Effect of Pravastatin on Low-Density Lipoprotein Oxidation and Myocardial Perfusion in Young Adults With Type 1 Diabetes

Tuula Janatuinen, Juhani Knuuti, Jyri O. Toikka, Markku Ahotupa, Pirjo Nuutila, Tapani Rönnemaa, Olli T. Raitakari

Objective—Diabetes has been associated with increased oxidative stress and impaired vascular function. Statins have been shown to reduce low-density lipoprotein (LDL) oxidizability and improve myocardial perfusion in hypercholesterolemic non-diabetic subjects. We studied whether pravastatin decreases LDL oxidation and improves myocardial perfusion in normocholesterolemic subjects with type 1 diabetes.

Methods and Results—In this randomized, double-blind study, myocardial perfusion was measured at rest and during dipyridamole stimulation with positron emission tomography and [15O]H2O during hyperinsulinemic euglycemia in 42 patients (age 30±6 years; LDL cholesterol 2.48±0.57 mmol/L) before and after 4-month treatment with pravastatin 40 mg/d or placebo. In addition, 12 healthy non-diabetic subjects were studied. LDL oxidation was measured by determining the level of baseline diene conjugation in lipids extracted from LDL. The level of LDL oxidation was similar in the pravastatin and placebo groups before treatment (23.9±4.6 versus 25.6±9.5 μmol/L, respectively) and decreased significantly during pravastatin treatment to 19.5±5.0 μmol/L (P<0.005). Myocardial perfusion reserve was significantly lower in diabetic patients compared with controls (4.15±1.29 versus 5.31±1.86, P<0.05) and did not change after treatment. Glycemic control and insulin sensitivity remained unchanged during treatment.

Conclusion—Pravastatin treatment, resulting in decreased LDL oxidation, did not improve myocardial perfusion reserve in subjects with type 1 diabetes.

Key Words: pravastatin ■ positron emission tomography ■ myocardial perfusion ■ LDL oxidation ■ diene conjugation

Patients with type 1 diabetes mellitus (T1DM) have a 2- to 4-fold increased risk for coronary artery disease.1 Endothelial dysfunction in the peripheral arteries2-3 and functional changes in the myocardial circulation4-5 have been demonstrated in young asymptomatic adults with T1DM. The mechanisms underlying vascular pathophysiology in T1DM are not fully understood. Several lines of evidence suggest that low-density lipoprotein (LDL) particles of patients with diabetes may be particularly susceptible to oxidation.6-7 Oxidative modification of LDL is a key early event in atherogenesis leading to increased uptake of LDL by monocyte-derived macrophages and fatty streak formation.8 In addition, oxidized LDL (oxLDL) has been shown to decrease the expression of endothelial nitric oxide synthase9 and impair coronary reactivity.10 Pravastatin attenuates oxidative susceptibility of LDL in hypercholesterolemic subjects.11-13 Clinical studies into the effects of statins on LDL oxidation in diabetes are limited and contradictory. Harada et al14 demonstrated a reduction in oxidative modification of LDL with pravastatin in patients with type 2 diabetes (T2DM). In the only study to our knowledge evaluating the effects of statin treatment on LDL oxidation in patients with T1DM, Zhang et al15 observed no change in thiobarbituric acid-reactive substance formation or the oxidation lag time during in vitro oxidation with copper after pravastatin treatment.

The purpose of our study was to investigate whether 4-month treatment with pravastatin decreases LDL oxidation in vivo and improves myocardial perfusion in young asymptomatic, normocholesterolemic patients with T1DM. We also evaluated the effects of pravastatin on insulin sensitivity, because previous reports on this issue have given contradictory results.16,17

Methods

Patient Selection and Study Design

Forty-six patients with T1DM participated in the study. The inclusion criteria were: age 18 to 40 years, diabetes duration 3 to 25 years.
no symptoms of cardiovascular disease or asthma, no use of cardiovascular medication or antioxidants, no proliferative retinopathy or previous constant microalbuminuria, flow-mediated vasodilation of the brachial artery <10%, HbA1c <10%, LDL cholesterol <4.0 mmol/L, and normal liver function. The patients were recruited by advertisement and from diabetes outpatient clinics. Twelve healthy nondonabetic men with similar age and body mass index studied earlier with an identical protocol4 served as controls. Serum human chorionic gonadotropin level was measured in all women to exclude pregnancy.

