(g-estimation) is to realize that U_i is a baseline variable identically distributed across the randomized groups. We define $U_i(\psi)$ to equal the right-hand side of (10) for given ψ. We also define $Z(\psi)$ to be a test statistic comparing the distribution of $U(\psi)$ in the two randomized groups, where we will use the log-rank test. The point estimate of ψ_0 is the value for which $Z(\psi)=0$, and this can be found by a search over a grid. A $100(1-\alpha)$ per cent confidence interval for ψ_0 is the range of values for which $|Z(\psi)|<z_{1-\alpha/2}$, where $z_{1-\alpha/2}$ is the $1-\alpha/2$ percentile of the standard normal distribution. One attractive point of this approach is that at the null value, it is non-parametric, because $U_i(0)=T_i$; hence, $Z(0)$ is the usual ITT log-rank test statistic.

However, if T_i is a censored time, then $U_i(\psi)$ is censored at

$$D_i(\psi)=\int_0^{C_i}\exp[-\psi S_i(t)]\,dt$$

where C_i is defined as the time between subject i's randomization and the fixed end of the follow-up date. Although C_i is known for uncensored as well as censored subjects, $D_i(\psi)$ is a function of $S_i(t)$ and may depend on the underlying prognosis. Therefore, even when censoring on the T-scale is non-informative, that is, an administrative censoring, censoring on the U-scale is likely to be informative, if $\psi_0\neq 0$ and there is non-random non-compliance. Thus, we cannot replace T_i by $X_i=\min(T_i, C_i)$ to calculate the pseudo-treatment-free event time.

To avoid this problem, Robins and Tsiatis [10] defined a new censoring time $C_i(\psi)=C_i$ if $\psi\leqslant 0$ and $C_i(\psi)=C_i\exp(-\psi)$ if $\psi>0$, according to the direction of treatment effect. For given ψ, let $X_i(\psi)=\min[C_i(\psi), U_i(\psi)]$ and $\Delta_i(\psi)=I[U_i(\psi)>C_i(\psi)]$ to be the new follow-up time and censoring indicator, respectively. $X_i(\psi)$ is observable since $T_i\geqslant C_i$ implies $U_i(\psi)>C_i(\psi)$. Because any function of $\{U_i(\psi), C_i\}$ is independent of random treatment assignment R_i, we have $\{U_i(\psi_0), \Delta_i(\psi_0)\}\coprod R_i$, where the symbol $\coprod$ means independent.

4.3. Results of simulations

Table II shows the results. The constant treatment effect model (3) with $M=3$ was applied in the intensity score analysis, where a logistic regression model (9) was used for the estimation of the propensity score at $t=2$ and 4. From Table II we see that both the AT and ITT estimates were largely biased toward the null in all situations (true value of treatment effect $=0.5$). The biases increased as the difference of non-compliance proportion between groups increased and as the censoring proportion decreased. The α-errors for the ITT estimate were close to the nominal level of 5 per cent, reflecting that the ITT approach provides a valid test for the null hypothesis of no treatment effect even in the presence of non-random non-compliance.

As expected, the g-estimates performed well in all situations, because the data generation process was based on the SAFT model (10). Note that the powers for the ITT and g-estimate were about the same, reflecting that even though the g-estimation approach uses non-compliance information it does not increase the power against the null hypothesis when compared with the ITT approach.

The intensity score estimates were nearly unbiased and their coverage probabilities were close to the nominal level of 95 per cent in all situations. The α-errors were controlled under the correctly specified parametric model (9). The intensity score estimates gave smaller MSE and narrower confidence intervals than those of the g-estimates, except in the censoring proportion $=90$ per cent. The powers were slightly increased compared with the g-estimates.

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Table II. Results of simulation studies for AT, ITT, g-estimation, and IS method.

Method	Non-compliance	Censoring (per cent)	Bias	MSE	CI length	95 per cent CP	Power	α Error
AT	45 *versus* 15 per cent	0	−0.415	0.175	0.183	0.0	44.3	100.0
		30	−0.405	0.170	0.216	0.0	41.4	100.0
		90	−0.230	0.074	0.564	64.0	47.5	30.4
	30 *versus* 10 per cent	0	−0.363	0.134	0.180	0.0	84.3	95.0
		30	−0.353	0.127	0.212	13.7	77.7	100.0
		90	−0.190	0.056	0.559	73.7	57.8	22.2
ITT	45 *versus* 15 per cent	0	−0.305	0.095	0.176	0.0	99.4	5.6
		30	−0.295	0.090	0.209	0.1	97.0	5.8
		90	−0.138	0.041	0.567	82.6	71.1	4.8
	30 *versus* 10 per cent	0	−0.253	0.066	0.177	0.0	99.9	4.3
		30	−0.243	0.062	0.209	0.4	99.8	6.1
		90	−0.108	0.033	0.566	87.2	78.4	4.6
g-estimation	45 *versus* 15 per cent	0	0.006	0.013	0.541	95.1	99.4	5.6
		30	0.008	0.018	0.615	94.3	97.0	5.8
		90	0.001	0.037	0.854	94.6	70.9	4.9
	30 *versus* 10 per cent	0	0.001	0.009	0.454	95.4	99.9	4.3
		30	0.003	0.015	0.509	97.0	100.0	6.1
		90	−0.001	0.032	0.825	96.5	78.3	4.6
Intensity score	45 *versus* 15 per cent	0	−0.046	0.005	0.274	95.7	100.0	5.2
		30	−0.019	0.005	0.287	94.5	100.0	4.6
		90	0.060	0.061	0.959	97.8	74.3	4.7
	30 *versus* 10 per cent	0	−0.045	0.004	0.257	95.2	100.0	4.5
		30	−0.018	0.005	0.262	95.2	100.0	4.6
		90	0.053	0.046	0.840	98.0	82.4	4.7

AT, as-treated; MSE, mean-squared error; CI, confidence interval; CP, coverage probability.

5. ANALYSIS OF MEGA STUDY DATA

In the analysis of the MEGA study data, we divided the follow-up period into 10 time intervals with equal space (1 year). Patients were classified as a non-complier in a time interval if he/she switched to the other trial treatment at least once during the interval.

5.1. Estimation of the propensity score

To estimate the propensity score at each time t ($t=0,\ldots,9$), the logistic regression model (4) was used, in which four time-dependent factors as well as 12 baseline factors shown in Table I were included as covariates $H_i(t)$. For the four time-dependent factors, the most recent recorded values were included as covariates $H_i(t)$ in model (4). All TC values were excluded accounting for the multicollinearity of covariates. Among baseline factors, missing data were observed in the values of BMI (0.24 per cent), current smoking (0.18 per cent), and drinking (0.17 per cent). The missing values of BMI were imputed by the mean value of 23.8 (kg/m^2). The latter two factors were imputed by zero (no smoking and no drinking, respectively). Four time-dependent factors were three lipids (TG, HDL-C, and LDL-C) and treatment actually received before time t. For the

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Table III. Predictors of receiving the pravastatin treatment at $t=3$.

Predictors	Odds ratio	95 per cent CI
Baseline covariates		
Assigned treatment	4.645	3.536, 6.102
Age (years)	1.008	0.991, 1.026
Women	0.916	0.663, 1.264
BMI (kg/m^2)	1.008	0.968, 1.050
Current smoker	1.262	0.884, 1.800
Current drinking	0.932	0.684, 1.271
Medication history	1.484	1.086, 2.029
Hypertension	1.169	0.915, 1.493
Diabetes	1.247	0.938, 1.658
TG (mg/dL)	1.001	0.998, 1.003
HDL-C (mg/dL)	0.992	0.974, 1.010
LDL-C (mg/dL)	1.013	1.003, 1.023
Time-dependent covariates		
TG (mg/dL) at $t=2$	1.003	1.001, 1.005
HDL-C (mg/dL) at $t=2$	1.030	1.014, 1.046
LDL-C (mg/dL) at $t=2$	1.010	1.001, 1.015
Treatment received at $t=2$	240.2	179.2, 321.7

CI, confidence interval; medication history: hypercholesterolemia medication history.

missing data of lipid values (21.5 per cent), the regression imputations were separately conducted, where 11 baseline factors, allocation group, and the last observed lipid value were included as covariates in each prediction model.

