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ARTICLE

Intensive treat-to-target statin therapy and severity of diabetic retinopathy complicated by hypercholesterolaemia

Tomoaki Murakami[1] · Satoshi Kato[2] · Takashi Shigeeda[3] · Hiroshi Itoh[4] · Issei Komuro[5] · Masahiro Takeuchi[6] · Nagahisa Yoshimura[7] · for the ophthalmology substudy of EMPATHY Investigators

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Abstract

Objectives To compare the effects of intensive and standard statin therapy on severity of diabetic retinopathy (DR) complicated by hypercholesterolaemia in a prespecified substudy of the standard vs. intEnsive statin therapy for hypercholesteroleMic Patients with diAbetic retinopaTHY (EMPATHY) study.

Methods Among 5144 patients in the multicentre, prospective, randomized EMPATHY study, this substudy considered 157 patients with seven-field fundus photographs of sufficient quality taken during study enrolment and at the 3-year visit. Eighty-five and seventy-two patients received intensive and standard statin treatments, respectively, in a treat-to-target manner. The primary endpoint was a two-step change in the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity scale at 36 months. Surrogate markers included changes in hard exudates, changes in visual acuity, and additional ocular treatments during study follow-up.

Results Intensive and standard treatment groups did not differ significantly in terms of changing two or more steps on the DR severity scale ($P = 0.4380$). In patients with severe DR, defined as ≥47 on the severity scale, exploratory analysis showed more frequent improvement of DR, by at least one step, with intensive vs. standard treatment (83.3% vs. 40.0%; $P = 0.0346$). The intensive and standard groups did not differ in changes on the hard exudates severity scale ($P = 0.3460$), logarithm of minimum angle of resolution visual acuity ($P = 0.5500$), or additional ocular treatment during follow-up.

Conclusions Intensive and standard statin treatment may have similar effects on DR in the population of all patients with DR and hypercholesterolaemia, but intensive therapy may be more beneficial in patients with severe DR.

Introduction

Diabetic retinopathy (DR) is a leading cause of vision loss in working-age adults [1]. Hyperglycaemia, systemic hypertension, and dyslipidaemia are the main risk factors for DR [2–5]. Interventions for hyperglycaemia and hypertension have been shown to retard the progression of DR, as shown in the Diabetes Control and Complications Trial, United Kingdom

Members of the ophthalmology substudy of EMPATHY Investigators are listed in Supplementary Data.

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✉ Tomoaki Murakami
mutomo@kuhp.kyoto-u.ac.jp

[1] Department of Ophthalmology, Kyoto University Graduate School of Medicine, Kyoto, Japan

[2] Department of Ophthalmology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[3] Ideta Eye Clinic, Kumamoto, Japan

[4] Department of Endocrinology, Metabolism and Nephrology, Keio University School of Medicine, Tokyo, Japan

[5] Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[6] Department of Clinical Medicine (Biostatistics and Pharmaceutical Medicine), School of Pharmacy, Kitasato University, Tokyo, Japan

[7] Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Osaka, Japan

Prospective Diabetes Study, and Diabetic Retinopathy Candesartan Trials [6–8]. Less is known, however, about the effects of lipid-lowering treatment on DR pathogenesis.

Steno-2 showed that the multifactorial intensive treatment of hyperglycaemia, hypertension, dyslipidaemia, and microalbuminuria retards DR progression in patients with type 2 diabetes and microalbuminuria [9], and the lipid-lowering drug fenofibrate has been found to decrease the onset and progression of DR [10, 11]. Statins, another major class of lipid-lowering drugs, decrease the level of low-density lipoprotein cholesterol (LDL-C), and reduce the risk of cardiovascular disease [12]. Also of note, animal experiments suggest that statins reduce leucocyte–endothelial interactions and vascular permeability in diabetic rodents [13]. However, it remains unclear whether oral statin-induced lowering of LDL-C has beneficial effects on DR progression.