Blood samples for oxLDL and other lipid parameters were taken after an overnight fast on the positron emission tomography (PET) study mornings. After the initial PET study, the diabetic patients were randomized in a double-blind manner to receive either pravastatin 40 mg/d or placebo for 4 months. Pravastatin (Pravachol) 40-mg tablets and matching placebos were provided by Bristol-Myers Squibb, Finland. The PET study and laboratory tests were repeated after the treatment period. Retinal photography, autonomic nerve function tests, and measurement of urinary albumin-to-creatinine ratio were performed on diabetic patients once during the study.

The study protocol was accepted by the local Ethical Committee. The study was conducted according to the principles expressed in the Declaration of Helsinki. The study protocol and the potential risks were explained in detail to the patients; thereafter, a written informed consent was obtained.

Biochemical Analysis
OxLDL was measured by determining the level of baseline diene conjugation in lipids extracted from LDL.18 In brief, serum LDL was isolated by precipitation with buffered heparin. Lipids were extracted from LDL samples by chloroform-methanol, dried under nitrogen, then redissolved in cyclohexane and analyzed spectrophotometrically at 234 nm. Serum total cholesterol, HDL cholesterol, and triglyceride concentrations were measured using standard enzymatic methods (Roche Diagnostics GmbH, Mannheim, Germany) with a fully automated analyzer (Hitachi 917 Automatic Analyzer). Serum LDL cholesterol concentration was calculated using the Friedewald formula.19 Plasma glucose was determined by the glucose oxidase method (Analox GM9 Analyzer). Glycosylated hemoglobin (HbA1c) formula.19 Plasma glucose was determined by the glucose oxidase method (Roche Diagnostics GmbH). Serum insulin concentrations were measured at baseline and at 60-minute intervals during clamp using a time-resolved immunofluorometric assay (Autodefia; Wallac, Turku, Finland). Liver function was tested by measuring serum alanine aminotransferase and creatinine kinase using the IFCC reference methods at 37°C (Roche Diagnostics GmbH). Urinary albumin-to-creatinine ratio was measured from overnight urine samples. Albumin concentration was measured by an immunonephelometric method (Dade Behring Inc) and creatinine kinetically with the Jaffe reaction (Roche Diagnostics GmbH).

PET Study Protocol
The PET studies were performed after an overnight fast. Alcohol and caffeine were prohibited 12 hours before the study. On the study morning, the patients took one-half of their neutral protamine Hagedom (NPH) insulin and no short-acting insulin. A catheter was inserted in the antecubital vein of the right arm for insulin (1 mU/kg/min), glucose, [15O]H2O, and dipyridamole infusions and in the antecubital vein of the left arm for blood sampling. A hyperinsulinemic–euglycemic clamp was started 60 minutes before the PET scans. Serum total insulin concentration was measured every 60 minutes and plasma glucose concentration every 5 to 10 minutes during clamp. After achieving euglycemia, plasma glucose was kept constant with an infusion of 20% glucose at a rate determined by plasma glucose measurements. Myocardial perfusion was measured at rest and 6 minutes after the beginning of 4-minute infusion of dipyridamole (0.56 mg/kg) with [15O]H2O. Insulin sensitivity (M value) was calculated from the infusion rates of glucose during clamp.

Production of [15O]H2O
For production of $^{15}$O, a low-energy deuteron accelerator Cyclone 3 was used. $^{15}$O-labeled water was produced using an automatic $^{15}$O/H2O production system.20 Sterility and pyrogenicity tests were performed to verify the purity of the product.