Table III shows the odds ratio of each factor associated with receiving the pravastatin treatment at time $t=3$. The results for other time points (not shown) were essentially similar to those shown in Table III. For the baseline covariates, patients who were assigned to the pravastatin group and have hypercholesterolemia medication history tended to receive the pravastatin treatment. As expected, the previous use of pravastatin also predicted the use of pravastatin subsequently.

5.2. Estimation of treatment effect adjusting for treatment changes

Table IV shows the estimates of treatment effect by several methods. Hazard ratios for stroke event, which was one of the secondary endpoints in the MEGA study, were also presented. Analysis models for stroke were the same as those for CHD events, and similar results for factors associated with receiving the pravastatin treatment were observed (not shown) as shown in Table III. For both CHD and stroke events, two analyses were conducted, where each endpoint was evaluated at 5 or 10 years, respectively. Two intensity score estimates were obtained: one (intensity score 1) was the constant treatment effect by applying model (3) and the other (intensity score 2) was the cumulative treatment effect by applying model (7).

Both the intensity score and g-estimation methods gave the larger treatment effects for pravastatin than the ITT ones for all endpoints. The adjustment effects were larger in the stroke events. The statistically significant effect in the stroke event at 10 years was observed by the intensity score 1 (hazard ratio = 0.51; 95 per cent CI: 0.28–0.95). The results from intensity score 2, in particular

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Table IV. Estimates of treatment effect for CHD and stroke events.

	CHD				Stroke			
	5 years		10 years		5 years		10 years	
Method	HR	95 per cent CI	HR	95 per cent CI	HR	95 per cent CI	HR	95 per cent CI
ITT	0.70	0.50, 0.97	0.67	0.49, 0.91	0.65	0.43, 0.97	0.83	0.57, 1.21
Intensity score 1	0.68	0.44, 1.05	0.59	0.36, 0.99	0.44	0.25, 0.79	0.51	0.28, 0.95
Intensity score 2	0.68	0.46, 1.02	0.66	0.27, 1.60	0.53	0.31, 0.90	0.45	0.17, 1.21
g-estimation	0.65	0.30, 0.91	0.64	0.39, 0.83	0.54	0.26, 0.87	0.63	0.33, 1.26

HR, hazard ratio; CI, confidence interval; intensity score 1, constant treatment effect from model (3); intensity score 2, cumulative treatment effect from model (7); g-estimation, semi-parametric randomization-based analysis using model (10).

at 10 years, gave the wider confidence intervals than those from intensity score 1, which probably reflects the sparse data problems in estimating $\beta_I(t)$. The confidence intervals for the g-estimates contained the null value of 1 whenever the ITT result was not significant.

6. DISCUSSION

In this paper, we developed the intensity score approach for time-to-event outcomes with censoring to estimate the causal treatment effect in the presence of non-random non-compliance. The proposed approach has three major advantages over the g-estimation based on the SAFT model (10). The first advantage is that an artificial recensoring scheme (Section 4.2) is necessary requirement for the g-estimation to account for administrative censoring correctly, while the proposed approach can treat the censoring uniquely within the framework of standard regression models. The rationale for recensoring in the g-estimation is that if the potential baseline failure time U_i is independent of treatment assignment, the same should be true for any function of U_i and C_i since C_i is a baseline covariate. Therefore, there are several choices for an observable random variable that is a function of $\{U_i, C_i\}$ as a basis for inference [13, 16, 22].

The second major advantage of the proposed approaches is that they can be easily extended to the estimation of time-dependent treatment effects such as (6), where the technique of g-estimation has been difficult to apply in practice to the multi-parameter model. Although the constant treatment effect model (1) is very simple, model (6) is more robust to the estimation of dynamic sequential treatments conditional on past medical history. This robustness property of model (6) will be compromised with the sacrifice of the precision as shown in Table IV. To avoid the sparse-data problems, Brumback *et al.* [9] proposed the use of parametric constraints among the $\beta_I(t)$ such as $\beta_I(t) = a_0 + a_1 t$ depending on context.

The third advantage is its ease of application, that is, the g-estimate can be obtained in three steps: we compute propensity scores, derive intensity scores, and fit an ordinary regression model for any outcome variable, although the correction term must be subtracted from the estimating function to obtain the consistent estimator.

Nevertheless, the g-estimation has a number of advantages over the proposed approach. First one is that it is a semi-parametric randomization-based approach, that is, it preserves the validity of tests of the null hypothesis regardless of what determinants of outcome have influenced a

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patient's decision to comply. Furthermore, the g-estimation provides estimated effects that are of the same sign as the ITT effect and that are only statistically significant if the ITT analysis is statistically significant. In relation to this point, a major drawback of the intensity score approach is that one must be able to specify a correct model for the conditional probability of treatment, $\Pr[S_i(t)|H_i(t)]$, for each t up to the end of follow-up, although the increase of power will be anticipated. Unfortunately, the assumption of no unmeasured confounders (2) is a non-identifiable assumption and is not testable from the observed data. Furthermore, even when assumption (2) is approximately true, we require strong modeling assumptions, since there are many covariates in $H_i(t)$. It is unlikely that these modeling assumptions would be precisely correct. In the MEGA study, many clinically important prognostic factors were measured and all of them were used as covariates to estimate the propensity score at each time. In addition to the prediction model shown in Table III, the analyses based on other prediction models, such as a parsimonious model using a variable selection procedure or full models in which time-dependent covariates, were entered as the difference from the baseline or the absolute past two values, and the intensity score estimates were shown to be insensitive to the selection of the prediction models conditional on the measured covariates.

Another advantage of the g-estimation over the intensity score approach is that one can use the SAFT model (10) to estimate the effect of a treatment on outcome in studies, where at each time t there is a covariate level such that all patients with that level of the covariate are certain to receive the identical treatment. For example, this circumstance implies that the intensity score approach should not be used for the analysis of non-compliance data, in which treatment switching was observed in only one group, because the intensity score at each time will be zero for patients in the complete compliance group. Robins [23] and Robins *et al.* [24] discussed a similar problem, that is, structural zero, for the adjustment of time-dependent confounding and showed that the IPTW (inverse probability of treatment weighted) estimators, which are based on the propensity score, are biased for the data with structural zero.

As Brumback *et al.* [9] have discussed, the intensity score approach resembles the IPTW estimation method based on the marginal structural model (MSM). Although the MSM is useful for estimating the causal effect of the pre-specified treatment regime such as always treat or treat on alternate month [23, 24], it is much less useful for modeling the interaction of treatment with a time-dependent covariate and for estimating the effect of a dynamic treatment plan in which the treatment on a visit depends on a subject's evolving covariate history. It is important to recognize that actual medical treatment regimes including non-compliance data are usually dynamic, and the SNMM is more suitable for parametrizing such dynamic effects. Another difference between the SNMM and the MSM is that the latter makes fewer assumptions than the former by not requiring treatment effects to be constant across strata of covariate history, because the IPTW estimators can be interpreted as standardized parameters [24, 25]. Thus, in theory, the IPTW estimator is more robust than the intensity score one.