The standard vs. intEnsive statin therapy for hypercholesteroleMic Patients with diabetic retinopaTHY (EMPATHY) study was designed to compare the effects of intensive and standard lipid-lowering treat-to-target therapies on reducing the incidence of cardiovascular events in patients with hypercholesterolaemia and DR but no history of coronary artery disease [14–16]. We also obtained and evaluated fundus photographs from EMPATHY to conduct a prespecified ophthalmology substudy investigating the superiority of intensive statin therapy for DR progression.

Methods

Study design

This is a prespecified ophthalmology substudy of the EMPATHY study, which used a multicentre, prospective, randomized, open-label, blinded endpoint (PROBE) design and enrolled patients at hospitals and family practice clinics across Japan [14–16]. This substudy adhered to the Declaration of Helsinki and Japanese ethical guidelines for clinical studies. The institutional review board of each participating centre reviewed and approved the study protocol.

Participants

Patients in the EMPATHY study who had seven-field fundus photographs taken at enrolment and after three years (36 ± 3 months) were eligible for participation in our substudy [14–16]. The primary eligibility criteria in the EMPATHY study were elevated LDL-C and DR without a history of coronary artery disease [15]. All patients provided written informed consent. The substudy consisted primarily of patients in the EMPATHY study who had been enrolled from ophthalmology departments at or near primary prevention sites (hospitals and clinics) (Supplementary Methods). Patients without efficacy data were excluded from consideration.

Randomisation and masking

Patients were allocated to intensive or standard therapy based on the randomisation schedule in the EMPATHY study [15]. The investigator contacted the data centre, which provided a computer-generated allocation sequence stratified by sex, age, and baseline haemoglobin A1c (HbA1c). Since the main study was conducted in a treat-to-target manner, a PROBE design was selected. The endpoints in the EMPATHY study and ophthalmology substudy were assessed in a blinded manner to eliminate bias.

Procedures

The participants in this substudy were treated according to the protocol in the EMPATHY study. Patients were randomly assigned to oral intensive statin therapy (targeting LDL-C below 70 mg/dL) or standard statin therapy (targeting LDL-C between 100 and 120 mg/dL), as described previously [15].

Outcomes

The primary endpoint in this study was a change of two steps up or down (improving or worsening) on the DR severity scale at the 3-year visit (Supplementary Methods). Fundus photographs were obtained in seven fields, corresponding to the Early Treatment Diabetic Retinopathy Study (ETDRS) standard photographs, at each hospital or clinic [17]. Two retinal specialists, masked to patient identity, evaluated the seven-field photographs based on the ETDRS DR Severity Scale in the reading centre (Supplementary Table 1). Disagreements on severity level were resolved by discussion between the two specialists.

Secondary endpoints included changes in the ETDRS hard exudates severity scale, patient scores on the logarithm of the minimum angle of resolution visual acuity (logMAR VA), and patient need for additional retinal photocoagulation or other ocular treatment (Supplementary Methods and Supplementary Table 2). The best-corrected decimal VA was measured in each hospital or clinic and converted into logMAR VA. Data were provided from medical records on the history of panretinal photocoagulation, focal/grid macular photocoagulation, vitrectomy, and ocular medical therapy (steroid and anti-vascular endothelial growth factor [VEGF] drugs) during the study periods.

If the fundus photographs provided a sufficiently high-quality image for only one eye, that eye was selected for further investigation. If the image quality was sufficient for both eyes, we selected the eye with more severe DR at the

Table 1 Demographic characteristics.

