.62–1.15)
HbA1c (%), mean (SD)	8.1 (0.9)	8.1 (0.9)		1.69 (0.42–6.84)
TC (mg/dL), mean (SD)	221.3 (36.5)	198.7 (32.6)		1.19 (1.15–1.23)
HDL cholesterol (mg/dL), mean (SD)	56.0 (18.2)	56.5 (18.4)		0.97 (0.90–1.05)
LDL cholesterol (mg/dL), mean (SD)	134.5 (33.5)	117.1 (29.8)		1.19 (1.14–1.24)
Non-HDL cholesterol (mg/dL), mean (SD)	165.3 (37.6)	142.2 (33.3)		1.19 (1.15–1.23)
Triglyceride (mmHg), median (IQR)	134.0 (97.0–191.0)	110.0 (80.0–156.0)		1.01 (1.01–1.02)
SBP (mmHg), mean (SD)	138.2 (16.8)	136.8 (16.3)		1.06 (0.97–1.15)
DBP (mmHg), mean (SD)	74.4 (10.0)	75.4 (9.7)		0.91 (0.79–1.05)
BMI (kg/m^2), mean (SD)	24.4 (3.1)	23.7 (3.5)		1.75 (1.17–2.61)
Nephropathy, *n* (%)	97 (48.0)	464 (47.8)		1.05 (0.79–1.38)
Retinopathy, *n* (%)	98 (48.5)	465 (47.9)		1.07 (0.81–1.41)
Smoking at baseline, *n* (%)	19 (9.4)	138 (14.2)		0.68 (0.42–1.09)
History of ischemic heart disease, *n* (%)	38 (18.8)	145 (14.9)		1.28 (0.90–1.83)
History of cerebrovascular disease, *n* (%)	32 (15.8)	119 (12.3)		1.28 (0.88–1.88)
Prescription of statin treatment, *n* (%)	123 (60.9)	241 (24.8)		3.99 (3.00–5.31)
Time-dependent[§]				
HbA1c (%), mean (SD)	7.8 (1.0)		7.6 (1.1)	1.77 (0.50–6.25)
TC (mg/dL), mean (SD)	220.7 (37.2)		196.3 (34.4)	1.06 (1.02–1.10)
HDL cholesterol (mg/dL), mean (SD)	55.6 (16.6)		55.0 (18.3)	0.99 (0.91–1.08)
LDL cholesterol (mg/dL), mean (SD)	134.6 (34.7)		117.1 (29.3)	1.05 (1.01–1.10)
Non-HDL cholesterol (mg/dL), mean (SD)	165.2 (37.6)		141.4 (34.9)	1.07 (1.03–1.11)
Triglyceride (mmHg), median (IQR)	136.5 (97.0–185.0)		110.0 (79.0–151.5)	1.01 (1.00–1.02)
SBP (mmHg), mean (SD)	137.0 (16.1)		135.7 (16.0)	1.00 (0.91–1.09)
DBP (mmHg), mean (SD)	72.8 (10.0)		73.5 (9.6)	0.91 (0.79–1.04)
BMI (kg/m^2), mean (SD)	24.5 (3.1)		23.7 (5.1)	1.21 (0.92–1.58)

[†]Data are means and SD of data across all periods not initiating atorvastatin for all patients ($n = 1,173$). [‡]Estimates per 10 units increase for continuous variables and that treating absent property as reference for dichotomous ones from standard univariate Cox models with a time-invariant covariate for baseline characteristics, and with a time-dependent covariate for time-dependent characteristics. [§]Data are updated values at the time of initiating atorvastatin administration for initiators and means across each time for non-initiating period. BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; IQR, inter-quartile range; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol.