In the analyses of the MEGA study data, we observed the larger adjustment effects in the stroke events in spite of the fact that factors associated with non-compliance were nearly the same for CHD and stoke events in each group. The explanatory analyses among the non-compliant cases were conducted to investigate the relation between the non-compliance rate (/year) of each case and the occurrence of each event. These analyses showed that, in the diet group, the effect of non-compliance rate on the non-occurrence of stroke events (odds ratio = 144; 95 per cent CI: 1.3–∞; 5 stroke events among 865 non-compliant cases) was larger than that of CHD events (odds ratio = 14.5; 95 per cent CI: 1.7–150; 19 CHD events among 844 non-compliant cases), while,

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in the pravastatin group, the effect of non-compliance rate on the occurrence of stroke events (odds ratio = 5.7; 95 per cent CI: 1.2–26; 16 stroke events among 2440 non-compliant cases) was also larger than that of CHD events (odds ratio = 1.3; 95 per cent CI: 0.3–5.3; 20 CHD events among 2441 non-compliant cases). These facts may explain the larger discrepancy between the ITT estimate and the causal one observed in stroke events.

In the MEGA study, like any other clinical trial, dropout of patients during the study period was observed. In addition to the usual loss to follow-up cases, there was another problem of dropouts due to the refusal of further follow-up at 5 years [17, 18]. In this paper, we considered all these dropout cases as non-informative censoring cases. Because observed dropout proportions were not different among treatment groups (loss to follow-up: 546/3966 = 0.14 in diet group and 594/3866 = 0.15 in pravastatin group; refusal of follow-up by patients: 278/3966 = 0.07 in diet group and 270/3866 = 0.07 in pravastatin group), the effect of these dropouts on the comparison of treatment group may seem to be small. However, these non-administrative censorings may be informative and hence a source of selection bias. To adjust for selection bias due to non-administrative censoring, the IPCW (inverse probability censoring weighted) method has been proposed [26–28]. The underlying idea of the IPCW method is to base estimation on the observed outcomes but weight them to account for the probability of being uncensored. We analyzed the MEGA study data using the IPCW method which can adjust for some types of dependent censorings, and confirmed that there were no large differences between the ITT estimates and the IPCW ones for both CHD and stroke events [29]. Our intensity score method can also incorporate the IPCW method, and this will be a future work.

APPENDIX A

We show that the correction term $N\beta_I C$ must be subtracted from the WLS estimating function to obtain a consistent estimator of β_0 in (1), where $C=(1/N)(\sum_{t=0}^{M-1}\hat{I}_i(t))\omega_i(\sum_{t=0}^{M-1}E(S_i(t)|H_i(t);\hat{\theta}))$ and $\omega_i=\exp(-\mu)\cdot T_i\cdot\exp(-\beta_I\sum\hat{I}_i(t))$. We define the 'estimated' potential outcome under no treatment:

$$\log\hat{T}_{0i}\equiv\log T_i-\beta_0\sum_{t=0}^{M-1}S_i(t)$$

Under model (1) and assumption (2), the estimated potential outcome is mean independent of future treatment given past history, which implies that $E[\hat{I}_i(t)\cdot w_i\cdot(\log\hat{T}_{0i}-\mu)]=0$, $t\leqslant M-1$. Therefore,

$$E\left(\sum_{t=0}^{M-1}\hat{I}_i(t)\cdot w_i\cdot\left[\log T_i-\mu-\beta_0\sum_{t=0}^{M-1}S_i(t)\right]\right)=0 \tag{A1}$$

Now, the WLS estimating equation that $\hat{\beta}_I$ solves under model (3) has unconditional mean zero if and only if $E(\sum_{t=0}^{M-1}\hat{I}_i(t)\cdot w_i\cdot[\log T_i-\mu-\beta_I\sum_{t=0}^{M-1}\hat{I}_i(t)])=0$. Substituting $\hat{I}_i(t)=S_i(t)-E[S_i(t)|H_i(t);\hat{\theta}]$ yields

$$E\left(\sum_{t=0}^{M-1}\hat{I}_i(t)\cdot w_i\cdot\left[\log T_i-\mu-\beta_I\sum_{t=0}^{M-1}S_i(t)+\beta_I\sum_{t=0}^{M-1}E[S_i(t)|H_i(t);\hat{\theta}]\right]\right)=0 \tag{A2}$$

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Comparing (A1) with (A2), it follows that $\hat{\beta}_I$ is consistent for β_0 if for any t, $\hat{I}_i(t) \neq 0$ and $E(\sum_{t=0}^{M-1} \hat{I}_i(t) \cdot w_i \cdot \sum_{t=0}^{M-1} E[S_i(t)|H_i(t); \hat{\theta}]) = 0$.

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Antiplatelet Cilostazol Is Beneficial in Diabetic and/or Hypertensive Ischemic Stroke Patients

Subgroup Analysis of the Cilostazol Stroke Prevention Study

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Key Words
Antiplatelet · Diabetes · Hypertension · Lacunar infarction · Stroke prevention

Abstract
Background and Purpose: Although antiplatelets are known to be effective for secondary prevention of cerebral infarction, the number needed to treat is rather large and the effects in stroke patients with complications such as hypertension or diabetes are inadequately defined. This study was conducted to examine the effect of such complications on recurrence of cerebral infarction, and to assess the effect of cilostazol, an antiplatelet agent, in these high-risk subjects. ***Methods:*** A post hoc subgroup analysis of the already reported Cilostazol Stroke Prevention Study, which was a placebo-controlled double-blind trial, has been carried out to clarify the influence of various complications on recurrence in the placebo group and the effects of cilostazol in 1,095 patients with noncardioembolic ischemic cerebrovascular disease. Treatment continued for an average of 1.8 ± 1.3 years (maximum 4.8 years). ***Results:*** The recurrence rate of the diabetic stroke patients was significantly higher compared with the nondiabetics in the placebo group (9.4 vs. 4.7%/year, $p = 0.01$). Furthermore, our study showed that the relative risk reduction (RRR) for recurrence of infarction was 41.7% with cilostazol. This treatment provided a significant benefit in patients with lacunar infarction (RRR 43.4%, $p = 0.04$), with diabetes (RRR 64.4%, $p = 0.008$), or with hypertension (RRR 58.0%, $p = 0.003$). ***Conclusions:*** Diabetic patients are particularly at risk for recurrence of cerebral infarction. Cilostazol is useful for the prevention of the recurrence of vascular events in patients with lacunar infarction, and is probably effective in high-risk patients with diabetes and/or hypertension.

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A meta-analysis performed by the Antithrombotic Trialists' Collaboration [1] indicated that antiplatelet agents such as aspirin, ticlopidine, dipyridamole or clopidogrel are effective in preventing recurrence of vascular events in patients with stroke or transient ischemic attack. However, the calculated number needed to treat (NNT) was 28 for recurrence of vascular events during the 29-month observation period and 40 for recurrence of cerebral infarction over 3 years of observation [1]. This means that 40 patients have to take these medications for more than 2 years in order to rescue 1 patient from recurrence of cerebral infarction. Moreover, the effects of antiplatelets on subtypes of nonembolic stroke, such as lacunar infarction, which may have a different pathogenesis from atherothrombotic infarction, remain an enigma. Numerous adverse reactions have been reported in association with the use of these antiplatelets, and new medications have been sought that would provide more effective action with fewer side effects.

The Cilostazol Stroke Prevention Study (CSPS) was a multicenter double-blind placebo-controlled, randomized clinical trial performed between 1992 and 1996 to study the long-term safety and effectiveness of the antiplatelet drug cilostazol [2, 3]. Cilostazol prevents platelet aggregation by increasing cyclic adenosine monophosphate (cAMP) levels in platelets via inhibition of cAMP phosphodiesterase, thus reducing the risk of recurrence of cerebral infarction [2]. In addition, cilostazol is reported to have biological actions beyond antiplatelet activity, such as a vasodilatory action [4, 5], a vascular endothelial cell protection [6] and improvement of lipid metabolism [7]. The use of aspirin for the prevention of recurrence of cerebral infarction was not approved by the Japanese Ministry of Health, Labour and Welfare at the time of the CSPS, which covered more than 1,000 CT- or MRI-proven ischemic stroke patients, so this trial was placebo controlled, which would no longer be possible for new studies, for ethical reasons. It was also the first prospective study classifying patients into subtypes of ischemic stroke, that is, atherothrombotic infarction, lacunar infarction and undetermined type.

