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ORIGINAL ARTICLE

Usefulness of aggressive lipid-lowering therapy with rosuvastatin in hypercholesterolemic patients with concomitant type 2 diabetes

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Introduction

Results of epidemiological studies in diabetic and non-diabetic patients implemented in Japan and overseas have shown that diabetic patients are at increased risk for consequences of coronary artery disease such as myocardial infarction [1–4]. In addition, results of a large-scale study evaluating the risk of occurrence of complications of coronary artery diseases, etc. in type 2 diabetic patients indicated the importance of LDL cholesterol (-C) as a risk factor for coronary artery disease [5, 6]. Moreover, the Hisayama Study in Japan showed that LDL-C levels ≥120 mg/dl significantly increased the risk of occurrence of arteriosclerotic disease (Relative Risk = 2.8) [7] in diabetic patients. Anti-inflammatory markers such as hs-CRP and adiponectin have drawn wide attention as factors affecting coronary artery disease [8, 9].

Type 2 diabetes is characterized by concomitant hypertriglyceridemia (TG) and hypo-HDL cholesterolemia (-C), though the frequency of simultaneous hyper-LDL-C is not low. In addition, type 2 diabetes is characterized by the fact that even if the LDL-C level is not high, glycosylated LDL and small dense LDL increase due to qualitative changes in glycosylated or miniaturized LDL particles, with simultaneous increase in remnant-like lipoprotein particles (RLP) [10–13]. The recommendations for primary prevention of cardiovascular diseases in patients with diabetes by the American Diabetes Association and the American Heart Association (2007) [14] indicate that because LDL particle size in diabetic patients is small and that these particles are of high density, diabetic patients are at high risk for the development of coronary artery disease if they have the same LDL-C level.

The guidelines for diabetes in Japan, Europe, and the United States recommend administration of statins for drug treatment of hyper-LDL-C in diabetic patients [14–17]. In addition, LDL-C management target levels have been set as follows. This level is ≤100 mg/dl in patients with a past history of coronary artery disease in the Japan Diabetes Society Guidelines [15]. The LDL-C goal for secondary prevention of coronary artery disease is <70–77 mg/dl in the guidelines of the European Society of Cardiology and the European Association for the Study of Diabetes [16]. The level is <100 mg/dl in diabetic patients with no risk for coronary artery disease and <70 mg/dl in those with at least one coronary risk factor in the statement by the American Diabetes Association and the American Heart Association [18]. Furthermore, the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (JAS GL 2007) [19] placed greater importance on diabetes than other factors in arteriosclerotic disease and classified diabetes in category III (high-risk group) equivalent to concomitant cerebral infarction and obstructive arteriosclerosis. As noted, strict target values for LDL-C have been set for improvement of lipid levels in diabetic patients, and the use of statins with strong LDL-C-lowering effects is desirable in drug treatment.

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The statins of this type currently in clinical use in Japan include rosuvastatin and atorvastatin. A preventive effect of ATV on cardiovascular events was reported in a foreign clinical study in type 2 diabetic patients [20]. The large-scale clinical study, The Collaborative AtoRvastatin Diabetes Study (CARDS), was conducted in UK and Ireland. In the study, which involved more than 2800 patients with type 2 diabetes, no history of heart disease, and relatively low levels of cholesterol, patients who took Lipitor had a 37% reduction in major CV events. RSV is believed to have a stronger LDL-C lowering effect than existing statins including ATV [21, 22], and it has been reported that it exhibited strong LDL-C lowering effects and HDL-C elevating effects as well as high rates of achievement of LDL-C management target levels in Japanese type 2 diabetic patients [23]. Also, a recent study (JUPITER) indicated that potent anti-inflammatory effect of RSV reduced mortality caused by coronary artery disease [24]. However, few findings have been obtained with regard to RSV from comparative trials with other statins in Japanese hypercholesterolemic patients with concomitant type 2 diabetes and its clinical positioning is unclear. In the present study, the clinical efficacies of RSV 5 mg and ATV 10 mg were compared in hypercholesterolemic patients with concomitant type 2 diabetes positioned as category III (high-risk group) in the JAS GL 2007.

