Evaluation of the effectiveness of sarpogrelate on the surrogate markers for macrovascular complications in patients with type 2 diabetes

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Abstract. Sarpogrelate, a selective 5-HT2 receptor antagonist, is known to have a significant effect on antiplatelet action. This study was a double-blinded, randomized, paralleled multicenter trial to compare the effects of sarpogrelate and aspirin on preventing macrovascular complications in patients with type 2 diabetes. The subjects were randomly assigned to either the sarpogrelate or the aspirin group. The baseline parameters for macrovascular complications, such as intima media thickness (IMT), ankle-brachial index (ABI), IL-6, serotonin, adiponectin, and hsCRP, were measured before drug administration. Changes were compared at 6 and 12 months after the administration of each drug. A total of 127 subjects (63 in the sarpogrelate group and 64 in the aspirin group) were pooled during the study period. No significant differences were found in baseline IMT or in other predictors of macrovascular complications. The mean IMT increased in both groups after 12 months, but there was no significant difference between the two groups. No significant change was found in the other predictors of macrovascular complications nor in the incidence of drug-related adverse events between the two groups. During the study period, no significant differences were found between the sarpogrelate group and aspirin group in the clinical indices or in the safety of the subjects related to macrovascular complications. This suggests that sarpogrelate may be clinically useful for the primary prevention of macrovascular complications in patients with type 2 diabetes.

Key words: Sarpogrelate, Aspirin, Type 2 diabetes mellitus, Macrovascular complications

DYSINSULINISM and insulin resistance are known causes of diabetes-related complications because they induce hyperglycemia, hyperinsulinemia, dyslipidemia, hypertension, and hemostatic disorder [1]. In particular, macrovascular complications are dangerous and can be fatal. The early prevention of the incidence and progression of atherosclerosis, which causes macrovascular complications, is an important therapeutic aim in the treatment of patients with diabetes [2]. At present, most clinical practice guidelines recommend aspirin as the first line medication for the prevention of macrovascular complications in patients with type 2 diabetes mellitus (T2DM) [3].

A recent study has reported that serotonin (5-HT2) is involved in peripheral circulatory disturbances [4]. Direct blood exposure to subendothelial collagen due to endothelial damage caused by arteriosclerosis can result in platelet adhesion, platelet aggregation, and serotonin discharge from platelets [5]. Serotonin binds to and activates the 5-HT2 receptor on the other platelet membranes, resulting in increased platelet aggregation. Moreover, serotonin binds with 5-HT2 receptors on the vascular smooth muscle cell membrane at the inhibitory site to contract vascular smooth muscles. As a result, serotonin inhibits blood flow by increasing the platelet thrombus inside the impaired blood vessels and by contracting the blood vessels from the outside [5, 6].

Repression of the serotonin 5-HT2 receptor functions would improve the symptoms of patients with peripheral circulatory disturbances by reducing the
incidence and progression of macrovascular complications. Such a treatment may be especially effective in the high-risk macrovascular disease group, which includes patients with T2DM. However, few studies have been performed regarding the effects of serotonin 5-HT2 receptor blockers on macrovascular complications in patients with T2DM [5]. There have been very few studies on the clinical effects of 5-HT2 receptor blockers compared to aspirin, which is the first line medication for the primary prevention of macrovascular complications [7, 8].

Sarpogrelate, which is a selective 5-HT2 receptor antagonist, has a significant effect on antiplatelet action and improves endothelial functions. It locally represses serotonin action only inside the lesion and does not affect the normal tissues [4, 9-14]. We performed this study to investigate if sarpogrelate has a positive effect on the surrogate markers for macrovascular complications in patients with type 2 diabetes. In addition, the effect is compared to that of aspirin, which is the first line medication for this type of situation.

**Materials and Methods**

**Study subjects**

This study was conducted with 146 T2DM patients pooled from three hospitals, Kyung Hee University Hospital, Seoul St. Mary’s Hospital, and Severance Hospital, between March 2005 and June 2007. The selection criteria for the subjects included T2DM diagnosis between the ages of 40 and 80 years with no history of ketoacidosis or ketonuria, a glycosylated hemoglobin (HbA1c) level of 8% or lower, an LDL cholesterol level of 160 mg/dL or lower, and a body mass index (BMI) less than 30 kg/m2 (with the reference values measured within the last three months). Subjects were excluded from the study if they felt it difficult to participate, had any other medical diseases that could affect the results or their safety, or if they had taken any other drugs which could aggravate bleeding tendency such as warfarin, clopidogrel, ticlopidine, and cilostazol (Table 1). The study protocol was approved by the Institutional Review Board at Kyung Hee University Hospital. Before participating, all subjects submitted written consent and received a sufficient explanation from the relevant medical staff.