Since we thought the CSPS data would be valuable for evaluating the efficacy of antiplatelet therapy for cerebral infarction, we reexamined the data and performed a post hoc subgroup analysis. The objectives of this report were to examine the effect of various complications on recurrence of cerebral infarction in the placebo group, and in particular, to assess the effect of cilostazol in patients at high risk.

Materials and Methods

The results of the general analysis of the CSPS have been reported elsewhere [2]. In brief, the study was performed between 1992 and 1996, at 183 institutes throughout Japan, covering 1,095 patients with a prior history of symptomatic cerebral infarction (transient ischemic attack and cardioembolic infarction were excluded from this study) that had developed 1–6 months before randomization. Diagnosis was confirmed by clinical signs and symptoms, and CT or MRI in all subjects. All patients provided written informed consent and were randomized to cilostazol (547 patients) or placebo (548 patients). Cilostazol was administered as a 100-mg tablet twice daily and placebo tablets were matched for appearance and administration schedule. Treatment continued for an average of 1.8 ± 1.3 years (maximum 4.8 years). Out of 1,095 patients, 1,067 were available for the intention-to-treat analysis.

For the efficacy analysis, a per protocol set of 526 patients in the cilostazol group (396 lacunar infarction, 73 atherothrombotic infarction, 57 undetermined type), and 526 patients in the placebo group (389, 68, and 69 patients, respectively) were available for subgroup analysis.

The criteria for hypertension were systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or current treatment with antihypertensives. The diabetes mellitus group contained subjects who were diagnosed as diabetic by the investigators, based on standard criteria, or who were already receiving antidiabetics. Hypercholesterolemia was defined as total serum cholesterol ≥220 mg/dl (5.67 mmol/l) or current treatment with cholesterol-lowering drugs. Prior ischemic heart disease was defined in terms of a history of angina pectoris or myocardial infarction.

Statistical results were calculated as follows. Annual recurrence rate was computed using the person-year method. Relative risk reduction (RRR) was determined from the incidence calculated by the person-year method. The standard error and 95% confidence intervals of these measures were estimated assuming an exponential distribution for the incidence of cerebral infarction. The log-rank test was used to compare the incidence of cerebral infarction in the two groups. Moreover, the heterogeneity of effects (RRR) among subgroups was investigated and statistically analyzed combining the results of the log-rank test for each subgroup. To investigate the effects of background factor and/or subgroup on the recurrence of cerebral infarction in the cilostazol group, univariate and multivariate analyses were performed using the Cox proportional hazards model, and the results were reported as hazard ratios (HRs). In the multivariate analysis, variables were selected by the backward elimination method.

Kaplan-Meier estimates were used for the calculation of NNT. Statistical tests were two-tailed, and a probability level of $p < 0.05$ was considered to indicate statistical significance, except for the investigation of interactions, where the level of significance was $p < 0.20$. Statistical analysis was performed using SAS version 8.02 software (SAS Institute Japan, Tokyo).

Results

Subgroup Analysis of the Placebo Group

The annual recurrence rate of cerebral infarction and the number of patients available for analysis were determined in subgroups of patients having various complications in the placebo-treated group, and the results are shown in figure 1a. The difference in recurrence between the diabetes group and the nondiabetes group was statistically significant (9.4 vs. 4.7%/year, p = 0.01) (fig. 1a).

We next evaluated the annual recurrence rate of cerebral infarction in subgroups of patients in the placebo-treated group receiving other drug treatments for various underlying diseases; these results are shown in figure 1b. In patients being treated with so-called cerebral enhancers, which were widely used at the time in Japan and act by improving cerebral blood flow and metabolism, or vasodilators including ibudilast, ifenprodil tartrate and nicergoline, which are known to have a mild antiplatelet effect, the incidence of recurrence was significantly less than in patients not receiving such treatment (p = 0.04) (fig. 1b). Administration of statins, ACE inhibitors or Ca antagonists was also associated with reduced (albeit nonsignificant) recurrence rates, although the patients not receiving these drugs were mostly nonhyperlipidemic and nonhypertensive. However, diabetic patients who were receiving antidiabetic drugs showed a higher recurrence rate of cerebral infarction than patients not taking these drugs, who were mostly nondiabetic (fig. 1b).

In figure 2, we show the results of both univariate and multivariate analyses in the placebo group. The effects of diabetes (HR 2.05, 95% CI 1.19–3.53) and use of cerebral enhancers or vasodilators (HR 0.57, 95% CI 0.34–0.96) were significant in the multivariate analysis. The incidence of events was 9.0%/year in patients with diabetes but without hypertension, while 9.5%/year in patients with both diabetes and hypertension, which suggests that both diabetes and hypertension independently affect incidence of events.

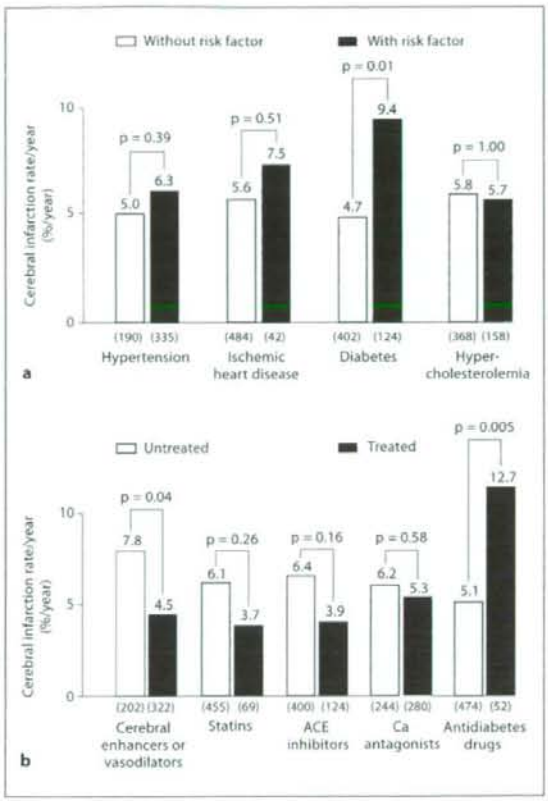

Fig. 1. Annual recurrence rate of cerebral infarction in placebo-treated patients with or without risk factors (**a**) and with or without other drug treatments for various underlying diseases (**b**). Bars show percent of patients with recurrence of cerebral infarction, with the number of patients in parentheses.

Effect of Cilostazol on Subtypes of Ischemic Stroke

As previously reported [2], the CSPS analysis showed an annual rate of cerebral infarction recurrence of 5.78% in the placebo group and 3.37% in the cilostazol group (RRR 41.7%, p = 0.02) (fig. 3a). The calculated NNT was 18.7 over 3 years of observation. Although the heterogeneity of effects (RRR) among subtypes of cerebral infarction did not reach significant difference, subgroup analysis with stratification by subtypes showed a recurrence rate of 5.25% in the placebo group and 2.97% in the cilostazol group for lacunar infarction (RRR 43.4%, p = 0.04) (fig. 3b). CSPS is the first evidence showing the effect of antiplatelet agents on lacunar infarction using a prospective design. The RRR with cilostazol treatment was 39.8% for atherothrombotic infarction and 44.5% for infarction of undetermined type.