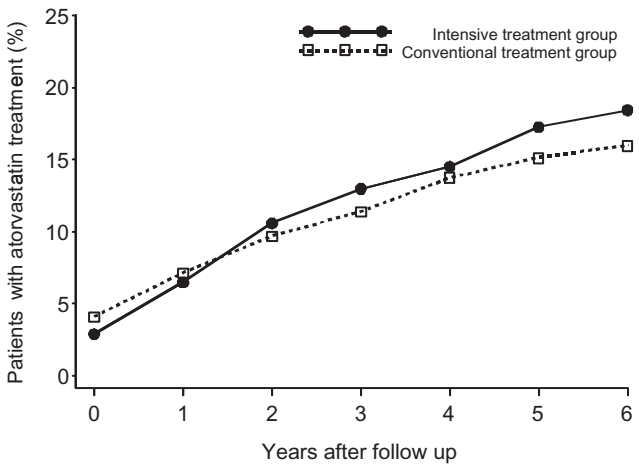

Figure 1 Change in proportion of patients with atorvastatin treatment.

treatment with atorvastatin; however, the same person could experience an event more narrowly defined after starting treatment. Table 5 suggests the almost significant preventive effect of atorvastatin on cardiovascular events (HR = 0.48, 95% CI = 0.19–1.16, $P = 0.10$, and HR = 0.32, 95% CI = 0.05–1.87, $P = 0.21$ in Models 4 and 5, respectively) and a significant preventive effect on diabetes-related events (HR = 0.30, 95% CI = 0.12–0.77, $P = 0.01$, and HR = 0.40, 95% CI = 0.09–0.89, $P = 0.03$ in Models 4 and 5, respectively). Table 5 also suggests the larger degree of atorvastatin effect tended to be estimated in the two structural models (Models 4 and 5) compared with conventional Cox models (Models 1 and 2), showing that there was confounding-by-indication and some confounder-mediated atorvastatin effect in the J-EDIT data (see Discussion section).

Furthermore, each cardiovascular event was divided into coronary vascular (8 in 490.5 person-years [16.3 per 1000 person-years] among atorvastatin-treated patients and 47 in 4830.3 person-years [9.7 per 1000 person-years] among untreated patients) and cerebrovascular events (1 in 507.1 person-years [2.0 per 1000 person-years] among atorvastatin-treated patients and 67 in 4807.3 person-years [13.9 per 1000 person-years] among untreated patients). If each model could have been fitted (in fact, limits of 95% CI for coronary vascular events and an estimate for cerebrovascular events cannot be obtained by *g*-estimation as a result of few events among the atorvastatin treatment period), atorvastatin seemed to slightly increase the coronary vascular risk (HR is approximately 1.5 from Models 4 and 5) and markedly decrease cerebrovascular risk (similarly, HR is approximately 0.1; full data not provided).

Atorvastatin also significantly reduced all-type events, which included all-cause deaths unrelated to diabetes, as well as diabetes-related events:[24] 10 patients (21.0 per 1000 person-years) in the atorvastatin-treated period and 198 patients (42.0 per 1000 person-years) in the untreated period experienced an event. Estimated HR (95% CI and *P*-values) were 0.36 (0.16–0.79, $P = 0.01$) and 0.35 (0.09–0.74, $P = 0.01$) in IPT weighted Cox model and RPSFT model, respectively.

Adverse events

With regard to blood glucose control by atorvastatin, the mean (standard deviation) HbA1c difference (%) between the last pretreatment and the first post-treatment values are –0.12 (1.06) among the 161 atrovastatin-treated patients after 1 year of follow up. We estimated that HbA1c levels during the atorvastatin-treatment period were higher by just 0.06% (95% CI = –0.08% to 0.21%, $P = 0.38$) compared with those in the atorvastatin-untreated period for all patients from an IPT weighted GEE. No serious adverse events associated with limiting prescription of atorvastatin were reported during the follow-up period.