**Methods**

The study was performed as a double-blinded, parallelled, randomized multicenter clinical trial. The subjects were assigned to either the sarpogrelate group or the aspirin group by simple randomization.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Inclusion and exclusion criteria of the study subjects</th>
</tr>
</thead>
</table>

**Inclusion criteria**

- Subjects diagnosed as type 2 diabetes mellitus
- Age more than 40 years and less than 80 years
- without any medical history of DKA or Ketonuria
- HbA1c less than 8.0%
- BMI less than 30 kg/m²
- LDL cholesterol less than 160 mg/dL

**Exclusion criteria**

- Medical history of malignancy
- Hepatic dysfunction (AST or ALT > 2.5 UNL)
- Renal dysfunction (creatinine > 1.6 mg/dL)
- Medical history of angina pectoris, congestive heart failure, cerebrovascular accident
- Patient of uncontrolled or untreated hypertension (SBP≥180 mmHg and/or DBP≥95 mmHg)
- Medical history of Buerger’s disease or any occlusive arteriosclerotic disease
- Patient of overt proteinuria (albumin ≥300 mg/day)
- Diabetic foot ulcer
- Clinically evident proliferative diabetic retinopathy or macular degeneration
- Medical history of hypersensitivity reaction to study medication or their metabolites
- Pregnant or breast feeding women
- Alcohol or drug addict
- Current medication users which could affect bleeding tendency (warfarin, clopidogrel, ticlopidine, and cilostazol)
- DKA, diabetic ketoacidosis; LDL, low density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; UNL, upper normal limit; SBP, systolic blood pressure; DBP, diastolic blood pressure
The respective groups were administered 300 mg/day of sarpogrelate or 100 mg/day of aspirin. The baseline values of macrovascular disease predictors were measured before the administration of the medication. These factors include intima-media thickness (IMT), ankle-brachial index (ABI), cardio ankle vascular index (CAVI), IL-6, serotonin, adiponectin, and hsCRP. Changes at six and 12 months after drug administration and the incidence of adverse drug reactions were compared between the groups.

The imaging test to measure IMT was conducted by one skilled sonographer at each hospital, using a B-mode high-resolution sonograph, to which a linear probe over 7.5 MHz was applied. The images were transmitted to a computer, and the IMT and plaque existence were analyzed with an IntimaScope (version 1.13E, Media Cross Co. Ltd., Tokyo, Japan). Both carotid arteries were divided into total carotid region, carotid opening, and carotid branch, and the maximum measurement in each region was obtained to define the maximum IMT. The mean IMT was defined as the value measured at 1 cm intervals of the far wall of the boundary toward the carotid ampullary region. To evaluate the ankle-brachial index (ABI) and the cardio ankle vascular index (CAVI), the VaSera VS-1000 (Fukuda Denshi Co. Ltd., Tokyo, Japan) was used. ABI was defined as the ratio of the systolic blood pressure measured at the ankle anterior dorsalis artery or posterior tibial artery to the upper limb systolic blood pressure measured at the brachial artery. The mean pulse transmission rate from aortic origin to the aorta, leg, and inferior horn region was measured. CAVI was defined as the ratio of the distance to the transmission time. Serum samples were immediately centrifuged, aliquoted, frozen at -70°C, and moved to the central laboratory (Research Institute of Endocrinology, Kyung Hee University, Seoul, Korea). Serum serotonin was measured using ELISA assay (Labor Diagnostika Nord GmbH & Co., Nordhorn, Germany), and hsCRP was measured using an HS-CRP assay kit (Siemens Health care Diagnostics Inc., IL, USA). The hsCRP level was estimated in fresh serum samples after centrifugation. The quantity of the respective CRP was calculated in micrograms per milliliter. Adiponectin was measured using radioimmunoassay (LINCO Research, MO, USA). IL-6 was measured using ELISA (R&D Systems, Inc., MN, USA).

The primary endpoint with respect to the efficacy of the result was defined as a change in IMT from the day of the test medication to the end of the study time. The second endpoint was defined as the changes in CAVI, ABI, serotonin, hsCRP, adiponectin, and IL-6. To assess the safety of sarpogrelate, adverse drug reactions and changes in laboratory test results were monitored.