Effect of Cilostazol on Ischemic Stroke Patients with Various Risk Factors

A significant difference in the heterogeneity of effects (RRR) was seen only in subgroups with diabetes and hypertension. RRR determined in the cilostazol group showed statistically significant differences in the sub-

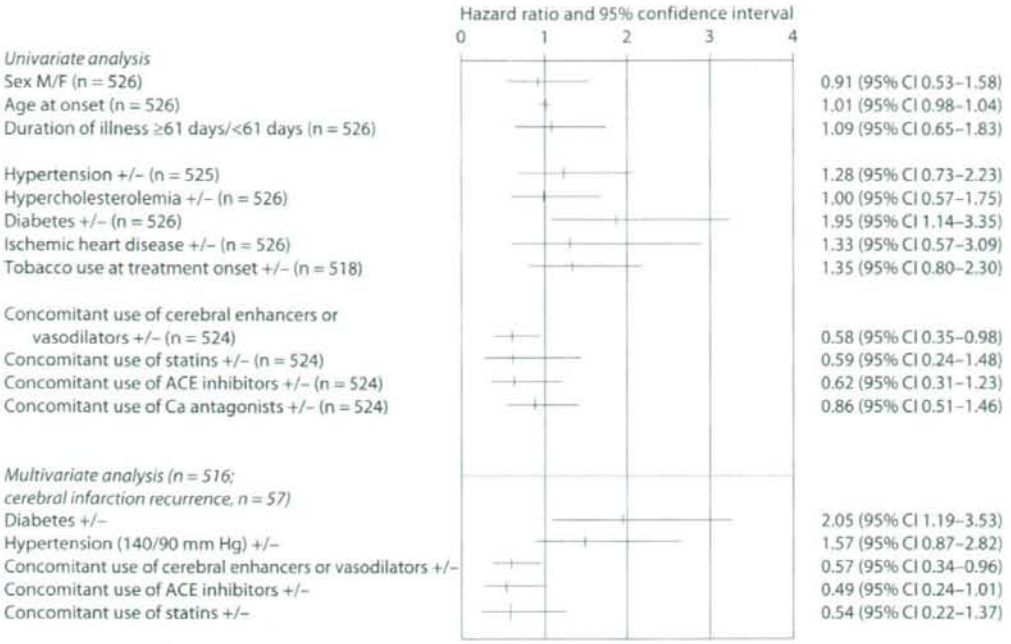

Fig. 2. Factors influencing recurrence of cerebral infarction in placebo-treated patients, showing HR and 95% confidence interval obtained by univariate and multivariate analyses (Cox proportional hazards model).

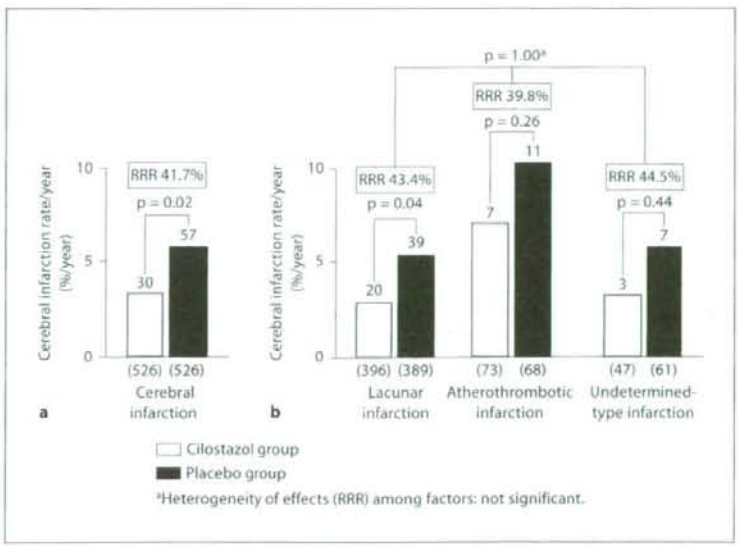

Fig. 3. Subgroup analysis of stroke recurrence stratified by clinical disease type. **a** Annual recurrence rate of all subjects. **b** Annual recurrence rate stratified by clinical subtype. Figures in parentheses indicate number of patients.

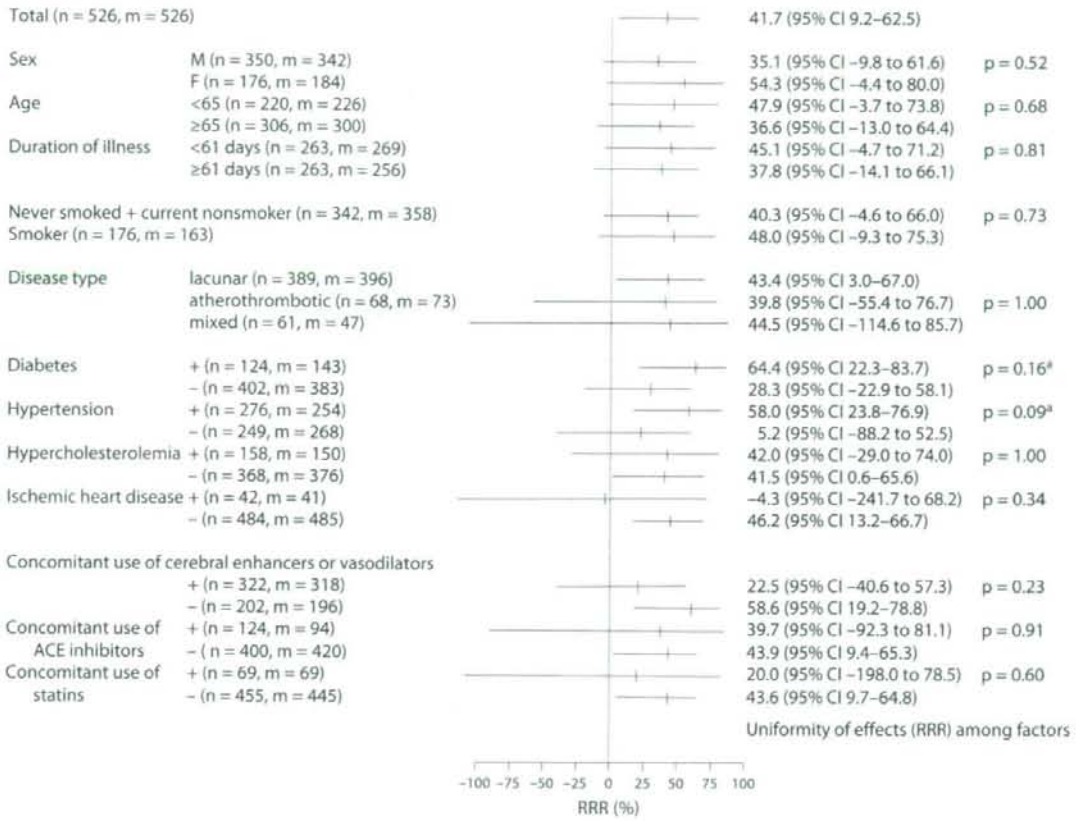

Fig. 4. RRR effects of cilostazol with 95% confidence intervals. The figures in parentheses indicate the number of patients treated with placebo (n) and the number of patients treated with cilostazol (m). [a] Heterogeneity of effects (RRR) among factors: significant.

groups of patients with diabetes (64.4%, 95% CI 22.3–83.7) and hypertension (58.0%, 95% CI 23.8–76.9), as well as in the subgroup with no findings of ischemic heart disease (46.2%, 95% CI 13.2–66.7) and in the subjects without hypercholesterolemia (41.5%, 95% CI 0.6–65.6) (fig. 4). Therefore, it is concluded that cilostazol is effective for the prevention of recurrence of cerebral infarction, particularly in stroke patients with diabetes or hypertension. Cilostazol treatment was nearly always associated with positive values for RRR, both in groups of patients receiving concomitant treatment for various types of underlying disease and in groups not receiving such treatment.