Discussion

We found that intensive cholesterol-lowering by atorvastatin reduced the risk of cardiovascular events (composite end-point of fatal/non-fatal myocardial infarction, angina pectoris, coronary intervention and fatal/non-fatal cerebrovascular disease) and diabetes-related events (composite end-point of sudden death, renal failure death, death as a result of hyperglycemia or hypoglycemia, diabetic gangrene, and congestive heart failure and cardiovascular events) in elderly Japanese patients with type 2 diabetes. It is true that the estimated effect of atorvastatin in the prevention of cardiovascular events could not reach statistical significance (despite the remarkable size [50–70% relative risk reduction] of point estimates of preventive effect from the structural models) as a result of rare events among patients in the atorvastatin-treatment period; however, a breakdown of composite events (Table 5) suggests that the main preventive effect of atorvastatin on diabetes-related events was a reduction of cardiovascular risk. These results are consistent with findings in the Treating to New Targets (TNT) study,[12] which showed intensive lipid-lowering treatment with 80 mg of atorvastatin statistically significantly reduced the hazard of cardiovascular events compared with 10 mg of atorvastatin in diabetic or non-diabetic patients aged 65 years or older.

Our analyses also showed that atorvastatin could more strictly control serum LDL and non-HDL cholesterol levels in elderly patients with type 2 diabetes (Tables 3 and 4). Estimated absolute differences of cholesterol levels between the atorvastatin-treated period and the untreated periods in the IPT weighted GEE (total, LDL and non-HDL cholesterols reduced by

Table 3 Mean serum cholesterol levels during follow up by subgroup defined by timing of initiation of atorvastatin

Year of starting atorvastatin	*n*	Mean of total cholesterol (mg/dL) Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
(a) Mean levels of total cholesterol								
0	41	**213.7**	**201.1**	**213.2**	**206.3**	**199.6**	**201.5**	**203.4**
1	39	234.1	**202.7**	**190.7**	**191.4**	**193.7**	**199.4**	**191.3**
2	39	230.2	225.5	**207.3**	**191.9**	**193.5**	**189.0**	**190.0**
3	24	220.8	221.0	221.0	**196.8**	**187.9**	**181.1**	**183.1**
4	23	214.4	209.2	216.2	225.7	**197.0**	**183.2**	**182.1**
5	24	210.3	210.0	216.4	207.1	213.3	**190.3**	**179.8**
6	12	213.3	206.5	209.2	206.0	204.9	190.3	**175.3**
None	971	198.7	196.0	197.3	196.2	193.1	191.5	191.3
Total	1173	202.6	198.5	199.3	197.2	193.8	191.6	190.9
(b) Mean levels of LDL cholesterol								
0	41	**123.5**	**114.0**	**124.3**	**118.7**	**111.2**	**113.6**	**116.2**
1	39	144.1	**115.9**	**106.4**	**104.8**	**110.2**	**112.9**	**109.4**
2	39	140.3	138.8	**121.7**	**108.8**	**109.8**	**111.6**	**106.2**
3	24	138.0	143.0	142.8	**117.7**	**109.6**	**103.5**	**108.5**
4	23	131.4	129.2	132.9	141.1	**114.3**	**105.8**	**102.4**
5	24	126.0	126.5	135.1	128.3	130.3	**106.4**	**99.7**
6	12	129.3	123.5	123.1	122.6	118.2	106.7	**96.5**
None	971	116.9	116.6	118.1	117.4	115.1	113.9	113.7
Total	1173	119.8	118.3	119.2	117.5	114.8	113.2	112.6
(c) Mean levels of non-HDL cholesterol								
0	41	**154.8**	**141.7**	**151.4**	**145.5**	**141.0**	**142.9**	**145.9**
1	39	180.6	**148.7**	**137.7**	**138.2**	**139.1**	**146.0**	**137.8**
2	39	172.4	167.4	**151.6**	**135.1**	**135.9**	**132.2**	**130.5**
3	24	166.2	171.4	173.3	**146.7**	**137.9**	**130.1**	**132.6**
4	23	159.5	154.8	163.0	171.4	**141.8**	**130.0**	**125.4**
5	24	156.0	155.1	160.5	151.8	155.2	**131.5**	**122.2**
6	12	153.0	148.4	154.7	150.3	147.5	134.7	**120.9**
None	971	142.0	141.7	142.6	141.0	138.7	136.7	136.6
Total	1173	146.0	144.0	144.6	141.9	139.2	136.7	136.0

Bold numbers indicate on-treatment values. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