**Statistical analysis**

Statistical analysis and data management were carried out with the Statistical Package for Social Science (SPSS, version 13.0; SPSS Inc., Chicago, IL, USA). All statistical analyses were performed as intention to treat analysis (ITT). A Student’s *t*-test and Chi-square test were conducted to test the significance of the differences between the two groups in baseline characteristics and changes during the follow-up period. A repeated measures ANOVA was performed to determine the difference in therapeutic effects between the two groups during the follow-up period. A *p*-value of 0.05 or less was considered significant.

**Results**

**Patient characteristics**

A total of 146 subjects were pooled during the study period and randomly assigned to either the sarpogrelate group (72 subjects) or the aspirin group (74 subjects) (Fig. 1). Among the subjects in the sarpogrelate group, 11 were eliminated for either protocol violation (3 subjects) or consent withdrawal (8 subjects). Two subjects were eliminated for other reasons, resulting in 59 (81.9%) of 72 original subjects in the sarpogrelate group who completed the test. Among the subjects in the aspirin group, 17 were eliminated, either for protocol violation (3 subjects), consent withdrawal (12 subjects), or incidence of abnormal reactions (2 subjects). Thus, 57 (77.0%) of 74 original subjects in the aspirin group completed the test. There was no significant difference in the ratio of subjects who dropped out between the two groups (*p*=0.157).

The mean age of the subjects was 62 in the sarpogrelate group and 63 in the aspirin group, with no significant difference between the two groups. There was no significant difference between the two groups in anthropometric and biochemical parameters (Table 2).

**Changes in the IMT**

At baseline, the mean IMT was $0.77\pm0.22$ mm on the left and $0.72\pm0.14$ mm on the right. The maximum IMT was $0.94\pm0.37$ mm on the left and $0.88\pm0.21$ mm on the
Table 2 Baseline characteristics of the study subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sarpogrelate group (n=63)</th>
<th>Aspirin group (n=64)</th>
<th>p</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F, n)</td>
<td>23 / 40</td>
<td>27 / 37</td>
<td>0.567</td>
<td>50 / 77</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.9±6.6</td>
<td>62.6±9.3</td>
<td>0.641</td>
<td>62.2±8.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.7±8.4</td>
<td>159.0±8.1</td>
<td>0.821</td>
<td>158.9±8.2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>63.8±8.4</td>
<td>63.1±8.3</td>
<td>0.642</td>
<td>63.4±8.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2±2.0</td>
<td>24.9±2.3</td>
<td>0.456</td>
<td>25.0±2.2</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>129.3±14.9</td>
<td>129.9±15.7</td>
<td>0.847</td>
<td>129.6±15.3</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.7±8.8</td>
<td>80.3±9.0</td>
<td>0.727</td>
<td>80.0±8.9</td>
</tr>
<tr>
<td>Smoking (n, %)</td>
<td>16 (25.4)</td>
<td>22 (34.4)</td>
<td>0.269</td>
<td>38 (29.9)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.3±1.0</td>
<td>6.0±1.0</td>
<td>0.117</td>
<td>6.2±1.0</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>125.7±38.8</td>
<td>113.7±22.3</td>
<td>0.258</td>
<td>119.4±31.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>177.4±33.8</td>
<td>171.3±31.8</td>
<td>0.513</td>
<td>174.4±32.6</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>109.3±30.0</td>
<td>105.3±25.2</td>
<td>0.614</td>
<td>107.3±27.6</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>44.3±18.9</td>
<td>43.6±9.9</td>
<td>0.884</td>
<td>44.0±15.0</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>138.2±86.4</td>
<td>122.9±66.2</td>
<td>0.483</td>
<td>130.7±76.8</td>
</tr>
<tr>
<td>IMT average (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.77±0.26</td>
<td>0.76±0.17</td>
<td>0.773</td>
<td>0.77±0.22</td>
</tr>
<tr>
<td>Right</td>
<td>0.71±0.14</td>
<td>0.73±0.14</td>
<td>0.533</td>
<td>0.72±0.14</td>
</tr>
<tr>
<td>IMT Max (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.96±0.48</td>
<td>0.92±0.22</td>
<td>0.587</td>
<td>0.94±0.37</td>
</tr>
<tr>
<td>Right</td>
<td>0.87±0.21</td>
<td>0.88±0.21</td>
<td>0.769</td>
<td>0.88±0.21</td>
</tr>
<tr>
<td>CAVI (m/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>8.78±1.17</td>
<td>8.43±1.22</td>
<td>0.107</td>
<td>8.60±1.20</td>
</tr>
<tr>
<td>Right</td>
<td>8.83±1.09</td>
<td>8.53±1.32</td>
<td>0.174</td>
<td>8.68±1.21</td>
</tr>
<tr>
<td>ABI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1.11±0.10</td>
<td>1.10±0.10</td>
<td>0.546</td>
<td>1.10±0.10</td>
</tr>
<tr>
<td>Right</td>
<td>1.09±0.10</td>
<td>1.08±0.10</td>
<td>0.373</td>
<td>1.09±0.10</td>
</tr>
<tr>
<td>Serotonin (ng/mL)</td>
<td>73.17±43.11</td>
<td>73.07±53.89</td>
<td>0.990</td>
<td>73.1±48.6</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>1.14±2.28</td>
<td>1.82±3.32</td>
<td>0.186</td>
<td>1.48±2.86</td>
</tr>
<tr>
<td>Adiponectin (ug/mL)</td>
<td>5.02±3.61</td>
<td>7.13±7.03</td>
<td>0.035</td>
<td>6.08±5.68</td>
</tr>
<tr>
<td>IL-6 (ng/mL)</td>
<td>1.87±2.02</td>
<td>3.86±8.41</td>
<td>0.071</td>
<td>2.87±6.20</td>
</tr>
</tbody>
</table>

