**Oral Beraprost Sodium as a Prostaglandin I₂ Analogue for Vascular Events in Patients with Peripheral Arterial Disease: Meta-Analysis of Two Placebo-Controlled Randomized Trials**

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**Abstract**

**Objective**: To evaluate the effect of beraprost sodium (beraprost) on the vascular events occurring in patients with peripheral arterial disease (PAD) in a meta-analysis of placebo-controlled, randomized trials.

**Design**: Meta-analysis

**Methods**: Among the clinical trials of beraprost in patients with intermittent claudication associated with PAD, placebo-controlled, randomized trials with vascular events as outcome measures were selected. Two trials met the criteria, each of which was a comparative trial of beraprost (40 μg t.i.d.) and placebo (t.i.d.), with a six-month follow-up period.

**Results**: With both trials combined, the analysis included 594 patients in the beraprost group and 590 in the placebo group. The risk ratio was 0.608 (95%CI: 0.41 to 0.90, p=0.012), demonstrating the efficacy of beraprost on all vascular events. The risk ratio for lower limb deterioration was 0.598 (95% CI: 0.34 to 1.06, p=0.079), which was similar to that for all vascular events. A statistically insignificant but similar result was also obtained for cardio/cerebrovascular events with a risk ratio of 0.619 (95% CI: 0.36 to 1.07, p=0.085). Heterogeneity between the two studies was not found for any of the events.

**Conclusion**: The results demonstrated the efficacy of beraprost on the vascular events in patients with PAD. The potential benefit of beraprost on vascular events will require evaluation in a larger prospective investigation.

**Key words**: prostacyclin, beraprost sodium, meta-analysis, intermittent claudication, vascular event

**Introduction**

Beraprost sodium (beraprost) is an orally active prostaglandin I₂ (PGI₂) analogue, with antiplatelet¹ and vasodilating properties² and improvement of endothelial function³. Beraprost was launched in the Japanese market in 1992 and is currently marketed in 3 Asian counties to treat ischemic symptoms in chronic arterial occlusion and primary pulmonary

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hypertension.

Ilprost is also known to be a PGI₂ analogue. It is administered intravascularly (iv) and is targeted for more severe (Fontane stages III and IV) patients. The efficacy of ilprost has also been demonstrated by a meta-analysis⁹. Therefore, this study is limited to the efficacy of beraprost for more mild (Fontane stages II) patients.

Although PGI₂ analogues were expected to be clinically applied in various ways due to their physiological activities⁵,⁶, there are only a few reported placebo-controlled double-blind trials with PAD as the target disease to demonstrate efficacy in the treatment of arteriosclerotic disease⁷. Likewise, all reported trials of beraprost have only targeted PAD among arteriosclerotic diseases.

For beraprost, there have been four reported placebo-controlled, randomized, double-blind trials in patients with intermittent claudication (IC) due to PAD⁸⁻¹¹. Of these four, two phase 3 trials⁸⁻¹¹ had claudication and cardiovascular events as outcome measures. A BERCI-2 trial¹⁰ conducted in France and Italy demonstrated a significant improvement in claudication, while a study conducted in the United States¹¹ showed no statistically significant difference. Noteworthy was that the drug's tendency to improve cardiovascular events was observed in both studies; however, a statistically significant difference was absent, which indicates that beraprost has not been fully proved to be effective for cardio/cerebrovascular events including myocardial infarction, cardiovascular death, and stroke as endpoints.

A meta-analysis of the two phase 3 trials was performed to evaluate the effect of beraprost on vascular events in more than 1,000 patients. The present meta-analysis not only assesses the value of beraprost in reducing vascular events but also provides important information for conducting clinical trials with cardio/cerebrovascular events as a primary outcome measure.

Methods

1. Trial selection

As shown in Figure 1, for the time period of 1966 to 2003, a total of 224 articles were retrieved by the Medline database using the keyword “beraprost”. Limiting the search to the publication type of randomized controlled trial resulted in 13 articles. Among these 13 articles, 3 articles (Phase 1 trial) and 7 articles (other target diseases) were excluded as being unrelated to our study purpose. The remaining 3 articles⁸,¹⁰,¹¹ were thus regarded as candidates for evaluation. In addition, a single study⁹ was selected by a hand-search method. Since two of the studies⁸,⁹ did not deal with the endpoint of vascular events, the remaining two studies¹⁰,¹¹ were evaluated for the preventive effect of beraprost on vascular events. Of these two studies, one was the BERCI-2 trial¹⁰ involving
patients in France and Italy, while the other involved 897 patients in the United States (US trial). The primary outcome measure in these two trials was walking distance as evaluated by the treadmill test. In addition, vascular events were assessed as a secondary outcome measure.