Subjects and methods

The subjects were 100 patients classified in primary prevention category III (high-risk group) by JAS GL 2007 who consented to participate in the study from among hypercholesterolemic patients with concomitant type 2 diabetes undergoing medical examinations at our hospital between June and November 2007. They were randomized into either a RSV 5 mg group ($n = 50$) or ATV 10 mg group ($n = 50$), with administration and observation periods of 12 weeks each. Physicians independent of the study performed randomization according to the allocation table created and stored using random allocation software. Patients received dietary instruction before enrollment. Neither patient background factors nor levels of LDL-C, HDL-C, or TG (Table 1) at the start of administration differed significantly between the two groups. However, because two patients in the ATV 10 mg group dropped out of the study, drug efficacy was evaluated in 48 patients. Moreover, following parallel-group comparison, treatment was switched to RSV 5 mg in 27 of the patients completing administration of ATV 10 mg ($n = 48$) from whom consent was obtained, and drug efficacy was evaluated after 12-week observations (switching comparison period).

As efficacy endpoints, LDL-C, HDL-C, TG, LDL-C/HDL-C ratios, rate of achievement of LDL-C management target values in the JAS GL 2007, rate of achievement of LDL-C/HDL-C ≤ 1.5, HbA1c, RLP-C, small dense LDL, oxidized (PC) LDL, apo B48, adiponectin, and high-sensitivity CRP were measured at the start of administration, 12 weeks after the start of administration, and 12 weeks after drug switching, and changes in the endpoints before-to-after initiation of administration and differences between the RSV and ATV groups in the parallel-group comparison period were determined. In addition, changes in the endpoints were evaluated between completion of ATV 10 mg treatment and after 12-week treatment of RSV 5 mg in the switching comparison period. Furthermore, for safety evaluation, occurrence of adverse reactions including abnormal laboratory test values was investigated in the parallel-group comparison period and the switching comparison period.

In order to determine the number of patients to be studied, it was assumed that the rates of decrease in LDL-C levels at the time of 12-week administration of RSV 5 mg/day and ATV 10 mg/day would be 55 and 49%, respectively, with a standard deviation of 10%. The number of patients required to verify the superiority of drugs in difference in mean level in each treatment group was 45 per group with a significance level (two-sided) of $\alpha = 0.05$ and a power $(1 - \beta)$ of 0.8. However, considering the possibility of drop-out, the number of patients per group was set at 50. The paired *t*-test was used for comparison of each lipid value before-to-after administration of each statin, and the unpaired *t*-test for

Table 1 Summary of demographic characteristics

	RSV $n = 50$	ATV $n = 50$
Sex		
Male	12 (24.0%)	12 (24.0%)
Female	38 (76.0%)	38 (76.0%)
Age (years)	68.1 ± 10.5	68.5 ± 9.8
BMI	26.2 ± 5.3	25.9 ± 4.8
CHD history	4	2
Diabetes duration (years)	11.1 ± 7.4	9.4 ± 6.3
Therapeutic regimens for diabetes		
Dietary	13 (26.0%)	15 (30.0%)
Oral drugs	24 (48.0%)	25 (50.0%)
Insulin	13 (26.0%)	10 (20.0%)
Patients with oral antihypertensive drugs		
ARB	19 (38.0%)	20 (40.8%)
CCB	5 (10.0%)	8 (16.3%)
LDL-C (mg/dl) at the start of treatment	172.7 ± 21.5	173.5 ± 32.1
HDL-C (mg/dl)	61.0 ± 16.4	58.2 ± 13.1
TG (mg/dl)	160.2 ± 81.0	156.4 ± 81.2

BMI body mass index; *ARB* angiotensin II receptor blocker; *CCB* calcium channel blocker

comparison of each lipid level after administration of each statin. The significance level was 5% for two-sided tests, and results are shown as the mean ± standard deviation.

Prior to the start of the study, we obtained approval from the Ethics Committee of National Hospital Organization Utsunomiya National Hospital.