mean±S.D. IMT indicates intima media thickness; CAVI indicates cardio ankle vascular index; ABI indicates ankle-brachial index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; LDL, low density lipoprotein; HDL, high density lipoprotein; hsCRP, high sensitive C-reactive protein.
Effect of sarpogrelate on type 2 DM

During the study period, the IMT increased in both the sarpogrelate group and the aspirin group. In the sarpogrelate group, the measured IMT was 0.79±0.25 mm on the left and 0.75±0.13 mm on the right after 24 weeks and 0.80±0.26 mm on the left and 0.75±0.14 mm on the right after 48 weeks. In the aspirin group, the measured IMT was 0.74±0.16 mm on the left and 0.70±0.14 mm on the right after 24 weeks and 0.80±0.25 mm on the left and 0.78±0.25 mm on the right after 48 weeks (Table 3). However, the changes in IMT were similar between the two groups, showing no significant difference.

The ratio of the subjects whose IMT value decreased by more than 15% during the follow-up period was 15.9% and 14.1% in the sarpogrelate group and the aspirin group, respectively, with reference to the average IMT on the left. The values were 14.3% and 12.5% in the sarpogrelate group and the aspirin group, respectively, with reference to the average IMT on the right. The differences in the ratios between the two groups were not significant (p=0.775, 0.768).

Change in the atherosclerosis markers

The baseline serotonin value was 73.17±43.11 ng/mL in the sarpogrelate group and 73.07±53.89 ng/mL in the aspirin group, with no significant difference (p=0.990, Table 2). The baseline hsCRP value was 1.14±2.28 mg/L in the sarpogrelate group and 1.82±3.32 mg/L in the aspirin group, with no significant difference (p=0.186). The baseline IL-6 value was 1.87±2.02 ng/mL in the sarpogrelate group and 3.86±8.41 ng/mL in the aspirin group, with no significant difference (p=0.071). Conversely, the baseline adiponectin value was 5.02±3.61 ug/mL in the sarpogrelate group and 7.13±7.03 ug/mL in the aspirin group, with a significantly higher level in the aspirin group (p=0.071). Conversely, the baseline adiponectin value was 5.02±3.61 ug/mL in the sarpogrelate group and 7.13±7.03 ug/mL in the aspirin group, with a significantly higher level in the aspirin group (p=0.071).

Table 3 Changes of vascular endothelial cell function variables from baseline to 12 and 24 weeks later