2. General protocol
Both trials consisted of patients who met the inclusion criteria after a single-blind placebo run-in-phase and who were randomly assigned to receive either beraprost (40 µg t.i.d.) or a placebo (t.i.d.) for six months.

3. Outcome assessments
The present analysis used vascular events as outcome measures. Since the US trial and the BERCI-2 trial were conducted according to similar protocols, these two trials had the same definition of cardiovascular events including: death of cardiovascular origin (confirmed or sudden death), nonfatal myocardial infarction, unstable angina, stroke or transient ischemic attack, critical leg ischemia (rest pain necessitating an urgent medical intervention or a surgical procedure to avoid amputation), subacute critical ischemia (continuous rest pain for >2 weeks requiring analgesics), peripheral angioplasty, peripheral bypass surgery, and amputation at any level.

To avoid any potential bias by the investigator in event evaluation, in the US trial, all vascular events were adjudicated by an independent Critical Cardiovascular Events Committee, while, in the BERCI-2 trial, every potential vascular event was fully documented and evaluated blindly by three experienced cardiologists.

4. Study patients
Both trials had similar inclusion criteria with the exception of patient age (BERCI-2: 35-75 years; US trial: 40-80 years) and concomitant medication (aspirin, clopidogrel, and ticlopidine were allowed in the US trial but not in the BERCI-2 trial).

5. Endpoints
The primary endpoint was defined as all vascular events for this meta-analysis. These events include lower limb deterioration and cardio/cerebrovascular events, which were assessed separately. Lower limb deterioration was regarded as a measure of PAD progression, while cardio/cerebrovascular events were evaluated to focus on ischemic heart disease and ischemic stroke.

6. Statistical analysis
Statistical analysis was performed according to the intention-to-treat population for the primary studies. P-values were computed using the Mantel-Haenszel chi-square test based on a 2x2 contingency table. A fixed effects model was used to estimate the pooled risk ratio based on a 2x2 table and its 95% confidence interval (CI) according to Mantel-Haenszel method. Heterogeneity between the trials was examined using the Cochran's Q-test. A two-sided p-value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed by using Comprehensive Meta-Analysis® software version 1.0.23.

Results

1. Baseline characteristics
At randomization after the run-in-period, the BERCI-2 trial consisted of 209 patients in the beraprost group and 213 patients in the placebo group, while the US trial had 385 and 377 in the beraprost and placebo groups, respectively. Baseline characteristics are shown in Table 1. As compared with the patients in the BERCI-2 trial, those in the US trial had slightly lower ankle-brachial indices (ABIs) and shorter maximum walking distances (MWDs). In addition, they were more likely to have hypertension, diabetes mellitus, or dyslipidemia. In the US trial, 65%, 6.3%, and 0.5% of the patients concomitantly used aspirin, clopidogrel, and ticlopidine, respectively.

2. Incidence of vascular events
Vascular events occurred in 29 patients (6.9%) in the BERCI-2 trial and 71 patients (9.3%) in the US trial. Cardio/cerebrovascular events other than lower limb events were documented in 7 patients (1.7%) in the BERCI-
Overall, the incidence was higher in the US trial. Comparison between beraprost and the placebo revealed that beraprost was associated with a reduced incidence of vascular events in both trials: events occurred in 10 beraprost-treated patients (4.8%) and 19 placebo-treated patients (8.9%) in the BERCI-2 trial while 28 beraprost-treated patients (7.3%) and 43 placebo-treated patients (11.4%) were reported to have had events in the US trial (Table 2). Both trials showed similar risk reductions for vascular events with 46.4% in the BERCI-2 trial and 36.2% in the US trial. The number needed to treat was also quite similar, 24 for the US trial and 25 for the BERCI-2 trial.

3. Meta-analysis

Figure 2 shows the results of the meta-analysis of the two trials examining vascular events. The pooled risk ratio was 0.608, indicating a significant risk reduction of beraprost on all vascular events (95%CI : 0.41 to 0.90, p = 0.079) and the pooled risk ratio for cardio/cerebrovascular events was 0.619 (95%CI : 0.36 to 1.09, p = 0.085); these were statistically insignificant but similar to that for all vascular events. Heterogeneity among the two studies was not found in the risk ratio for any of these endpoints.

Discussion

1. Risk of vascular events in patients with PAD

The incidence of cardio/cerebrovascular events was 1.7% in the BERCI-2 trial and 5.9% in the US trial, finding that highlights an increased risk of cardio/cerebrovascular events in patients with PAD. The incidence of nonfatal cardiovascular events in patients with IC has been reported to be 2-4% annually. The value for BERCI-2 was similar to the previous reported one; however, the US trial gave a higher incidence only for six months.