Image Acquisition, Processing, and Corrections
The patients were positioned supine in a 15-slice ECAT 9310/18-2 tomograph (Siemens/CTI Inc, Knoxville, Tenn), with a measured axial resolution of 6.7 mm and 6.5 mm in plane. To correct for photon attenuation a 5-minute transmission scan was performed before the emission scans with a removable ring source containing germanium 68; 1450±120 MBq of $[15O]H_2O$ was injected intravenously for 2 minutes and dynamic scanning was started for 6 minutes (6×5 seconds, 6×15 seconds, 8×30 seconds) after an increase in radioactivity was detected. Heart rate, blood pressure, and ECG were monitored during the studies. All data were corrected for dead time, decay, and photon attenuation, and were reconstructed in a 128×128 matrix. For image processing, a Bayesian iterative reconstruction algorithm using median root prior with 150 iterations and the Bayesian coefficient of 0.3 was applied.21

Calculation of Regional Myocardial Perfusion
Large regions of interest (ROI) were placed on representative transaxial slices in each study covering anterior, lateral, septal, and whole free walls of the left ventricle. Because no regional perfusion differences could be seen, the average value from the whole left ventricular ROI was used in further analysis. The ROIs were drawn on the resting images and copied to the hyperemic images. The first 10 frames of the dynamic scan were used to subtract the left ventricular blood pool from the perfusion images for visualization of the myocardium. The arterial input function was obtained from the left ventricular time activity curve using a previously validated method,22 in which corrections were made for the limited recovery of the left ventricular ROI and the spillover from the myocardial signals. Values of regional perfusion (expressed in mL·min$^{-1}$·g$^{-1}$) were calculated according to the previously published method using the single compartment model.23 Myocardial perfusion reserve (MPR) was defined as the ratio of hyperemic perfusion to perfusion at rest.

Retinal Photography
Retinal photography was performed after mydriatic installation with a Canon CR4–45NM fundus camera. One 45-degree field photograph, including areas of papilla and macula, was taken from each eye and analyzed by an experienced diabetologist.

Autonomic Nerve Function Tests
Heart rate, heart rate variability, and blood pressure were monitored at resting conditions and during the Valsalva maneuver, and an orthostatic test and isometric hand grip test were performed. The results were interpreted as pathological if ≥3 of the measured parameters were outside the range of values of an age- and gender-matched healthy population.

Statistical Analysis
Results are presented as mean value±SD. Comparisons between the groups were analyzed using the Student $t$ test and the effects of treatment using repeated-measures ANOVA. Associations between study variables were assessed by calculating the Pearson correlation coefficients. A 2-tailed $P<0.05$ was interpreted as statistically significant. All statistical analyses were performed using SAS statistical program package.

Results
Study Subjects
Of the 46 TIDM patients participating, 1 discontinued the study after initiating the study medication and 3 had to be
Serum Lipids, oxLDL, and Glycemic Control

LDL cholesterol concentration was lower (P<0.05) and HDL cholesterol higher (P<0.005) in T1DM patients compared with controls. No difference in total cholesterol or triglycerides was seen between the groups (Table 2).

Pravastatin, but not placebo, decreased serum total cholesterol on average by 1.12±0.33 mmol/L (25%) and LDL cholesterol concentrations by 0.88±0.34 mmol/L (36%) (P<0.0001 for both). No significant changes in triglyceride or HDL cholesterol concentrations were seen (Table 2).

The level oxLDL was similar in the pravastatin and placebo groups at baseline. OxLDL decreased significantly during pravastatin treatment (P<0.005), whereas no change in oxLDL was seen with placebo (Table 2). The ratio of oxLDL to native LDL, however, increased (P<0.005) because of a more pronounced decrease in native LDL (Table 2).

HbA\textsubscript{1c} level was similar in the pravastatin and placebo groups at baseline and did not change during treatment (Table 2).