Results

Changes in lipid levels before-to-after statin administration

RSV 5 mg and ATV 10 mg each significantly decreased LDL-C levels and the LDL-C/HDL-C ratios compared with before administration and significantly increased HDL-C levels. LDL-C level after administration of RSV 5 mg was reduced from 172.7 ± 21.5 mg/dl to 83.0 ± 20.6 mg/dl ($P < 0.001$), while that after administration of ATV 10 mg was reduced from 173.6 ± 32.1 mg/dl to 94.9 ± 22.7 mg/dl ($P < 0.001$). LDL-C/HDL-C ratios after administration of RSV 5 mg and ATV 10 mg were decreased from 3.06 ± 0.98 to 1.33 ± 0.48 ($P < 0.001$) and from 3.17 ± 1.02 to 1.67 ± 0.60 ($P < 0.001$), respectively (Table 2). Moreover, both RSV 5 mg and ATV 10 mg significantly decreased RLP-C level, small dense LDL, oxidized LDL, and apo B48 compared with before administration. However, levels of adiponectin and high-sensitivity CRP exhibited no significant change before-to-after administration in either group.

Comparison of rates of change in lipid levels before to after each administration of RSV 5 mg and ATV 10 mg

The rates of decrease in LDL-C levels after administration of RSV 5 mg and ATV 10 mg were 51.8 and 43.5%, respectively; RSV 5 mg yielded a significantly high rate of

Table 2 Changes and rate of changes in lipid levels

	Before administration Mean ± SD (Median)	After administration Mean ± SD (Median)	Rate of change (%) Mean ± SD (Median)
LDL-C (mg/dl)			
RSV 5 mg	172.7 ± 21.5 (171.2)	83.0 ± 20.6*** (78.7)	−51.8## (−52.9)
ATV 10 mg	173.6 ± 32.1 (179)	94.9 ± 22.7*** (88.2)	−43.5 (−49.7)
HDL-C (mg/dl)			
RSV 5 mg	61.0 ± 16.4 (58.5)	66.2 ± 15.4*** (63.5)	10.3# (11.3)
ATV 10 mg	58.2 ± 13.1 (55)	60.2 ± 12.5* (60)	4.2 (5.6)
TG (mg/dl)			
RSV 5 mg	160.2 ± 81.0 (154)	114.4 ± 54.3*** (112)	−22.6# (−24.7)
ATV 10 mg	156.4 ± 81.2 (131)	136.3 ± 71.0 (126)	−2.8 (−15.7)
LDL-C/HDL-C			
RSV 5 mg	3.06 ± 0.98 (2.93)	1.33 ± 0.48*** (1.25)	−55.9## (−56.3)
ATV 10 mg	3.17 ± 1.02 (3.10)	1.67 ± 0.60*** (1.54)	−45.0 (−50.2)
RLP-C (mg/dl)			
RSV 5 mg	7.2 ± 3.5 (6.15)	3.6 ± 2.0*** (3.15)	−43.7## (−46.0)
ATV 10 mg	7.2 ± 4.1 (6.1)	4.6 ± 2.8*** (4.2)	−30.2 (−33.7)
Small dense LDL-C (mg/dl)			
RSV 5 mg	44.5 ± 21.7 (41.95)	21.8 ± 10.9*** (19.85)	−44.8 (−55.7)
ATV 10 mg	49.5 ± 22.9 (46.7)	27.0 ± 12.8*** (24.5)	−42.5 (−49.6)
Oxidized LDL-C (U/ml)			
RSV 5 mg	8.7 ± 6.1 (6.3)	7.1 ± 6.2*** (5.3)	−18.4 (−23.1)
ATV 10 mg	9.9 ± 6.6 (8.3)	7.6 ± 5.7*** (6.15)	−21.8 (−22.7)
Apo B48 (μg/ml)			
RSV 5 mg	8.6 ± 6.7 (6)	5.3 ± 4.2** (3.9)	−23.3 (−29.6)
ATV 10 mg	7.5 ± 5.9 (5.8)	5.7 ± 4.1** (5.1)	−18.7 (−26.1)

RLP remnant-like particles

Evaluation in 50 patients with RSV 5 mg and 48 patients with ATV 10 mg

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ (comparison of levels before and after administration), # $P < 0.05$, ## $P < 0.01$ (comparison with ATV 10 mg)

reduction of LDL-C level ($P < 0.01$). Similarly, rates of change in HDL-C level and LDL-C/HDL-C ratio were examined. HDL-C levels increased by 10.3 and 4.2%, respectively, in the RSV and ATV groups, while LDL-C/HDL-C ratios decreased by 55.9 and 45.0%, respectively. The rates of increase in HDL-C level and of decrease in LDL-C/HDL-C ratio after administration of RSV 5 mg were significantly superior to those after administration of ATV 10 mg (rate of increase in HDL-C level: $P < 0.05$, rate of decrease in LDL-C/HDL-C level: $P < 0.01$). The HDL-C decreased in 7 patients in the RSV and 14 patients in the ATV. Moreover, the rate of decrease in RLP-C level in the RSV group was significantly superior to that in the ATV group ($P < 0.01$) (Table 2).