Item	Intensive therapy ($n = 85$)	Standard therapy ($n = 72$)	P value
Gender (male/female)	41/44	28/44	0.2397
Age (year)	65.0 (56.0–71.0)	63.5 (57.0–70.0)	0.6982
Height (cm)	159.0 (152.2–165.0)	157.3 (150.1–166.9)	0.5341
Body weight (kg)	62.60 (56.60–70.30)	65.10 (57.10–74.00)	0.1822
BMI (kg/m^2)	24.81 (23.01–27.02)	26.12 (23.56–29.37)	0.0245
Abdominal circumference (cm)	86.1 (80.7–95.5)	94.0 (84.3–101.3)	0.0083
Hypolipidaemic agents at provisional enrolment (yes/no)	41/44	40/32	0.3630
Smoking status			0.3739
Current smoker	11	11	
Past smoker	22	12	
Non-smoker	52	49	
Duration of diabetes (year)	9.8 (5.0–16.0)	14.2 (8.0–20.5)	0.0239
Diabetic neuropathy (present/absent)	28/57	26/46	0.6769
Diabetic nephropathy (present/absent)	44/41	33/39	0.4588
Systemic hypertension (present/absent)	60/25	47/25	0.4767
Arteriosclerosis obliterans (present/absent)	2/83	0/72	0.1902
Other complications and medical history (present/absent)	62/23	56/16	0.4846
HbA1c (%)	7.20 (6.70–8.10)	7.60 (7.05–8.20)	0.0160
LDL-C (mg/dL)	106.0 (83.0–122.0)	109 (85.0–126.0)	0.3833
Systolic BP (mmHg)	136.0 (124.0–145.0)	136.0 (124.0–151.0)	0.6239
Diastolic BP (mmHg)	76.0 (71.0–81.0)	77.0 (70.0–85.0)	0.7807
logMAR VA	0.000 (−0.079–0.155)	0.000 (−0.079–0.097)	0.5500
Past history of photocoagulation (yes/no)	39/46	29/43	0.4801
Past history of vitreoretinal surgery or ocular medical therapy (yes/no)	30/54	20/52	0.2896

Data presented as interquartile range.

BMI body mass index, *HbA1c* haemoglobin A1c, *LDL-C* low-density lipoprotein cholesterol, *logMAR VA* logarithm of the minimum angle of resolution visual acuity, *BP* blood pressure.

time of enrolment, or the right eye if both eyes had the same DR severity at that time. The severity of retinopathy was assessed on the ETDRS DR severity scale.

Statistics

Values were expressed as the median (interquartile range). Continuous and categorical variables were evaluated using the Wilcoxon rank-sum test and a chi-square test with Yates' correction, respectively. The changes in severity scales for DR (primary endpoint) and hard exudates (secondary endpoint) were analysed using the van Elteren test stratified by HbA1c (<8.4% or ≥8.4%). Statistical differences in the changes in logMAR VA were evaluated by analysis of covariance (ANCOVA), using HbA1c and logMAR VA at enrolment as covariates. The presence of additional ocular treatment during the study period was compared using the Mantel–Haenszel test stratified by HbA1c. Fisher's exact test and logistic regression analysis were applied to the exploratory analyses of DR severity.

Results

The main EMPATHY study enrolled 5995 patients. This substudy screened 219 of those patients, enrolled at 47 sites (40 hospitals and 7 clinics) between May 2010 and October 2013. From among that group, 198 were assigned to intensive ($n = 105$) or standard ($n = 93$) statin therapy at randomisation in the EMPATHY study. We excluded patients for whom efficacy data were missing, and ultimately analysed findings from 85 and 72 patients in the intensive and standard statin therapy groups, respectively, (Supplementary Figure).

Although the two groups differed little in most systemic parameters at baseline, there were statistically significant inter-group differences in body mass index, abdominal

Table 2 DR severity scale before and after two lipid therapies.

DR severity scale, *n* (%)	Intensive therapy		Standard therapy	
	Baseline	Last observation	Baseline	Last observation
Absent	1 (1.2)	9 (10.6)	1 (1.4)	8 (11.3)
Questionable	1 (1.2)	0 (0.0)	1 (1.4)	0 (0.0)
Minimal non-proliferative	3 (3.5)	0 (0.0)	3 (4.2)	0 (0.0)
Mild non-proliferative	47 (55.3)	3 (3.5)	47 (65.3)	3 (4.2)
Moderate non-proliferative	15 (17.6)	61 (71.8)	9 (12.5)	51 (71.8)
Moderately severe non-proliferative	4 (4.7)	1 (1.2)	3 (4.2)	1 (1.4)
Severe non-proliferative	2 (2.4)	2 (2.4)	1 (1.4)	0 (0.0)
Mild proliferative	5 (5.9)	9 (10.6)	4 (5.6)	5 (7.0)
Moderate proliferative	3 (3.5)	0 (0.0)	1 (1.4)	2 (2.8)
Severe proliferative	4 (4.7)	0 (0.0)	2 (2.8)	1 (1.4)
Advanced proliferative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inactive proliferative	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	85 (100.0)	85 (100.0)	72 (100.0)	71[a] (100.0)