8–10 mg/dL in each with statistical significance) might seem relatively small compared with the impression from Table 3 or previously reported studies.[7,12,14] The attenuated effects on cholesterol levels were estimated in the IPT weighted GEE, because Table 3 highlights the changes in cholesterol levels before and after atorvastatin treatment among 161 atorvastatin initiators during the follow-up period (among 202 atorvastatin-treated patients, 41 were treated by atorvastatin at the baseline); however, differences of cholesterol levels estimated from the weighted GEE were absolute differences between the levels that would have been observed had all patients been treated with atorvastatin and the levels had no patients been treated with atorvastatin at each time. In addition to the fact that cholesterol levels in atorvastatin-treated patients were higher than those in untreated patients at baseline and when they started atorvastatin (Table 2), cholesterol levels in untreated patients, including both non-statin users and other statin users, had remained at low levels during the follow-up period (cholesterol levels in "None" rows in Table 3). Although the relatively small reduction in absolute values of serum cholesterols by atorvastatin was estimated from the IPT weighted GEE, targeted levels of LDL cholesterol could be well achieved by atorvastatin (Table 4; odds ratio for the probability of achieving target levels in the IPT weighted GEE analysis was 2.75 with statistical significance).

Though we classified patients' treatment status into ever treated with or never treated with atorvastatin, patients might have received other statins (simvastatin, pravastatin and fluvastatin) during the never treated

Table 4 Achievement of targeted levels for low-density lipoprotein cholesterol during follow up by subgroup defined by timing of initiating atorvastatin

Year of starting atorvastatin	*n*	Achievement of target level for LDL cholesterol (%) Year 0	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
(a) Among patients with a history of ischemic heart disease								
0	7	**43**	**57**	**43**	**57**	**57**	**43**	**43**
1	9	33	**56**	**44**	**44**	**44**	**33**	**56**
2	7	0	0	**43**	**57**	**71**	**57**	**57**
3	3	33	33	33	**100**	**67**	**67**	**33**
4	6	17	17	0	0	**50**	**0**	**33**
5	2	0	0	0	0	0	**0**	**50**
6	4	0	0	25	0	25	50	**75**
None	145	26	28	26	26	31	32	38
Total	183	25	28	27	29	35	33	40
(b) Among patients without a history of ischemic heart disease								
0	34	**47**	**62**	**50**	**56**	**65**	**62**	**59**
1	30	17	**60**	**73**	**77**	**70**	**63**	**63**
2	32	31	34	**63**	**75**	**69**	**75**	**72**
3	21	19	19	24	**52**	**81**	**86**	**76**
4	17	24	29	18	18	**53**	**71**	**76**
5	22	27	36	36	50	45	**73**	**86**
6	8	25	25	50	38	63	75	**88**
None	826	55	57	53	56	58	60	59
Total	990	51	54	53	56	59	62	61
(c) Among all patients								
0	41	**46**	**61**	**49**	**56**	**63**	**59**	**56**
1	39	21	**59**	**67**	**69**	**64**	**56**	**62**
2	39	26	28	**59**	**72**	**69**	**72**	**69**
3	24	21	21	25	**58**	**79**	**83**	**71**
4	23	22	26	13	13	**52**	**52**	**65**
5	24	25	33	33	46	42	**67**	**83**
6	12	17	17	42	25	50	67	**83**
None	971	51	53	49	51	54	56	56
Total	1173	47	50	49	52	56	57	58

Bold numbers indicate on-treatment percentages. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 5 Hazard ratios of atorvastatin treatment compared with no atorvastatin use for each event

Model	Event type Cardiovascular HR	95% CI	*P*-value	Event type Diabetes-related HR	95% CI	*P*-value
1. Baseline-adjusted Cox model†	0.65	0.30–1.40	0.27	0.40	0.18–0.89	0.03
2. Time-dependent-adjusted Cox model†	0.78	0.36–1.67	0.52	0.49	0.22–1.09	0.08
3. Pooled logistic model†	0.75	0.34–1.63	0.46	0.49	0.21–1.10	0.08
4. IPT weighted Cox model‡	0.48	0.19–1.16	0.10	0.30	0.12–0.77	0.01
5. RPSFT model‡	0.32	0.05–1.87	0.21	0.40	0.09–0.89	0.03