Hyperinsulinemic–Euglycemic Clamp

During clamp, plasma glucose levels were 6.6±1.0 and 6.4±0.6 mmol/L in the baseline study and 6.6±1.3 and 6.6±1.2 mmol/L after treatment in the pravastatin and placebo groups, respectively. These levels are higher than the plasma glucose levels during clamp in the control subjects 5.2±1.2 mmol/L (P<0.005). Whole-body glucose uptake between 60 and 120 minutes was lower in T1DM patients compared with controls (32.2±12.8 versus 47.0±13.9 μmol/kg min, P<0.005) but was similar in the 2 treatment groups and did not change during treatment (Table 2).

Hemodynamic Variables During PET Studies

Resting blood pressure and heart rate were similar in the pravastatin and placebo groups at baseline and did not change by treatment (Table 3). Dipyridamole infusion induced a significant increase in heart rate, systolic blood pressure, and consequently rate-pressure product similarly in both groups before and after treatment.

Myocardial Perfusion

MPR at baseline was significantly lower in T1DM patients compared with controls (4.15±1.29 versus 5.31±1.86, P<0.05). The difference remained significant when the analysis was limited to nonsmokers.

Resting and hyperemic perfusion were similar in the 2 treatment groups at baseline, and consequently no difference in MPR was seen between the groups. No changes in the measures of myocardial perfusion were seen after pravastatin treatment (Figure).

Female subjects had significantly higher resting and dipyridamole-stimulated perfusion compared with males (1.19±0.24 versus 0.94±0.22 mL/min g\textsuperscript{-1}, P<0.005; and 4.84±1.33 versus 3.76±1.00 mL/min g\textsuperscript{-1}, P<0.005). However, no significant gender difference in MPR was seen

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**TABLE 1. Baseline Characteristics of the Study Subjects**

<table>
<thead>
<tr>
<th></th>
<th>T1DM Pravastatin</th>
<th>T1DM Placebo</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Age, y</td>
<td>30.2±5.6</td>
<td>28.9±6.5</td>
<td>30.8±4.1</td>
</tr>
<tr>
<td>Males/females</td>
<td>13/9</td>
<td>11/9</td>
<td>12/0</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>13.4±7.7</td>
<td>10.5±5.3</td>
<td>—</td>
</tr>
<tr>
<td>BMI, kg/m\textsuperscript{2}</td>
<td>24.7±2.5</td>
<td>24.6±2.6</td>
<td>23.5±1.4</td>
</tr>
<tr>
<td>Current smokers</td>
<td>7</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Background retinopathy</td>
<td>6</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
<td>1</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>U-albumin/creatinine &gt;3 mg/mmol</td>
<td>3</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

BMI indicates body mass index.

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**TABLE 2. Glycemic Control, Insulin Sensitivity, and Lipid Profile Before and After Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n=22)</th>
<th>Placebo (n=20)</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA\textsubscript{1c}, %</td>
<td>8.3±1.1</td>
<td>8.4±1.2</td>
<td>4.8±0.44</td>
</tr>
<tr>
<td>M value, μmol/kg min</td>
<td>30.2±11.5</td>
<td>32.9±11.9</td>
<td>34.4±14.2</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.42±0.5</td>
<td>3.30±0.43*</td>
<td>4.61±0.75</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.44±0.54</td>
<td>1.56±0.40*</td>
<td>2.52±0.61</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.60±0.33</td>
<td>1.48±0.29</td>
<td>1.51±0.29</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.84±0.33</td>
<td>0.57±0.24</td>
<td>1.25±0.98</td>
</tr>
<tr>
<td>OxLDL, μmol/L</td>
<td>23.9±4.6</td>
<td>19.5±5.0†</td>
<td>25.6±9.5</td>
</tr>
<tr>
<td>OxLDL/native LDL (ratio)</td>
<td>11.1±2.5</td>
<td>14.6±6.0†</td>
<td>11.5±3.2</td>
</tr>
</tbody>
</table>

*P<0.0001 vs baseline.
†P<0.005 vs baseline.
‡P<0.05 vs T1DM.
§P<0.005 vs T1DM.
||P<0.0001 vs T1DM.
No gender difference in the treatment effect of pravastatin on myocardial perfusion was seen.