DR diabetic retinopathy.

[a]We excluded one patient whose photographs were ungradable at 36 months.

Table 3 Change in DR severity scale from baseline to last observation.

Changes in DR severity scale	Intensive therapy	Standard therapy	*P* value
All cases	$n = 85$	$n = 71$	0.4380*
Two-step decrease or more	17 (20.0%)	10 (14.1%)	
One-step change or no change	63 (74.1%)	57 (80.3%)	
Two-step increase or more	5 (5.9%)	4 (5.6%)	
Severe cases (ETDRS grading at baseline ≥ 47)	$n = 18$	$n = 10$	
One-step decrease or more	15 (83.3%)	4 (40.0%)	0.0346**
Two-step decrease or more	8 (44.4%)	2 (20.0%)	0.2474**
Severe cases without additional ocular treatment	$n = 15$	$n = 9$	
One-step decrease or more	12 (80.0%)	3 (33.3%)	0.0361**
Two-step decrease or more	5 (33.3%)	1 (11.1%)	0.3509**

DR diabetic retinopathy, *ETDRS* early treatment diabetic retinopathy study.

**P* value by van Elteren test stratified by HbA1c.

***P* value by Fisher's exact test.

circumference, HbA1c, and duration of diabetes (Table 1). We found no significant differences in ETDRS DR severity scale grade, logMAR VA, or medical history of photocoagulation or other ocular interventions (vitreoretinal surgery or ocular medical therapy) at enrolment (Tables 1 and 2). The grade for hard exudates was higher in the intensive therapy group ($P = 0.0493$).

In the intensive group, LDL-C and total cholesterol decreased at 6 months and continued a more gradual decrease at 36 months (Supplementary Table 3). In contrast, these lipid variables did not change between baseline and 36 months in the standard group. These findings paralleled the main study for reductions in LDL-C in the intensive group at 6 months and after [15].

DR grading on the ETDRS severity scale did not differ significantly between the intensive and standard statin therapy groups at enrolment ($P = 0.1679$; Table 2). We excluded 1 patient from the standard group whose photographs were ungradable at 36 months and provided data on the remaining patients in each category on the DR severity scale at 36 months (Table 2). As the primary endpoint, DR severity improved by two steps or more in 17 patients (20.0%) in the intensive group and 10 patients (14.1%) in the standard group, and worsened by two steps or more in 5 patients (5.9%) and 4 patients (5.6%), respectively. We found no statistical difference in the change in DR severity grade between the intensive and standard groups ($P = 0.4380$; Table 3).

As an exploratory analysis, we investigated the frequency of improvement of one step or more on the DR severity scale. In all patients, such improvement occurred more frequently in the intensive group than in the standard

Table 4 Improvement in DR severity scale from baseline to last observation.

	Intensive therapy	Standard therapy	*P* value
Mild cases (DR severity scale at baseline < 47)	$n = 67$	$n = 61$	
One-step decrease or more	10 (14.9%)	8 (13.1%)	0.8045
Two-step decrease or more	9 (13.4%)	8 (13.1%)	1.0000
Cases with severe hard exudates (ETDRS grading at baseline ≥ 3)	$n = 27$	$n = 12$	
One-step decrease or more	7 (25.9%)	0 (0.0%)	0.0775
Two-step decrease or more	4 (14.8%)	0 (0.0%)	0.2916

DR diabetic retinopathy, *ETDRS* early treatment diabetic retinopathy study.