All models include the atorvastatin treatment status as a time-dependent covariate. †Including glycated hemoglobin A1c (HbA1c), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), systolic blood pressure (SBP) and diastolic blood pressure (DBP) as time-dependent covariates in outcome regression models. ‡Including HbA1c, TC, LDL, HDL, TG, SBP and DBP as time-dependent covariates in atorvastatin-treatment probability models. CI, confidence interval; HR, hazard ratio; IPT, inverse probability of treatment; RPSFT, rank-preserving structural failure time.

period. It is likely that mild cholesterol lowering with other statins (data not provided) shows similar beneficial effects as atorvastatin. For the purpose of ascertaining whether mild cholesterol lowering with statins reduces cardiovascular and diabetic-related events, we also estimated the effect of any statin instead of atorvastatin. A total of 14 patients per 634.2 statin-treated person-years and 107 per 4564.3 untreated person-years had cardiovascular events, and 15 per 631.8 statin-treated person-years and 141 per 4526.1 untreated person-years had diabetes-related events. Estimated HR are 0.67 (95% CI = 0.35–1.28, $P = 0.23$) for cardiovascular events and 0.56 (95% CI = 0.31–1.03, $P = 0.06$) for diabetes-related events from the IPT weighted Cox models (the RPSFT model gives similar results, data not provided). Although the preventive effects of any statin on cardiovascular and diabetes-related events were estimated, its effects were weaker than the effects of atorvastatin (Table 5). Because more beneficial effects of atorvastatin were shown, which includes a contrast of atorvastatin versus other statins rather than of any statin versus no statin, intensive control of cholesterol levels by atorvastatin seems important for the prevention of cardiovascular and diabetes-related events in elderly diabetic patients.

The J-EDIT data suggested that atorvastatin might slightly increase coronary vascular risk. It is difficult to confirm clinical meaning fullness of such slight increases in HR (~1.5 in Models 4 or 5) of coronary events with atorvastatin, as the number of coronary events in the atorvastatin treatment period was too small for confidence intervals to preclude the possibility of too wide a range of effects to interpret the result. Although the preventive effect of atorvastatin on coronary vascular event could not be shown in the present study as in previous studies,[1,2] we observed a strong preventive effect for cerebrovascular risk outweighing it (although the number of cerebrovascular events in the atorvastatin treatment period was also small). This can lead to a beneficial overall effect of atorvastatin on cardiovascular risk, especially in the Japanese population, which experience heavier burdens of cerebrovascular risk, compared with Caucasian populations. Furthermore, the reduced risk imposed by atorvastatin of diabetes-related events and all-cause mortality (5 per 523.2 person-years in treated patients and 89 per 4963.5 person-years in untreated patients: HR = 0.40 [95% CI = 0.12–1.29, $P = 0.12$] from an IPT-weighted Cox model; similar results with an RPSFT model) suggested that an unexpected event or adverse effect, including death, did not outweigh the benefit experienced by atorvastatin in the J-EDIT.

Mechanisms of the preventive effects for vascular events by statins have been of great interest. Determining whether the benefits experienced by atorvastatin can be attributed to atorvastatin treatment itself or to lowering cholesterol levels is a challenging task, but exploring the mechanisms is helpful to understand the present results. As we have showed that lower cholesterol levels were well achieved by atorvastatin (Tables 3 and 4 and the corresponding weighted GEE analyses), this might offer a clue to the cholesterol-lowering-mediated effect of atorvastatin if cholesterol levels independently predict the occurrence of vascular events. We tried to assess the prediction of the occurrence of vascular events based on LDL cholesterol target levels, using an IPT weighted Cox model including whether the LDL target levels were achieved as a "treatment" and atorvastatin treatment as a time-dependent confounder. We found that LDL levels lower than target values could reduce both cardiovascular events (HR = 0.72, 95% CI = 0.48–1.06, $P = 0.10$) and diabetes-related events (HR = 0.82, 95% CI = 0.58–1.17, $P = 0.29$) independently of atorvastatin, which might show the presence of an LDL-lowering-mediated effect of atorvastatin. Formal statistical assessment as to atorvastatin's cholesterol-lowering-mediated effects is the subject of future work, which might be carried out using the marginal structural models[33,34] or the structural nested models.[35,36]