In the Cardiovascular Health Study, ABI was closely correlated to the number of patients with myocardial infarction, angina, and congestive heart disease. ABIs, smoking, diabetes, hypertension, white cell count,
Table 2 Summary of the vascular events in intention-to-treat population

<table>
<thead>
<tr>
<th>Event</th>
<th>US trial</th>
<th>BERC1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Cardiovascular revascularization</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Limb deterioration</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Worsening limb ischemia</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Limb revascularization</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Limb amputation</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total: 28/385 (7.3%) vs. 43/377 (11.4%), difference 36.2% (95% CI 11.1-61.3), p-value 0.0002

<table>
<thead>
<tr>
<th>Event</th>
<th>US trial</th>
<th>BERC1-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk reduction</td>
<td>24</td>
<td>25</td>
</tr>
</tbody>
</table>

Fig. 2 Meta-analysis of two randomized trials of beraprost sodium therapy for vascular events
asymptomatic carotid disease and fibrinogen have all been reported as predictors of mortality\textsuperscript{13}).

The US trial included patients with lower ABI's and a high number of patients with diabetes mellitus, hypertension, or dyslipidemia. These factors may have affected the difference between the two trials.

2. Risk reduction of beraprost on cardio/cerebrovascular events and limb deterioration

In both trials, the total number of vascular events was not statistically significant, but it was relatively low in the beraprost group. In the US trial, there was a significant reduction in the combination of cardiovascular death and myocardial infarction in the beraprost group. As expected, the meta-analysis of two trials has demonstrated the significant risk reduction of beraprost in vascular events. Analyses showed similar risk reductions of 39% (p=0.012) for overall events, 40% (p=0.079) for lower limb events, and 38% (p=0.085) for cardio/cerebrovascular events. Since stratification reduced the number of events and statistical power, these figures failed to reach significant levels. Taken together, the results suggest that beraprost may prevent the progression of arteriosclerosis not only in peripheral arterial disease but also in “systemic arterial disease”.

A report by Antithrombotic Trialists’ Collaboration\textsuperscript{15} described 26 trials of antiplatelet agents in patients with IC due to PAD, estimating a 23% odds reduction for antiplatelet therapy. The present analysis with beraprost also gave a similar result. The goal of treatment in patients with intermittent claudication is to extend walking distance, and the prevention of the progression of lower limb disease is a therapeutic goal of PAD medications. The present meta-analysis showed promising effects of beraprost in preventing the progression of lower limb arteriosclerosis.

3. Relevance of these findings to PAD treatment in Japan

Ojiro and Yamazumi reported an epidemiological study of nursing homes for the elderly in Amami Island, Japan\textsuperscript{16}). The three-year survival rate was 66.3% for patients with arteriosclerosis obliterans (ASO) and 74.3% for non-ASO individuals (p=NS). ASO was frequently associated with cardiovascular deaths, with the most common cause of death being acute myocardial infarction (p<0.05). As in other countries, ASO is a disease with a poor life prognosis in Japan.

For the life prognosis of patients with ASO, Miyazaki et al. reported a retrospective study of pharmacologic interventions\textsuperscript{17}). In patients with ASO receiving various antiplatelet agents after undergoing femoral-peripheral artery bypass graft, a multiple logistic regression analysis including potential prognostic factors revealed that only beraprost significantly improved lifelong prognosis among antiplatelet agents such as aspirin and ticlopidine. This report suggests that beraprost also reduces vascular events in Japanese PAD patients.

These promising effects should be evaluated prospectively in future trials of beraprost with vascular events as the primary outcome. Six months is a widely accepted period for evaluating treadmill walking distance as a primary outcome. However, periods of a year or longer are suggested in such prevention trials to obtain clinical relevance.

4. Methodological limitation

The two selected studies\textsuperscript{8,11} have utilized the log-rank test for comparison between groups. They also presented the p-value obtained by a log-rank test. However, they did not show a hazard ratio and have just shown the number of events per total number of patients. Thus, the information obtained from articles was nothing but several 2×2 contingency tables. The present meta-analysis should combine the hazard ratio across the studies since the time to event was a primary outcome. However, their detailed data was not presented in the articles. So that, there was only a way to combine the risk ratios computed by 2×2 contingency tables. The bias caused by using a risk ratio rather than a hazard ratio is considered to be
quite small since the two studies had a common 6-month follow-up and the hazard is considered to be constant during this period.

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References