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Baseline</th>
<th>24 wks</th>
<th>48 wks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT average Left (mm)</td>
<td>Sarpogrelate</td>
<td>0.77±0.26</td>
<td>0.79±0.25</td>
<td>0.80±0.26</td>
<td>0.621</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>0.76±0.17</td>
<td>0.74±0.16</td>
<td>0.80±0.25</td>
<td></td>
</tr>
<tr>
<td>IMT average Right (mm)</td>
<td>Sarpogrelate</td>
<td>0.71±0.14</td>
<td>0.75±0.13</td>
<td>0.75±0.14</td>
<td>0.920</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>0.73±0.14</td>
<td>0.70±0.14</td>
<td>0.78±0.25</td>
<td></td>
</tr>
<tr>
<td>IMT max Left (mm)</td>
<td>Sarpogrelate</td>
<td>0.96±0.48</td>
<td>0.99±0.49</td>
<td>0.97±0.46</td>
<td>0.520</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>0.92±0.22</td>
<td>0.90±0.23</td>
<td>0.67±0.33</td>
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</tr>
<tr>
<td>IMT max Right (mm)</td>
<td>Sarpogrelate</td>
<td>0.87±0.21</td>
<td>0.91±0.21</td>
<td>0.88±0.19</td>
<td>0.773</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>0.88±0.21</td>
<td>0.82±0.19</td>
<td>0.92±0.34</td>
<td></td>
</tr>
<tr>
<td>CAVI Left (m/s)</td>
<td>Sarpogrelate</td>
<td>8.78±1.16</td>
<td>8.84±1.19</td>
<td>8.88±1.36</td>
<td>0.227</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>8.43±1.22</td>
<td>8.70±1.89</td>
<td>8.60±1.64</td>
<td></td>
</tr>
<tr>
<td>CAVI Right (m/s)</td>
<td>Sarpogrelate</td>
<td>8.83±1.09</td>
<td>9.05±1.53</td>
<td>8.78±1.07</td>
<td>0.147</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>8.53±1.32</td>
<td>8.60±1.55</td>
<td>8.63±1.48</td>
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</tr>
<tr>
<td>ABI Left</td>
<td>Sarpogrelate</td>
<td>1.11±0.11</td>
<td>1.10±0.10</td>
<td>1.09±0.10</td>
<td>0.492</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>1.09±0.10</td>
<td>1.06±0.11</td>
<td>1.07±0.12</td>
<td></td>
</tr>
<tr>
<td>ABI Right</td>
<td>Sarpogrelate</td>
<td>1.09±0.10</td>
<td>1.08±0.08</td>
<td>1.08±0.09</td>
<td>0.284</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>1.08±0.10</td>
<td>1.06±0.11</td>
<td>1.07±0.09</td>
<td></td>
</tr>
<tr>
<td>Serotonin (ng/mL)</td>
<td>Sarpogrelate</td>
<td>73.17±43.11</td>
<td>72.30±44.41</td>
<td>76.07±50.07</td>
<td>0.292</td>
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<tr>
<td></td>
<td>Aspirin</td>
<td>73.07±53.89</td>
<td>79.66±51.34</td>
<td>87.87±51.49</td>
<td></td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>Sarpogrelate</td>
<td>1.14±2.28</td>
<td>1.08±1.27</td>
<td>1.06±1.70</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>1.82±3.32</td>
<td>1.93±4.53</td>
<td>1.19±2.03</td>
<td></td>
</tr>
<tr>
<td>Adiponectin (ug/mL)</td>
<td>Sarpogrelate</td>
<td>5.02±3.61</td>
<td>5.74±4.94</td>
<td>5.73±6.44</td>
<td>0.071</td>
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<tr>
<td></td>
<td>Aspirin</td>
<td>7.13±7.03</td>
<td>6.28±6.62</td>
<td>7.16±8.47</td>
<td></td>
</tr>
<tr>
<td>IL-6 (ng/mL)</td>
<td>Sarpogrelate</td>
<td>1.87±2.02</td>
<td>1.90±2.39</td>
<td>1.57±1.15</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>3.86±8.41</td>
<td>3.39±4.80</td>
<td>2.70±5.36</td>
<td></td>
</tr>
</tbody>
</table>

mean±S.D. IMT indicates intima media thickness; CAVI indicates cardio ankle vascular index; ABI indicates ankle-brachial index; hsCRP, high sensitive C-reactive protein
Changes in serological markers during the study period were analyzed, but there was no significant difference in serum serotonin concentration between the two groups. The hsCRP and adiponectin levels were lower in the sarpogrelate group, though the difference was not significant. The IL-6 level was significantly lower in the sarpogrelate group (Table 3).

**Changes in the ABI and CAVI levels**

In the sarpogrelate group, the baseline CAVI value was 8.78±1.16 m/s on the left and 8.83±1.09 m/s on the right, and the baseline ABI value was 1.11±0.11 on the left and 1.09±0.10 on the right. In the aspirin group, the baseline CAVI value was 8.43±1.22 m/s on the left and 8.53±1.32 m/s on the right, and the baseline ABI value was 1.10±0.10 on the left and 1.08±0.10 on the right. There was no significant difference between the two groups (Table 2). Changes in CAVI and ABI during the follow-up period did not show any significant difference between the two groups (Table 3).