Several studies have reported the possibility that statins might increase diabetic risk by increasing blood glucose levels.[30–32] We examined whether the adverse effect of atorvastatin on HbA1c existed in J-EDIT patients during the follow-up period. The weighted GEE did not show that atorvastatin had increased HbA1c levels ($P = 0.38$), and the slight increase of HbA1c (0.06%) seemed to have little clinical impact on diabetic patients. We also carried out a weighted GEE analysis with all statins. Again, there was no clinically meaningful effect on HbA1c levels (increase by 0.02%, 95% CI = –0.05% to 0.10%, $P = 0.55$).

The present study has strengths and limitations. J-EDIT was the first intervention trial with atorvastatin that targeted elderly patients with type 2 diabetes mellitus. Because our data originally came from a randomized controlled trial providing longitudinal (or repeated measures) data on atorvastatin prescription and various clinical characteristics affecting both treatment and outcome, we were able to assess the effects of atorvastatin on several end-points during the follow-up period. We then adjusted for these clinical characteristics during the study using the statistical methods developed to adjust for time-dependent confounding, namely, the IPT weighting and *g*-estimation methods. These methods for time-varying treatments have increasingly gained widespread use in recent medical literature.[37,38] These methods were not used previously in guidelines[1,2,6] or meta-analyses[3–5] that examined the effects of statins on cardiovascular disease; they did not tackle the problem of outcome-related treatment changes. Although we treated the J-EDIT data as if they came from a cohort study, the present study provided consistent results previously reported mainly from intention-to-treat or

baseline-adjusted analyses in randomized controlled trials, strengthening the evidence for the beneficial effect of statins.[1–6]

In contrast, observational analyses in the present study largely depended on the assumptions that all confounders were collected in the data or that statistical models correctly approximated a real treatment–disease relationship, which cannot be verified by observed data. It is unlikely that all assumptions hold rigorously, we cannot exclude the likelihood of bias in our effect estimates.

The limited number of events restricted our analyses to a more detailed examination of end-points, especially on differences between the effects of atorvastatin on coronary vascular disease and on cerebrovascular disease. Longer or larger trials are needed to assess the mechanisms of prevention of cardiovascular disease by atorvastatin. In addition, our data contained no information on statin dose, which also makes it difficult to examine whether the benefits experienced by atorvastatin were a result of the statin itself or of lowered cholesterol levels.

Finally, the results from conventional Cox models showed an attenuated effect of atorvastatin compared with a greater risk reduction estimated through IPT weighted Cox models and RPSFT models. We attribute this discrepancy between the effects estimated from different models to an underestimation-bias in conventional methods. We suspected confounding-by-indication, that is, atorvastatin treatment was initiated more often among patients with a worse prognosis (Table 2), which would have resulted in disadvantageous effect estimates in the baseline-adjusted Cox models. In time-dependent-adjusted Cox models, in contrast, we would have blocked a part of the atorvastatin effect by including subsequent covariates in the models (the effect of atorvastatin on cholesterol levels was ascertained in Table 3 or 4), which would again have resulted in an underestimation of the effect of atorvastatin. Comparing results from different methods should clarify the usefulness of the structural modeling approaches that can appropriately adjust for time-dependent confounding in observational data where outcome-related treatment switching is suspected.

In conclusion, elderly patients with type 2 diabetes would experience risk reductions in cardiovascular and diabetes-related complications by intensive cholesterol lowering with atorvastatin. Our findings reinforce previous evidence for the beneficial effect of atorvastatin in younger populations with or without type 2 diabetes and in aged populations without type 2 diabetes.