Table 5 Systemic safety issues: adverse events and adverse drug reactions.

	Intensive therapy ($n = 85$)		Standard therapy ($n = 72$)		*P* value
	n of events	*n* of patients (%)	*n* of events	*n* of patients (%)	
Adverse events					
Total	260	66 (77.6)	270	59 (81.9)	0.5551
Serious	31	22 (25.9)	38	20 (27.8)	0.8571
Adverse drug reactions					
Total	6	5 (5.9)	6	5 (6.9)	1.0000
Serious	2	1 (1.2)	2	1 (1.4)	1.0000
Main adverse events					
Hepatobiliary disorders					
Total	4	4 (4.7)	4	3 (4.2)	1.0000
Serious	0	0 (0.0)	1	1 (1.4)	0.4586
Renal and urinary disorders					
Total	5	4 (4.7)	8	8 (11.1)	0.1462
Serious	1	1 (1.2)	1	1 (1.4)	1.0000
Rhabdomyolysis					
Total	0	0 (0.0)	0	0 (0.0)	1.0000
Serious	0	0 (0.0)	0	0 (0.0)	1.0000
Myopathy					
Total	0	0 (0.0)	0	0 (0.0)	1.0000
Serious	0	0 (0.0)	0	0 (0.0)	1.0000
Cancer[a]					
Total	3	3 (3.5)	4	3 (4.2)	1.0000
Serious	1	1 (1.2)	4	3 (4.2)	0.3335

[a]Including neoplasms benign, malignant, and unspecified, including cysts and polyps.

group (25 [29.4%] vs. 12 patients [16.9%]), but the difference was not statistically significant ($P = 0.0887$). Logistic regression analyses demonstrated that DR severity at baseline predicts two-step improvement of DR (odds ratio 1.391 [confidence interval, 1.103–1.678]; $P = 0.0039$). Therefore, we performed subset analyses of severe DR. In patients with severe DR (ETDRS grading at baseline ≥ 47), intensive statin therapy was more frequently associated with improvement of at least one step than was the standard therapy (15 patients [83.3%] vs. 4 patients [40.0%], $P = 0.0346$; Table 3). Patients with mild DR showed no differences in DR improvement of one step or more between the two groups (DR severity scale at baseline < 47) (Table 4). In patients with severe hard exudates (ETDRS grading at baseline ≥ 3), DR severity tended to improve more frequently with intensive therapy than standard therapy, but the difference was not statistically significant (Table 4).

In further investigation of the intensive and standard statin therapy groups at 36 months, we found no significant differences in the hard exudates severity scale (Supplementary Table 4) or the changes in logMAR VA (0.000 [−0.051 to 0.097] vs. 0.000 [−0.051 to 0.079]; $P = 0.5500$). Additional retinal photocoagulation was performed in 12 patients (14.1%) in the intensive group and 8 patients (11.1%) in the standard group ($P = 0.5628$; Supplementary

Table 5). During the 36 months, vitreoretinal surgery or ocular medical therapy was performed in 20 patients (23.5%) and 10 patients (13.9%), respectively ($P = 0.1296$), respectively. Lipid variables at baseline were not associated with DR worsening of two steps or more (Supplementary Table 6). Systemic adverse effects (AEs) did not differ between the two groups (Table 5), just as was seen in the main study [15]. There were no definitively ocular AEs in either group.

Discussion

Although many publications have reported the relationship between dyslipidaemia and biomarkers of DR, the efficacy of lipid-lowering therapy in slowing DR progression remains controversial. In the current study of the population of all patients with DR and hypercholesterolaemia, intensive treat-to-target statin therapy did not have clearly beneficial effects on changes in DR severity compared to the standard statin therapy. In patients with severe DR (ETDRS DR severity scale ≥ 47 at baseline), which is typically seen in severe non-proliferative DR (NPDR) and proliferative DR (PDR), improvement of the ETDRS severity grade by at least one step was seen more frequently with intensive therapy than with standard therapy. Notably, the intensive treatment tended to have greater effects on DR progression in patients with severe hard exudates at baseline. These findings suggest that using statins to achieve lower cholesterol levels might be beneficial in some but not in all patients with DR and hypercholesterolaemia.