As shown in figure 5a, cilostazol administration was associated with a significant (RRR 64.4%, p = 0.008) reduction in cerebral infarction recurrence among diabetic patients, and indeed the administration of cilostazol reduced the recurrence rate of ischemic stroke in diabetic patients to the same level as in nondiabetic subjects.

Cilostazol treatment was also associated with a significant reduction in cerebral infarction recurrence in ischemic stroke patients with hypertension (RRR 58.0%,

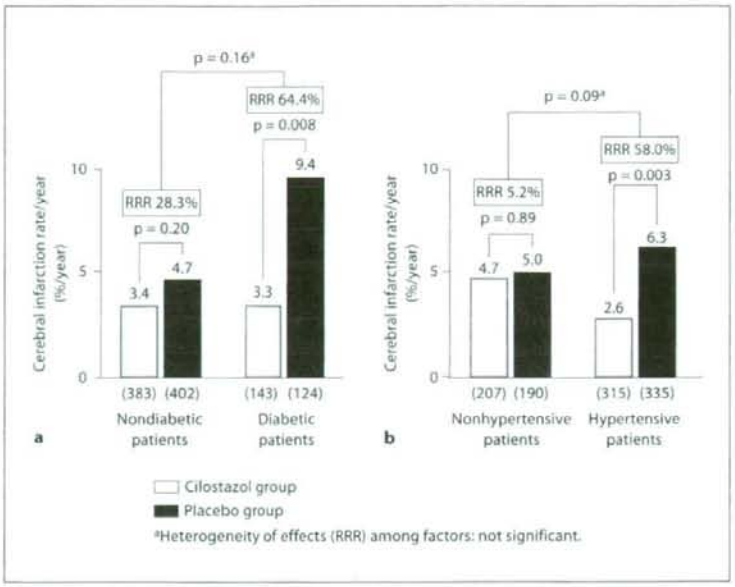

Fig. 5. Annual recurrence rate of cerebral infarction in patients with diabetes and hypertension treated with or without cilostazol. **a** Effects in the presence/absence of diabetes. **b** Effects in the presence/absence of hypertension. Figures in parentheses indicate number of patients.

p = 0.003) (fig. 5b). In nonhypertensive patients, the RRR was only 5.2%.

The incidence of bleeding by cilostazol was not significantly different from that of placebo.

Discussion

Risk Factors for Recurrence of Cerebral Infarction in the Placebo Group

When we studied recurrence of cerebral infarction in the placebo-treated patients stratified according to underlying complications, we found a higher incidence of recurrence for hypertension in comparison with patients lacking this risk factor, although the difference was not statistically significant. The lack of significance may be explained by the fact that antihypertensive treatment itself is effective in reducing the recurrence of stroke [8–10] (fig. 1b).

On the other hand, cerebral infarction patients with diabetes in the placebo group were at significantly greater risk for recurrence than those without diabetes. Earlier studies have shown that diabetic patients have a two- to fourfold greater risk of first-ever cerebral infarction than nondiabetic patients [11–14], and the present report also demonstrates that diabetes increases the risk of cerebral infarction recurrence, which is consistent with previous results [15–17].

However, findings from the UK Prospective Diabetes Study showed no reduction in the incidence of cerebral infarction in patients with type 2 diabetes, even when drug therapy reduced HbA1c by 0.9% for at least 10 years [18]. Another study found no association between glucose control and risk of recurrence of stroke among diabetic patients with a history of stroke [19]. This suggests that blood glucose control alone may be insufficient for decreasing the recurrence of cerebral infarction, which is consistent with our results (fig. 1b).

Effects of Cilostazol on Lacunar Infarction

The results of this subgroup analysis of the CSPS also showed that cilostazol significantly decreased the recurrence of stroke in patients with lacunar infarction. Although the heterogeneity of effects (RRR) among the subtypes did not reach significant difference, the RRR for inhibition of annual recurrence following lacunar infarction was 43.4% (p = 0.04). CSPS is the first evidence of the efficacy of antiplatelet drugs in lacunar infarction, whose findings are consistent with the results from a later reported ESPS-2 post hoc analysis [20]. On the other hand, the effect of cilostazol on atherothrombotic stroke was not statistically significant because of the small number

of patients available for analysis in the relevant subgroups, although the RRR was 39.8%.

Cilostazol acts as an antiplatelet by specially inhibiting phosphodiesterase III, blocking cAMP degradation and raising cAMP levels within the cytoplasm [2, 21, 22]. In addition, a vasodilatory action due to vascular relaxation has been reported [4, 5], as well as a protective effect on vascular endothelial cells [6], and beneficial effects on lipid metabolism [7]. Such actions would be expected to contribute to a decrease in cerebral infarction recurrence [23–25].

Although the etiology of lacunar infarction is still poorly understood, it appears to be elicited by thrombus formation, encouraged by abnormal lipid metabolism and hypertension-induced damage to endothelial cells. Also, flow cytometry using anti-CD62P antibodies and PAC-1 to quantify platelet activation has shown that patients with lacunar infarction, as well as atherothrombotic infarction, had a significantly higher activated platelet count than age-matched MRI-proven control subjects [26]. Although cilostazol is positioned as an antiplatelet drug, it has pleiotropic effects, including vasodilating action, vascular endothelial cell protection and improvement of the lipid pattern, and this may be the reason for the efficacy of cilostazol in reducing the recurrence of lacunar infarction.

Effect of Cilostazol on Diabetic/Hypertensive Stroke Patients

Aspirin is currently recommended as a grade A treatment in the American Diabetes Association guidelines for management of diabetes [27]. However, a meta-analysis by the Antithrombotic Trialists' Collaboration [1] showed no significant inhibition of recurrence of vascular events as a result of antiplatelet therapy in diabetic stroke patients. Data on cardiovascular disease in diabetic patients have also been reported from a multicenter, centrally randomized, open-label clinical trial study (the Primary Prevention Project) [28, 29]. That study assessed the primary preventative effects of low-dose aspirin in subjects with no history of cardiovascular disease, but having at least one risk factor, such as hypertension, diabetes, or hyperlipidemia. During the mean follow-up of 3.6 years, aspirin use significantly inhibited cardiovascular events (RRR = 23%). When a subgroup analysis was performed (diabetic vs. nondiabetic), the incidence of the primary endpoint in the diabetic group was 3.9% among patients taking aspirin and 4.3% in the control group, which was a nonsignificant difference; in the nondiabetic group, aspirin use significantly inhibited cardiovascular events (RRR = 41%). It was concluded that the use of aspirin did not significantly inhibit cardiovascular events in diabetic patients, and that mortality from cardiovascular disease actually tended to be higher in the aspirin-treated group [29]. Moreover, no data were presented on the prevention of recurrence of stroke in this paper.

Our data showed firstly that the recurrence rate of cerebral infarction was higher in diabetic stroke patients receiving antidiabetic drugs (fig. 1b). This may be attributable to the fact that such patients usually have severer diabetes than nontreated diabetic patients. However, our study also showed that cilostazol was effective for the secondary prevention of cerebral infarction in patients with diabetes (fig. 5a). The reason why a statistically significant reduction was found is mainly because the incidence of recurrence is much higher in diabetic patients and the administration of cilostazol reduced the recurrence rates in diabetic patients to as low a level as in nondiabetic patients (fig. 5a).

Cilostazol administration was also associated with a significant reduction in cerebral infarction recurrence in hypertensive patients (fig. 5b). This result also reflects the higher incidence of recurrence in the high-risk group. Reports indicate that cilostazol has a circulation-improving action, as well as an antiplatelet action, and this may be the reason for the lower NNT of cilostazol (18.7 over 3 years, recalculated in the present study from previously reported data [2]) for recurrence of cerebral infarction, compared with other antiplatelets.

In summary, our findings indicate that cilostazol can be expected to be particularly effective in lacunar infarction and, although this is a post hoc analysis, probably effective in patients with diabetes or hypertension, who are at high risk of ischemic stroke recurrence. These findings need to be supported by further research comparing different antiplatelet regimens.