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Conflict of interest

There is no conflict of interest. The J-EDIT Study Group has not cleared any potential conflicts.

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Appendix

Explanation and implementation of the IPT weighting and g-estimation methods

IPT weighting method for fitting the marginal structural models

As noted in the main text, time-dependent covariates would have been confounders for subsequent treatments and thus must have been adjusted for, but they would also have been affected by earlier treatments and adjustment for them should not have been made, in conventional models. One of the solutions to this dilemma is to use a weighted Cox model (Model 4 in the main text), adjusting baseline covariates with time-varying "stabilized" weights at time t:

$$SW_i(t) = \prod_{k=0}^{t} \frac{\Pr\left[A(k) = a_i(k) \middle| \bar{A}(k-1) = \bar{a}_i(k-1), L(0) = l_i(0)\right]}{\Pr\left[A(k) = a_i(k) \middle| \bar{A}(k-1) = \bar{a}_i(k-1), \bar{L}(k) = \bar{l}_i(k)\right]}$$

for patient i ($i = 1, \ldots, 1073$), where $A(k)$ denotes atorvastatin treatment (1 for initiated, 0 for never-initiated) and $L(k)$ denotes set of time-dependent covariates in Model 2 at the annual visit k ($k = 0, \ldots, 6$; $k = 0$ is at baseline visit); lower cased variables with indicator i are values of the variables actually observed for i; over-bar with k in parenthesis represents the history of the variable up to k; and $L(0)$ includes all adjusted baseline covariates. Because each term of $SW_i(t)$ of $k \leq t$ is proportional to the reciprocal of conditional probability of the actually received treatment for patient i at visit k given the past treatment and the covariate history up to visit k, this weighted model-fitting approach is called the "inverse-probability-of-treatment" (IPT) weighting method. We predicted conditional probabilities in $SW_i(t)$ for each patient i by the pooled logistic models fitted to regression of $A(k)$ on corresponding baseline and time-dependent variables: in the analyses, we included $A(k-1)$ for past treatment, $L(k-1)$ for time-dependent covariates (HbA1c, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, systolic and diastolic BP, and BMI), and $L(0)$ for the others. Time-dependent covariates $L(k)$ were adjusted by using them to calculate the IPT weights $SW_i(k)$ in this method rather than by adding them to the regressors as time-dependent explanatory variables in the Cox models. To correct outcome-related censoring, we also estimated the inverse-probability-of-censoring (IPC) weights in the same manner, and multiplied them by the estimated IPT weights. Then we approximated an IPT and IPC weighted Cox model by fitting a weighted pooled logistic model to each event probability, such as Model 3 (to cope with the limitation of PROC PHREG, which does not allow time-dependent weights in SAS version 9.2), that included only baseline covariates and a time-dependent atorvastatin treatment status. Formally, our IPT weighted Cox model estimators converge to the parameters of the marginal structural Cox model that models counterfactual event hazards that would have been observed had, possibly contrary to fact, all patients followed any specific regime of atorvastatin treatment during the follow-up period[17–19] under the assumption of consistency,[39] positivity[40] and no-unmeasured confounders (whether time-dependent or not). We could easily fit this weighted Cox model by PROC GENMOD, in which weights and repeated statements were specified, on SAS software.

G-*estimation method for fitting the structural nested models*

We modeled counterfactual time-to-event outcome U_i (years) that patient i would have had if the patient had never been prescribed atorvastatin throughout the follow-up period. The RPSFT model (Model 5) linked a counterfactual U_i to an observed time-to-event outcome T_i (years) as:

$$U_i = \int_0^{T_i} \exp[-\psi_0 A_i(t)]dt,$$

where ψ_0 is the targeted parameter: a positive sign implies atorvastatin extends time-to-event (i.e. beneficial effect); a negative sign implies atorvastatin contracts the time to event (i.e. harmful effect); and $\psi_0 = 0$ implies $U_i = T_i$ regardless of the value of $A_i(t)$ for all patients i (i.e. sharp causal null hypothesis[15] is true for the effect of atorvastatin throughout the follow-up period). For comparison with the other methods, we presented $\exp(-\psi_0)$, which represents the hazard ratio under the constant hazard, that is, U_i follows exponential distribution.