Comparison of rates of achievement of LDL-C management target levels after administration of RSV 5 mg and ATV 10 mg

The rate of achievement of LDL-C management target levels after administration of RSV 5 mg in the JAS GL 2007 was 98% and significantly higher than the rate of 89% after administration of ATV 10 mg ($P < 0.01$) (Fig. 1). In addition, the rate of achievement of LDL-C/HDL-C $\leq$ 1.5 was 64% in the RSV 5 mg group and 47% in the ATV 10 mg group. The rate of achievement after administration of RSV 5 mg was significantly higher than that after ATV 10 mg ($P < 0.01$) (Fig. 2).

Changes in lipid levels on switching from ATV to RSV

The LDL-C level and LDL-C/HDL-C ratio 12 weeks after switching from ATV 10 mg to RSV 5 mg were reduced from 87.9 $\pm$ 16.1 mg/dl to 81.1 $\pm$ 22.3 mg/dl ($P < 0.05$) and 1.57 $\pm$ 0.49 to 1.44 $\pm$ 0.57 ($P < 0.05$), respectively, compared with those at the end of ATV administration. Moreover, small dense LDL level was significantly decreased compared with that at the completion of ATV administration (Table 3).

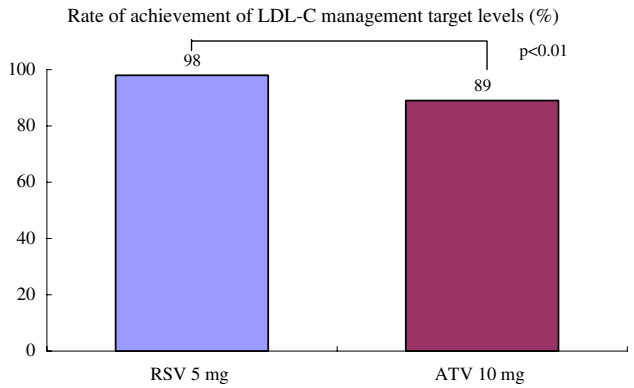

Fig. 1 Rate of achievement of LDL-C management target levels (%)

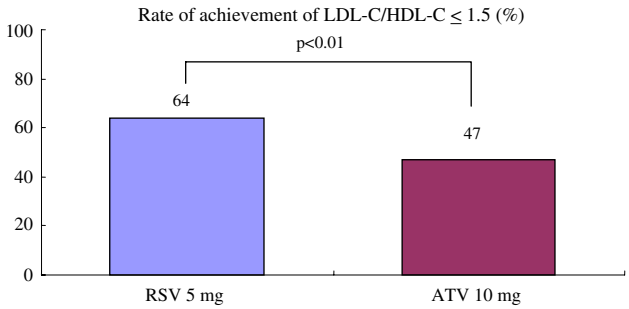

Fig. 2 Rate of achievement of LDL-C/HDL-C $\leq$ 1.5 (%)

Safety

In the present study, there were no adverse reactions either in the parallel-group comparison period or in the switching comparison period after administration of RSV 5 mg. On the other hand, two patients in the ATV 10 mg group discontinued administration of the drug due to adverse reactions (hepatic dysfunction in one patient and generalized malaise in one). These signs and symptoms were relieved by discontinuation of ATV and drugs administered in combination with it. The LFT was transient and recovered during the follow-up period. However, the causal relationship between these signs and symptoms and ATV was unknown. In addition, neither drug significantly changed HbA1c level before-to-after administration. Furthermore, there were no adverse reactions during administration of RSV 5 mg in the switching comparison period. Overall, neither drug exhibited safety findings which might prove clinical problems and both exhibited superior tolerability.