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原　著

MEGA Studyにおける同意撤回，治療変更の影響分析

―全期間と5年間の結果の相違は何故生じたか？―

Matsuyama Yutaka 松山　裕[1)]　Tanaka Yukari 田中夕香理[1)]　Yoshida Mizuki 吉田　瑞樹[2)]　Ohashi Yasuo 大橋　靖雄[1)]

はじめに

2006年にMEGA Studyの主解析の結果[1]がLancet誌に掲載された．MEGA Studyの主目的は，わが国における動脈硬化性疾患の既往のない軽度から中等度の高脂血症患者を対象に，プラバスタチン(メバロチン®)による治療の心血管系疾患発症抑制効果を検証することであった．具体的には，中央登録方式によるPROBE法(prospective randomized open-label blinded end-point)を用いて，年齢40～70歳，体重40 kg以上の男性および閉経後女性で，冠動脈疾患(CHD)または脳卒中の既往のない高脂血症(総コレステロール値220～270 mg/dL)患者を食事療法単独群または食事療法＋メバロチン(10～20 mg/日)併用群に無作為に割り付けた．一次評価項目は，致死的・非致死的な心筋梗塞，狭心症，心臓死および突然死，冠動脈血行再建術の施行のいずれかであるCHDの発症である．二次評価項目の1つが脳卒中の発症である．MEGA Studyの試験計画，組織，実施，成果の詳細に関しては，本誌の特集号[2]を参照していただきたい．

1994年2月から1999年3月までの間に同意の得られた15,210名の患者が登録され，総コレステロール値に関する組み入れ基準を満たした8,214名が2群に無作為化された．この8,214名のうち，382名(同意撤回94名，除外基準違反224名，無作為化後のデータ欠損64名)を除外した7,832名(食事療法単独群3,966名，食事療法＋メバロチン群3,866名)が解析対象集団である．追跡期間は当初5年間と設定されていたが，モニタリング委員会の勧告に基づき，イベント数を増やすためにさらに5年間試験が継続された．5年目に試験延長の同意を得た患者については2004年3月まで追跡が継続された．主たる解析結果であるCHDの累積発症率を図1に示す．メバロチンのCHD発症抑制効果を表すハザード比の大きさは0.67(95%信頼区間：0.49～0.91，p＝0.010)であった．

図1に関して統計的な観点から気になる点は，①試験途中での脱落者が解析結果(p値)に与える影響，②治療不遵守(ノンコンプライアンス)が解析結果(ハザード比)に与える影響の2点である．

①のlog-rank検定によるp値が妥当であるためには，試験途中での対象者の脱落(観察打ち切り)がその後に観察されるかもしれないCHD発症とは無関係であることが要求される．このような脱落を，ランダムな脱落，あるいは当該のイベント(CHD)に関して情報を有していないという意味で「情報のない打ち切り(non-informative censoring)」と呼ぶ．MEGA Studyのような長期間にわたる試験では対象者の脱落は不可避であり，また，MEGA Study固有の問題として5年時点での再同意の問題が存在する．

MEGA Studyにおけるイベント発症状況を表1に示す．試験終了による打ち切りとは，対象者の予後とは無関係に事前に定められた時点(2004年3月31日)でCHDイベントを起こすことなく試験終了した患者であり，「情報のない打ち切り」と考えられる．5年時点での再同意で同意を撤回した対象者には，施設都合と

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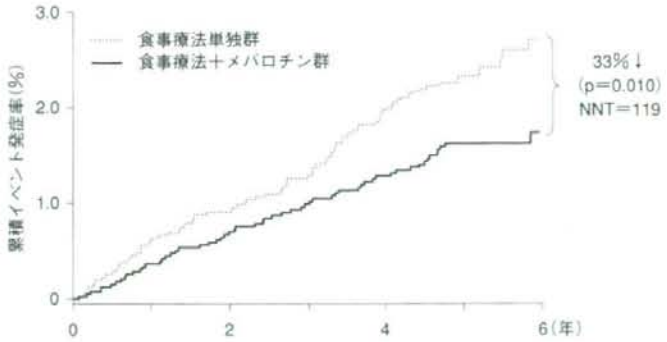

対象症例数(名)	0	1y	2y	3y	4y	5y	6y
食事療法単独群	3,966	3,758	3,648	3,529	3,430	2,476	830
食事療法＋メバロチン群	3,866	3,642	3,490	3,385	3,307	2,434	859

図1　一次評価項目－冠動脈疾患(CHD)－

(文献1より引用)

表1　MEGA Studyにおけるイベント発症状況

イベントの種類	食事療法単独群		食事療法＋メバロチン群	
	人　数	%	人　数	%
CHDイベント	101	2.5	66	1.7
追跡不能，CHD以外の原因による死亡	546	13.8	594	15.4
5年時での患者都合による同意撤回	278	7.0	270	7.0
5年時での施設都合による同意撤回	165	4.2	162	4.2
試験終了による打ち切り	2,876	72.5	2,774	71.8
合　計	3,966	100	3,866	100

患者都合の2種類存在する．施設都合は，各施設のIRBが対象者の意思にかかわらず試験の継続可否を検討し，継続不可と判断した場合であり，患者都合は，継続可の施設の対象者に対して試験継続の再同意を各患者に対して実施し，同意を撤回した場合である．前者の施設都合による同意の撤回に関しては，対象者の予後とは無関係な理由による脱落であるため，「情報のない打ち切り」と考えても問題はないが，後者の患者都合による同意の撤回は，予後が悪い(あるいは良い)対象者ほど同意を撤回している可能性が否定できず，通常の解析の前提条件である「情報のない打ち切り」とみなすことはできないかもしれない．同様に，試験途中での追跡不能例，CHD以外の原因による死亡例も，予後の悪い(CHDを発症しやすい)対象者ほど脱落例となっている可能性が高いと思われる．このような状態は，「情報のある打ち切り(informative censoring)」と呼ばれ，その存在下では通常のlog-rank検定による累積発症率の比較のp値は妥当ではないことが知られている．「情報のある打ち切り」が否定できない場合には，そのような脱落例を補正することで「同意拒否，追跡不能などによる脱落が存在しなかった場合に観察されたであろう治療効果」を求め，すべての脱落例を単なる打ち切り例とみなした通常の解析結果(図1)の頑健性を検討する必要がある．もし，両者の結果が大きく食い違う場合には脱落理由を詳細に検討し，脱落が当該の試験結果全体に与える影響を議論することが重要となる．

一方，②のハザード比の値に関しては，「無作為割り付け後の治療状況がどのようなものであっても，割り付け群どおりに解析する」というITT(intent-to-treat)の原則に基づいた解析結果である．ITT解析は，有効性評価のための検証的比較臨床試験の標準的解析方針であり，無作為割り付けによって保証される比較可能性を保持する，つまり解析対象者の事後的な選択に伴うバイアスを防ぐために用いられる．ITT解析は実践的(pragmatic)な解析方針であり，その解釈は，治

表2　MEGA Studyにおいて治療法の交換を一度でも経験した対象者

	割り付け治療群	%	対象者数
試験開始から5年間	食事療法単独群	19.9	790
	食事療法＋メバロチン群	53.4	2,064
試験開始から10年間	食事療法単独群	21.3	844
	食事療法＋メバロチン群	63.1	2,441

表中の%，対象者数は，食事療法単独群ではメバロチン治療を一度でも受けた患者，食事療法＋メバロチン群ではメバロチン治療を一度でも休薬した患者の割合，対象者数を表す．

表3　IPCW解析の単純な例

群	真のデータ	観察データ	観察確率
A	1，1，1	1，?，?	1/3
B	2，2，2	2，2，2	1
C	3，3，3	?，3，3	2/3
全体平均	2	13/6	