We defined a random variable $U_i(\psi)$ as equal to the right-hand side of the aforementioned RPSFT model equation evaluated at ψ instead of true ψ_0. Note that despite unknown ψ_0, we can obtain $U_i(\psi)$ from observed T_i and $A_i(t)$ by substituting an arbitrary value for ψ. If we correctly specify ψ as true ψ_0, $U_i(\psi)$ is the counterfactual time-to-event outcome U_i under no treatment. Then the model parameter ψ_0 can be estimated by the g-estimation technique that requires modeling the conditional probabilities of initiating atorvastatin at each time k as functions of past treatments and the covariates history up to k. In the analyses used in the present article, we fitted the pooled logistic model used in the fitting process of Model 4 (in order to estimate SW in the IPT weighting) to the probabilities of $A(k) = 1$, including also $U_i(\psi)$ as a regressor in this time. The definition of no-unmeasured confounding implies that the conditional probability of initiating treatment given all potential confounders does not depend on any counterfactual outcomes. Because

$U_i(\psi_0) = U_i$ is a counterfactual outcome, it should not predict the treatment probability under the no-unmeasured confounders condition and thus a coefficient of $U_i(\psi_0)$ in the regression model for treatment probability should be 0. Hence, if we obtained 0 for the coefficient of $U_i(\psi)$ in repeated fitting procedures over different values for ψ, the substituted value ψ yielding such $U_i(\psi)$is the "*g*-estimate" of ψ_0.

However, owing to administrative censoring at 6 years after follow up and loss to follow up in the J-EDIT, $U_i(\psi)$ cannot be calculated for all patients. So, we used an artificial time-to-event variable $X_i(\psi) = \min\{U_i(\psi), \min(C_i, C_i \times \exp[-\psi])\}$ for patient i and the patient considered to occur event only if $U_i(\psi) \leq \min(C_i, C_i \times \exp[-\psi])$, where C_i is the observed censoring time for censored patients or set to six for patients who had an event. We used this "artificial ψ-censoring" indicator[20–23] $\Delta_i(\psi)$ (0 for ψ-censored, 1 for a considered event evaluated at ψ) in place of $U_i(\psi)$ in actual *g*-estimation procedure. Note that $X_i(\psi)$ and $\Delta_i(\psi)$ can be computed for all patients regardless of their censoring status in real data, because censored patients in real data were necessarily ψ-censored at every value of ψ (i.e. that $T_i > C_i$ implies $U_i(\psi) > \min(C_i, C_i \times \exp[-\psi])$ for all ψ). For correcting selection bias as a result of non-administrative censoring (i.e. loss to follow up during the study), $\Delta_i(\psi)$ was weighted (multiplied) by an IPC weight of the patient's probability of remaining uncensored through the last visit before an event or the administrative end of follow up, whichever came first.[21,23] The weight for each patient was estimated from the pooled logistic model for conditional probability of being uncensored at each k given treatment and covariate history. Confidence intervals were constructed by test-based method, where 95% confidence intervals for ψ_0 consisted of those values of ψ for which the robust Wald test in the atorvastatin-treatment probability model failed to reject the hypothesis that a coefficient of IPC weighted $\Delta_i(\psi)$ equals 0 at the 5% level.[20,21] Similarly, *P*-values for the null hypothesis of $\psi_0 = 0$ were obtained from the robust Wald test in the *g*-estimation procedure evaluated at $\psi = 0$. The RPSFT models are also regarded as the structural accelerated failure time models,[23] and are the simplest case of structural nested failure time models.[22] This *g*-estimation procedure requires the consistency and no-unmeasured confounding assumptions, but not the positivity assumption under the correct structural modeling assumption.[23] We repeatedly carried out the procedures in PROC GENMOD so as to obtain the *g*-estimates and the 95% confidence limits by grid searching.