Discussion

In the present study, RSV 5 mg and ATV 10 mg each significantly improved LDL-C and HDL-C levels and LDL-C/HDL-C ratio in hypercholesterolemic patients with concomitant type 2 diabetes compared with before administration. Moreover, in a comparison of efficacy between drugs, RSV 5 mg exhibited significantly superior improvement of lipid levels compared with ATV 10 mg. In addition, a foreign comparative study of RSV and ATV in patients with concomitant type 2 diabetes reported that RSV 10 mg improved lipid levels significantly better than ATV 10 or 20 mg [25, 26]. In foreign clinical studies in hypercholesterolemic patients directly comparing the efficacy of RSV and ATV with the same doses as used in the present study, 12-week administration of RSV 5 mg improved lipid levels significantly better than administration of ATV 10 mg [27, 28]. The results of the present study, together with the findings of these studies, indicate that RSV 5 mg yields

Table 3 Changes and rate of changes in lipid levels

	Before switching	After switching	Rate of change (%)
LDL-C (mg/dl)	87.9 ± 16.1	81.1 ± 22.3*	−7.5
HDL-C (mg/dl)	59.2 ± 14.4	59.8 ± 10.5	2.4
TG (mg/dl)	128.0 ± 67.5	119.4 ± 46.1	−5.7
LDL-C/HDL-C	1.57 ± 0.49	1.44 ± 0.57*	−8.9
RLP-C (mg/dl)	4.4 ± 2.1	3.8 ± 1.5	−3.1
Small dense LDL-C (mg/dl)	28.3 ± 12.3	21.0 ± 8.50*	−15.1
Oxidized LDL-C (U/ml)	6.7 ± 2.8	5.8 ± 3.0	−8.0
Apo B48 (μg/ml)	5.8 ± 3.8	5.2 ± 3.3	−1.4

RLP remnant-like particles

Comparison of levels with switching of ATV 10 mg to RSV 5 mg: evaluation in 27 patients

* $P < 0.05$ (comparison of levels before and after switching of drugs)

significantly better lipid improvement than ATV 10 mg in Japanese hypercholesterolemic patients.

In high-risk patients, such as those with hypercholesterolemia with concomitant diabetes, the guidelines in Japan [15, 19] have also set more strict target values for lipid management, and the achievement of lipid management target levels is now one of the indications for the use of therapeutic drugs. The rates of achievement of the LDL-C management target levels in the present study were 98% in the RSV 5 mg group and 89% in the ATV 10 mg group, both of which were high. However, the rate with RSV 5 mg was significantly higher. In addition, because it was reported that ratios of LDL-C/HDL-C $\leq$ 1.5 led to plaque regression [29], ratios of LDL-C/HDL-C $\leq$ 1.5 have recently been considered target levels for diabetic patients or for secondary prevention after lowering of LDL-C to its target level [30]. In the present study as well, rates of achievement of LDL-C/HDL-C ratios $\leq$ 1.5 were determined. The rate of achievement in the RSV 5 mg group was significantly higher than that in the ATV 10 mg group. The efficacy of switching of ATV 10 mg to RSV 5 mg was studied in hypercholesterolemic patients [31], and results of subgroup analysis in patients with concomitant diabetes indicated rates of achievement of LDL-C management target levels and LDL-C/HDL-C ratios that were evidence of significant lipid improvement. These findings suggest that RSV 5 mg is superior in efficacy of lipid improvement and is useful for high-risk hypercholesterolemic patients.

The CARDS study in 2,838 patients with type 2 diabetes reported the efficacy of ATV 10 mg in preventing cardiovascular events [20]. On the other hand, a subanalysis of the ASCOT-LLA study, which involved administration of ATV 10 mg to hypertensive patients, revealed no preventive effects of the drug in cardiovascular events in 2,532 diabetic patients [32]. The efficacy of ATV in preventing cardiovascular events in diabetic patients has thus not been established. Although no study has examined the efficacy of RSV in preventing cardiovascular events in diabetic patients, its efficacy in improving lipid levels or yielding good improvement of surrogate endpoints of rates of achievement of lipid management target levels in concomitant type 2 diabetic patients have been reported both in Japan and abroad [25, 26, 33]. In addition, JUPITER study demonstrated the significant benefit on people with elevated high-sensitivity C-reactive protein levels which is the inflammatory biomarker. The efficacy of RSV in preventing cardiovascular events in hypercholesterolemic patients with concomitant type 2 diabetes, as well as patients with coronary artery disease whose LDL-C should be rigidly managed, needs to be examined in the future, since it was not examined in the present study.