**Subgroups**
The results did not change when all patients with a diabetic complication (retinopathy, autonomic neuropathy, or albuminuria) were excluded from the analysis. When the patients with a diabetic complication (n=8 in the pravastatin group and n=4 in the placebo group) and current smokers (n=7 in the pravastatin group and n=6 in the placebo group) were analyzed as subgroups, the same trends in lowering oxLDL were seen. Also in these subgroups, no changes in myocardial perfusion were observed.

**Discussion**
The purpose of our study was to investigate whether 4-month treatment with pravastatin decreases LDL oxidation in vivo and thereby improves myocardial vascular reactivity in young normcholesterolemic subjects with T1DM. Pravastatin treatment significantly lowered native LDL and oxLDL; however, no improvement in hyperemic perfusion or MPR was seen.

The method for the direct measurement of oxLDL used in the present study measures the baseline level of diene conjugation in circulating LDL. Rearrangement of double bonds in polyunsaturated fatty acids, ie, the formation of conjugated dienes, is an early event of lipid peroxidation resulting from free radical activity. In diabetes, hyperglycemia may increase superoxide anion formation. In addition, hypercholesterolemia increases superoxide production; thus, reduction of cholesterol levels may directly reduce LDL oxidation. Experimental studies have provided evidence that pravastatin may also suppress superoxide production by mechanisms unrelated to cholesterol reduction. In addition, pravastatin alters the chemical composition of LDL by lowering its cholesterol content and increasing its protein fraction, thus decreasing its susceptibility to oxidation. In line, we found that pravastatin 40 mg/d decreased significantly the level of baseline diene conjugation in LDL lipids. This is in concordance with previous results showing decreased susceptibility of LDL to oxidation with pravastatin in hypercholesterolemic nondiabetic subjects and patients with T2DM. A recent study from our laboratory demonstrated that patients with multivessel disease on statin therapy had significantly lower levels of baseline diene conjugation than nonusers, although the concentrations of LDL cholesterol did not differ. The results confirm the beneficial effects of pravastatin on LDL oxidation and extend it to patients with T1DM.

**TABLE 3. Hemodynamic Data During PET Studies in Diabetic Patients**

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate (beats/min)</th>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Diastolic Blood Pressure (mm Hg)</th>
<th>Rate–Pressure Product (mm Hg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Hyperemia</td>
<td>Rest</td>
<td>Hyperemia</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>66±13</td>
<td>100±15*</td>
<td>120±9</td>
<td>125±10†</td>
</tr>
<tr>
<td>Follow-up</td>
<td>65±10</td>
<td>95±14*</td>
<td>118±12</td>
<td>124±10†</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>68±12</td>
<td>100±13*</td>
<td>119±12</td>
<td>123±11†</td>
</tr>
<tr>
<td>Follow-up</td>
<td>68±10</td>
<td>101±9*</td>
<td>116±10</td>
<td>125±14†</td>
</tr>
</tbody>
</table>

*P<0.001 between rest and hyperemia.
†P<0.05 between rest and hyperemia.

(4.28±1.73 in females versus 4.05±0.85 in males, P=0.57).
Statins decrease the cholesterol content of hepatocytes, leading to upregulation of LDL receptors in the liver and decreased LDL cholesterol concentrations in the plasma. Oxidation of LDL particles may be associated with structural changes in LDL apolipoprotein B-100, leading to reduced uptake of circulating LDL via hepatic LDL receptors. This may explain the increase in the ratio of oxLDL to LDL during pravastatin treatment. The absolute decrease in oxLDL may be explained by less LDL being present to be oxidized, and/or the reduced oxidative stress and susceptibility of LDL to oxidation resulting from statin treatment, as discussed.