Since multiple systemic factors and past treatments influence DR progression, we had to consider confounding factors. In this substudy, DR severity at baseline predicted two-step improvement in DR. Because subsequent multivariate analyses showed no superiority of the intensive therapy after adjustments for confounding factors (unpublished data), we speculated a ceiling effect in mild DR cases. Therefore, we planned subset analyses for severe DR. The intensive statin treatment showed greater effects on one-step DR improvement than the standard treatment in severe DR cases. In addition, the prespecified items did not include potential confounding factors, e.g., insulin use and anti-VEGF treatment, that might lead to hidden biases. These statistical concerns suggest that all significant factors should be stratified in a future prospective study including severe DR.

The Steno-2 study indicated the importance of a multifactorial intervention, including lipid-lowering therapy, in the management of DR. The Fenofibrate Intervention and Event Lowering in Diabetes study and ACCORD-Eye study also demonstrated the beneficial effects of fibrates on DR progression [10, 11, 18]. In contrast, the Collaborative Atorvastatin Diabetes Study showed that atorvastatin did not significantly impact DR progression when compared to placebo [19]. These findings from post-hoc endpoint analysis appear to be consistent with the prespecified endpoint analysis in this study, which showed no difference in change in DR severity between the intensive and standard groups. However, treating to a target of lower LDL-C levels might be mildly effective in patients with severe NPDR or PDR. The onset and progression of DR consist of multiple steps; systemic hypertension generally contributes more to the progression of existing DR than to its onset [3]. Similarly, hypercholesterolaemia might promote pathogenesis in severe NPDR or PDR, which may be improved by intensive treat-to-target statin therapy [4]. Our exploratory analysis did not yield definitive conclusions; further prospective studies are needed to elucidate whether treating to a target of lower LDL-C levels retards the progression of severe NPDR or PDR complicated by hypercholesterolaemia.

DR is a form of diabetic microangiopathy, and neuroinflammation modulates its pathogenesis. High concentrations of LDL-C produce cytotoxic effects on vascular endothelial cells and potentiate vasoconstriction in the vascular beds, both of which may contribute to the progression of nonperfused areas in DR [20], and modifications of LDL-C promote inflammatory and thrombotic responses in atherosclerosis [21]. The lipid-lowering treatment might reverse these pathological responses, and concomitantly improve the pathogenesis in severe NPDR or PDR. Another explanation might be the modification of VEGF signalling by statins. VEGF plays a pivotal role in retinal neovascularization and clinical progression to PDR [22]. Hypoxia is generally considered a potent inducer of VEGF expression in the nonperfused areas of DR, and stimulation of biochemical pathways and cytokines may also contribute to VEGF expression in DR [23]. A few basic research studies have demonstrated that statins reduce VEGF expression, which is mediated by the regulation of oxidative stress, and inhibit VEGF signalling and concomitant endothelial cell proliferation [24–26]. These data might explain the beneficial effects of intensive statin therapy on severe NPDR or PDR.

Diabetic macular oedema (DMO) is another vision-threatening DR, and many publications have documented the association between dyslipidaemia and DMO, and between dyslipidaemia and hard exudates containing lipid deposits [5, 27]. There were no differences in changes in the severity of hard exudates between the two groups in the current study. This finding appears to be consistent with a meta-analysis of randomized controlled trials showing no significant efficacy of the lipid-lowering drugs against worsening DMO or hard exudates [28]. In contrast, an exploratory analysis demonstrated that severe hard exudates at baseline might predict greater efficacy of intensive

therapy on DR severity. Further studies should be planned to examine the effects of intensive treat-to-target therapy for DR with severe hard exudates complicated by hypercholesterolaemia. This study did not investigate the efficacy of intensive statin therapy on DMO based on optical coherence tomography measurements; such testing should be considered in future studies.