表中の「?」は欠測データを表す．

療割り付け後に起こった治療の変更，副作用など，すべてのことはその治療が現実の臨床の場に導入された場合にも当然起こり得ることであり，ITT解析はそのすべてを治療方針として一括して解析していることによっている．しかし，ITT解析にも問題がないわけではない．最も大きな問題点は，割り付けられた治療を遵守しなかった対象者が増えるにつれて，治療効果のITT推定値と薬剤の薬理学的有効性との間の乖離が大きくなることである．

MEGA Studyにおいて，治療法の交換（食事療法単独群に割り付けられたがメバロチンの投与を受けた，あるいはメバロチン群に割り付けられたが休薬した）を一度でも経験した対象者数を**表2**に示す．食事療法単独群に割り付けられた患者の約20%が少なくとも1回はメバロチンを服用しており，メバロチン群に割り付けられた患者の約50～60%がメバロチンを一度でも休薬している．一般に，**表2**のような治療法の交換が生じている場合には，ITT解析による治療効果は保守的になることが知られている．「保守的になる」とは，ハザード比が1に近づく，すなわちメバロチンの効果が過小評価され，有意差が出にくくなることを指す．コンプライアンスが低下するほど解析結果が保守的になるのがITT解析の特徴であり，検証を目的にした試験においては，この特徴ゆえにITTが主たる解析として用いられているといってもよい．しかし，ノンコンプライアンスが非常に多い場合には，その影響を補正した「コンプライアンスが完全に保たれた場合に観察されたであろう治療効果」を求めることが，薬剤の真の効果を知る上で重要となる．

そこで，本稿では，**図1**の解析結果を補足するための上述の2つの解析（脱落補正とノンコンプライアンス補正）を紹介する．なお，いずれの解析手法も方法論の論文として既に統計専門雑誌[3,4]に受理されており，数理的な側面を含む詳細はそれらを参照していただきたい．

脱落データを補正した解析

脱落データを補正した解析方法として近年注目を浴びているのが，IPCW（inverse probability of censoring weighted）解析[3,5]である．この解析方法の考え方は単純で，観察されたデータ（対象者）をそれぞれの観察確率の逆数で重みづけた解析である．例えば，非常に単純な例として，**表3**のようなデータを考える．観察すべき全体での真の平均値は2であるが，実際にはA群で2名，C群で1名の対象者が脱落したため，観察平均値は13/6となり，真値2に一致しない．ここで，各群における観察確率を計算すると，A群が1/3，B群が1，C群が2/3であり，その確率の逆数を重みとした以下の重み付き平均値を計算すると2となり，真値に一致することがわかる．

$$\frac{1\times\frac{3}{1}+(2+2+2)\times 1+(3+3)\times\frac{3}{2}}{\frac{3}{1}+1+1+\frac{3}{2}+\frac{3}{2}}=2$$

上述の観察確率の逆数で重みづけたIPCW解析は，例えば，ある対象者の観察確率が1/3であれば，その対象者と同じような治療・共変量歴をもった脱落者が，（自分自身を除いて）背後に$(1/3)^{-1}-1=2$名存在す

ると考え，そのような脱落者2名も考慮した解析になっている．言い換えれば，観察確率を正しく求めることさえできれば，IPCW解析により「脱落がなかった場合に観察されたはずの治療効果」を推定可能といえる．

IPCW解析で問題となるのは，各対象者の観察確率の推定である．一般に，観察確率（あるいは，脱落確率）は未知であり，データから推定しなければならない．対象者が脱落するかどうかは，治療群，様々な患者背景因子，あるいは脂質値のような時間とともに変化する因子など，多くの要因の複雑な関数と考えられる．そのため，観察確率を推定する際には，できる限り多くの要因を考慮することが原則であるが，それらの要因は当該疾患の予後因子であり，かつ脱落にも影響する因子でなければならない．

観察確率を推定するためにどのような予後因子を用いるかでIPCW解析の結果が大きく変化することを，以下の単純な仮想例で考えてみる．100名の対象者を5年間追跡したとして，2年目に5名のCHD発症と3名の脱落を観察し，残りの92名は5年目時点で生存していたとする．人年法による単純なCHD発症率は，

$$\frac{5}{(5\times2)+(3\times2)+(92\times5)}=10.5(/1{,}000人年)$$

である．ここで，2年目のCHD発症者5名はすべて男性で，脱落例を含む残りの95名は女性であったとする．このシナリオのもとでは，性別はCHD発症の強い予後因子であるが（男性の場合CHDを発症している），脱落に強く影響する因子ではない（女性だからといって必ず脱落するわけではない）．このような状況で，IPCW解析に必要な観察確率を性別を考慮して求めると，男性の観察確率は1（脱落例は存在しない），女性は2年目時点までは1，それ以降は1×92/95となる（女性は脱落しなければ5年目で試験終了なので，脱落した3名の観察期間を5年とみなす）．したがって，性別に依存した脱落を補正したIPCW推定値は，

$$\frac{5\times1}{(5\times2\times1)+(95\times2\times1)+(92\times3\times95/92)}=10.3(/1{,}000人年)$$

となり，単純な結果からほとんど変化しない．

別のシナリオとして，2年目にCHDを発症した5名と脱落した3名はすべて総コレステロール値が高い対象者であり，残りの92名は総コレステロール値が低い対象者であったとする．この状況のもとでは，総コレステロール値はCHD発症の強い予後因子であり，脱落にも強く影響する因子である．IPCW解析に必要な観察確率を総コレステロール値の高低を考慮して求めると，総コレステロール値が高い対象者の観察確率は5/8（ただし，脱落者3名は2年目に発症とみなすため，観察人年は2年とする），低い対象者は1となる．したがって，総コレステロール値に依存した脱落を補正したIPCW推定値は，

$$\frac{5\times8/5}{(5\times2\times1)+(3\times2\times1)+(92\times5\times1)}=16.8(/1{,}000人年)$$

となり，脱落したCHD発症リスクが高い対象の影響を補正することで単純な結果（10.5/1,000人年）より大きなCHD発症率を得ることができる．このIPCW推定値は，脱落がなかった場合に観察されたはずのCHD発症率と解釈される．したがって，CHD発症に対する様々な予後因子を同時に考慮した観察確率からIPCW推定値を求めることで，予後に関連した脱落（情報のある打ち切り）を補正することが可能となる．一方，そのような手続きで求められたIPCW推定値が単純な結果と大きく異ならなければ，当該データで観察された脱落は予後とは無関係（情報のない脱落）である可能性が高いと推察される．

上述のように，IPCW解析を行う際には，どのような予後因子が脱落に強く影響しているかを慎重に検討する必要がある．MEGA Studyにおいて観察された脱落発症曲線を**図2**に示す．それぞれ，**表1**の「追跡不能，CHD以外の原因による死亡」「5年時での患者都合による同意撤回」をイベントとみなした場合の累積発症率（%）である．前者（左図）に関しては，メバロチン群の方が追跡期間を通して脱落割合が高く，一方，後者（右図）に関しては，5年目時点でのみ脱落が生じており，わずかではあるが食事療法単独群の方が同意撤回割合が高いことがわかる．

それぞれの理由による観察確率を推定するための統計モデルとして，前者に関しては時間依存性比例ハザードモデル（脱落ハザードをモデル化），後者に関してはロジスティック回帰モデル（5年時点での同意撤回確率をモデル化）を用い，いずれのモデルも治療群ごとに異なる回帰パラメータを想定した．それぞれのモデルの説明変数（脱落に関係する予後因子）としては，ベースライン要因として12因子（年齢，性別，BMI，現在の喫煙歴，現在の飲酒歴，高脂血症治療歴，高血圧，糖尿病，総コレステロール（TC），トリグリセリド（TG），HDLコレステ