In nondiabetic subjects, statin treatment generally improves vascular endothelial function. Studies in patients with diabetes, however, have provided contradictory results. Sheu et al did not observe improvement in peripheral endothelial function with simvastatin in hypercholesterolemic subjects with T2DM. Similarly, van Venrooij et al were unable to demonstrate improvement in peripheral endothelial function using aggressive lipid-lowering with atorvastatin in T2DM. On the contrary, atorvastatin has been shown to improve endothelial function in patients with T1DM. No previous studies have evaluated the effects of statins on myocardial vascular function in patients with T1DM. Despite significant reductions in native and oxLDL levels, we found no improvement in hyperemic perfusion or MPR with pravastatin. We have previously demonstrated in healthy subjects an inverse association between myocardial perfusion responses and oxLDL, suggesting that oxLDL may disturb vascular function. The finding that significant reduction in circulating oxLDL was not associated with improved myocardial perfusion responses may reflect the complex nature of vascular pathophysiology in diabetes. In diabetes, other pathophysiologic mechanisms, such as hyperglycemia per se, may outweigh the contribution of short-term changes in oxLDL on myocardial reactivity.

PET enables measurement of myocardial perfusion and MPR quantitatively and accurately in humans. The variation coefficient of myocardial perfusion measurements using PET and [15O]H2O has been demonstrated to be 14±11% at rest and 16±9% during hyperemia. Dipyridamole causes accumulation of intracellular adenosine that has a direct vasodilatory effect on smooth muscle cells via purinergic vascular receptors. In addition, an increase in shear stress caused by increased flow induces the release of vasodilating substances from endothelial cells and elicits more prominent vasodilatation in vessels with preserved endothelial function. Buus et al demonstrated by simultaneous administration of nitric oxide synthase inhibitor NG-nitro-l-arginine that a significant amount of the adenosine induced hyperemic response is endothelium-dependent. Therefore, the hyperemic response to dipyridamole may be regarded as an integrated measure of vascular smooth muscle relaxation and endothelial function. Because disturbances in both endothelial and smooth muscle cell function have been reported in T1DM, the impairment in coronary reactivity seen in the present study in T1DM patients may be caused by either or both of these mechanisms. Because diabetic women had higher flow values than diabetic men, the difference in diabetic men versus healthy men was even more pronounced.

As expected, insulin sensitivity was reduced in T1DM compared with nondiabetic subjects of similar age and body mass index. Pravastatin treatment had no influence on glycemic control or insulin sensitivity. This observation is clinically important, because there has been a concern about the effects of statins on glucose metabolism. In a recent study, 12-week treatment with simvastatin increased fasting plasma insulin levels in hypercholesterolemic subjects, suggesting that statins may impair insulin sensitivity. We used the gold standard method, insulin clamp, to measure insulin sensitivity and found no effect of pravastatin treatment on measured M values.

We studied subjects with normal cholesterol levels and good to satisfactory glycemic control who are likely to be representative of the majority of young patients with T1DM not generally receiving lipid-lowering therapy. Only 6 subjects had evidence of diabetic complications other than background retinopathy. The subgroup analyses, although too small for firm conclusions, suggest that the results may also apply to smokers and patients with diabetic complications. Our results can be applied to the patients with T1DM with no or minimal diabetic complications.

Study Limitations
Because of lack of healthy female control subjects, the degree of impairment in MPR in diabetic women is difficult to state. However, it is known that the relative impact of diabetes as a risk factor for coronary artery disease is even more pronounced in women than in men. During clamp, plasma glucose levels were higher in T1DM patients compared with the historical controls. It has been shown that short-term hyperglycemia in T1DM has no effect on MPR; thus, it is unlikely that the minor difference in glucose levels would explain the difference in MPR. Because perfusion changes probably occur at least in part by regression of atherosclerosis, it can be speculated whether the time frame of 4 months is long enough to demonstrate a positive treatment effect.

Conclusions
In conclusion, 4-month treatment with pravastatin decreases LDL oxidation in young normocholesterolemic patients with T1DM. However, no improvement in MPR could be demonstrated, indicating that reduction in oxLDL values per se in not enough to improve MPR in these patients.

Acknowledgments
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References


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