This substudy had several limitations. The number of patients was small, creating the potential for selection biases. The aforementioned exploratory study suggests that future large cohorts with balanced groups should recruit more than 190 participants with severe DR (≥47), based on sample size calculation (α error = 0.05, power = 0.8). We evaluated a single time point; repeated evaluation should be planned for better analyses. In this treat-to-target study, LDL-C was within the target range in less than 50% of patients [16]. Future studies with a higher proportion of achievement might provide more definitive conclusions. Recent advances in ultrawide field fundus images might enable the observation of peripheral lesions, and the correspondence between ultrawide and ETDRS seven-field photographs is currently a topic of considerable interest [29]. Two retinal specialists subjectively evaluated the photographs in this study, but recent advances in artificial intelligence provide computer-assisted screening of DR that may allow even more objective evaluation of fundus images in future studies [30]. Since the participants were all Japanese, further studies should investigate whether these data can be generalized to other races and ethnicities.

In conclusion, the intensive treat-to-target statin therapy did not improve DR severity in patients with DR and hypercholesterolaemia in this ophthalmology substudy of the EMPATHY study. In future studies, larger cohorts should be planned to elucidate the efficacy of intensive statin therapy in patients with severe NPDR and PDR complicated by hypercholesterolaemia.

Summary

What was known before

- Hyperglycaemia, systemic hypertension, and dyslipidaemia are major risk factors for DR.
- Fenofibrates decrease the onset and progression of DR.
- Statins reduce the risk of cardiovascular diseases.

What this study adds

- Intensive treat-to-target statin therapy did not have beneficial effects on DR severity in patients with DR and hypercholesterolaemia.
- Intensive therapy might provide improvement in patients with severe DR complicated by hypercholesterolaemia.
- Intensive therapy did not affect severity of hard exudates.

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Compliance with ethical standards

Conflict of interest TM reports personal fees from Shionogi & Co., Ltd. during the conducting of the study. SK reports grants from Shionogi & Co., Ltd. during the conducting of the study. TS reports personal fees and non-financial support from Shionogi & Co., Ltd. during the conducting of the study. HI reports grants and personal fees from Shionogi & Co., Ltd. during the conducting of the study, and grants and personal fees from Takeda Pharmaceutical Company Limited, Nippon Boehringer Ingelheim Co., Ltd. Daiichi Sankyo Company, Limited, MSD K.K., Mitsubishi Tanabe Pharma Corporation, Shionogi & Co., Ltd. and Taisho Toyama Pharmaceutical Co., Ltd. grants from Sumitomo Dainippon Pharma Co., Ltd. Astellas Pharma Inc., Kyowa Hakko Kirin Co., Ltd. Teijin Pharma Limited, Mochida Pharmaceutical Co., Ltd. Ono Pharmaceutical Co., Ltd. Chugai Pharmaceutical Co., Ltd. Eli Lilly Japan K.K., and personal fees from Nipro Corporation and SBI Pharmaceuticals Co., Ltd. outside the submitted work. IK reports personal fees from Shionogi & Co., Ltd. during the conducting of the study, grants and personal fees from Takeda Pharmaceutical Company Limited, Nippon Boehringer Ingelheim Co., Ltd. Astellas Pharma Inc., Daiichi Sankyo Company, Limited, and Otsuka Pharmaceutical Co., Ltd. and grants from MSD K.K., Shionogi & Co., Ltd. GlaxoSmithKline K.K., Sanofi K.K., Genzyme Japan K.K., Sumitomo Dainippon Pharma Co., Ltd. Mitsubishi Tanabe Pharma Corporation, and Bristol-Myers Squibb Company outside the submitted work. MT reports personal fees from Shionogi & Co., Ltd. during the conducting of the study. NY reports personal fees from Shionogi & Co., Ltd. during the conducting of the study, and personal fees from Shionogi & Co., Ltd. outside the submitted work.

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