**Safety assessment**

Thirteen adverse drug reactions were found in eight subjects (12.5%) from the sarpogrelate group, and 13 abnormal reactions were found in ten subjects (15.2%) from the aspirin group. There was no significant difference between the two groups (p=0.662).

**Discussion**

At present, several studies have been performed on the use of sarpogrelate for the prevention of diabetes-related complications in T2DM patients. Sarpogrelate has been shown to be effective in the prevention of diabetic neuropathy and diabetic nephropathy. It is also known to be effective in the recovery of insulin resistance and in the prevention of neurogenic bladder caused by autonomic nervous system complications in type 2 diabetes patients [15-21]. Additionally, studies have shown that sarpogrelate is effective in preventing peripheral circulatory disturbances. The risk of cardiovascular and cerebrovascular diseases may be reduced in type 2 patients who take sarpogrelate [7-12]. However, few studies have compared the effects of sarpogrelate with those of other drugs [7, 8, 22, 23]. In S-ACCESS, a comparative study of antiplatelet drugs for the prevention of secondary cerebral infarction, there was no significant difference between aspirin and sarpogrelate in preventing secondary cerebral infarction [8]. Weber et al. reported that combined treatment with aspirin and clopidogrel showed the greatest promise in preventing secondary cerebral infarction [22]. The current study is a head-to-head comparison of the effects of sarpogrelate and aspirin, the first line medication for the prevention of macrovascular complications in type 2 diabetes patients.

Our results show that the IMT value (IMT average left/right and IMT maximum left/right), which was the primary endpoint, did not show a significant decrease in either the sarpogrelate group or the aspirin group. There was no significant difference between the two groups in the ratio of the subjects whose IMT value decreased by more than 15%. No significant difference was found in the changes of the ABI and CAVI values, which were the secondary endpoints. Among the serological markers, the adiponectin, IL-6, and hsCRP values were more favorable in the sarpogrelate group than in the aspirin group. The incidence of abnormal reactions was not significantly different between the two groups. The results suggest that sarpogrelate may play a role in the prevention of macrovascular diseases in patients with T2DM, and that additional benefits of the drug can be expected. In particular, when compared with other studies, our study makes an objective comparison of the various risk factors of macrovascular diseases. Various serological markers, IMT, CAVI, and ABI are sensitive and effective predictors of cardiovascular diseases, and so were selected as the outcome variables [21-27].

The effect of aspirin on the prevention of macrovascular diseases has been well established by many studies. The effect of sarpogrelate cannot be sufficiently proven by the current study, which was conducted on a small scale for a short period of time. However, the results of this study provide useful data for the treatment of patients who need another treatment option due to adverse effects related to the use of aspirin or other thienopyridine alternatives. These adverse effects include resistance to the medication’s effect and gastrointestinal bleeding [28, 29]. Until now, cilostazol, ticlopidine hydrochloride, and clopidogrel studies have been conducted regarding alternatives for aspirin. The results showed that cilostazol and ticlopidine hydrochloride were equal to aspirin in preventing macrovascular diseases, and that clopidogrel had a greater effect than aspirin. Although these studies demonstrated that aspirin alternatives have equal or superior effects to aspirin, further studies are necessary to determine the
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long-term effects.

Our study has some limitations. First, the drop-out ratio of the subjects was higher (20.5%) than expected. This might have affected the significance comparisons for the clinical indices between the two groups. In addition, the baseline risk of cardiovascular diseases was not very high in the pooled subjects, and cardiovascular disease-related factors, rather than the significant difference in the incidence of cardiovascular diseases, was set as the end point. It was not sufficiently verified if the results from the two groups had the same clinical effect on a significant incidence of cardiovascular disease. Moreover, variation due to the raters could not be completely excluded, even though the IMT was measured by skilled raters in each of the centers. Despite these limitations, our study is significant because it is the first to show that sarpogrelate may be used safely for the prevention of cardiovascular diseases in type 2 diabetes patients, and that it has a clinical significance on the surrogate markers for macrovascular complications in patients with type 2 diabetes comparable to that of aspirin. In conclusion, no significant difference was found between the two groups in the clinical indices or in the safety of sarpogrelate related to macrovascular complications. However, the serological markers were more favorable in the sarpogrelate group than in the aspirin group. This indicates that sarpogrelate could be effectively used as an aspirin alternative for the prevention of macrovascular complications in patients with T2DM.

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