In type 2 diabetes, increase of RLP and the appearance of lipoproteins such as small dense LDL and oxidized LDL are observed. RLP is a metabolic intermediate of TG-rich lipoproteins such as chylomicrons, but its retention in the blood after meals causes postprandial hyperlipidemia, which provokes and promotes arteriosclerosis. High RLP level is a risk factor for coronary artery disease irrespective of LDL-C and HDL-C levels [34], and a 3-year follow-up of patients with coronary artery disease reported that patients with high RLP-C levels had a significantly bad prognosis compared to those with low RLP-C levels [35]. In the present study, a significant rate of decrease in RLP-C levels was observed with administration of RSV 5 mg and ATV 10 mg, and a comparison of groups showed that the rate of decrease of RLP-C level with RSV 5 mg was significantly higher. Currently, no correlation between decrease in RLP-C and suppression of occurrence of cardiovascular diseases has been clarified yet, and drugs effective in reducing RLP-C have not been established either, but the results of the present study indicate that RSV 5 mg may serve as a drug to reduce RLP-C.

In the present study, levels of small dense LDL, oxidized LDL, and apo B48 were significantly reduced after administration of RSV 5 mg or ATV 10 mg. Small dense LDL particles are small and high in density, and readily remain in blood because their ability to bind to LDL receptors decreases; in addition, they readily invade the vascular endothelium because they are small and are susceptible to oxidation. Because small dense LDL blood concentration is significantly higher in patients with diabetes or coronary artery disease than in healthy individuals

[36] and it is a strong and independent risk factor for coronary artery disease [37], it has been considered a strongly arteriosclerosis-provoking lipoprotein. In addition, it has been believed that oxidized LDL resulting from oxidant stress is ingested by macrophages, which then form foam cells, leading to the development of atheromatous arteriosclerotic lesions. There is a positive correlation between oxidized LDL level and plaque volume [38], and it has been suggested that oxidized LDL plays a very important role in the occurrence of acute coronary artery disease [39]. Although apo B48 is an apoprotein specific to chylomicrons, it was isolated from arteriosclerotic lesions, as was the case for apo B100 [40]. The incidence of cardiovascular disease is correlated with apo B concentration in the blood [41], and apo B48 is known to be a significant risk factor for cardiovascular disease [42].

As described above, the relationships among RLP, small dense LDL, oxidized LDL, and apo B48 and coronary artery disease are being clarified, although the association between changes in levels of these lipoproteins due to medical treatment and coronary artery disease remains unclear. However, because it has been reported that increased small dense LDL level without high LDL-C level is involved in the development of arteriosclerosis due to lipid abnormality in type 2 diabetic patients, management of these lipoproteins in type 2 diabetic patients will be of increasing importance in the future. In the present study, administration of RSV 5 mg significantly improved lipoprotein levels compared with before administration. This drug thus appears to be useful in treating hypercholesterolemic patients with concomitant type 2 diabetes. The study groups were predominantly female; however, investigations based on subgroups such as demographics were not our aim in this study. It was considered that it was highly meaningful to investigate only one dose of each agent as the starting dose level, and thus further dose levels will be investigated in future studies.

There were no adverse reactions to RSV 5 mg in the present study, while two patients in the ATV 10 mg group dropped out of the study because of adverse reactions. However, neither drug exhibited findings potentially problematic in terms of safety, and the superior tolerability of both drugs was confirmed.

Summary

In hypercholesterolemic patients with concomitant type 2 diabetes, RSV 5 mg significantly improved LDL-C and HDL-C levels and the LDL-C/HDL ratio compared with ATV 10 mg, and also exhibited high rates of achievement of lipid management target levels in the Japan Atherosclerosis Society Guidelines. In addition, because administration of RSV 5 mg significantly improved risk factors for coronary artery disease such as RLP and small dense LDL in patients with type 2 diabetes, it appears to be useful in treating hypercholesterolemic patients with concomitant type 2 diabetes.

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