—Regular Articles—

Studies on the Effectiveness and Safety of Cilostazol, Beraprost Sodium, Prostaglandin E_1 for the Treatment of Intermittent Claudication

Masayuki HASHIGUCHI,[a,b] Keiko OHNO,*[,a] and Ryoko SAITO[a]

Department of Medication Use Analysis and Clinical Research, Meiji Pharmaceutical University,[a] 2–522–1 Noshio, Kiyose, Tokyo 204–8588, Japan and Division for Evaluation and Analysis of Drug Information, Center of Clinical Pharmacy and Clinical Sciences, School of Pharmaceutical Sciences, Kitasato University,[b] 5–9–1 Shirokane, Minato-ku, Tokyo, 108–8641 Japan

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To study the effectiveness for the treatment of intermittent claudication (IC) of three drugs with antiplatelet effects, cilostazol, beraprost sodium, and prostaglandin E_1 (PGE_1), by using a systemic review of literature and a meta-analysis. A search was undertaken for studies reported between 1966—2002 in the MEDLINE database, and references in published articles and reviews were obtained. Data for maximum walking distance (MWD), pain-free walking distance (PFWD), and adverse clinical events were extracted from the articles that met the inclusion criteria. The pooled estimates of the weighted mean differences (WMD) of MWD and PFWD for cilostazol were 52.19 m [95% confidence interval (CI) 32.08, 72.31] and 39.75 m [95% CI 23.39, 56.10], and those for PGE_1 were 100.27 m [95% CI 15.76, 184.78] and 55.73 [95% CI 21.54, 89.92], respectively. These differences were statistically significant between the test drugs and placebo. However there was no statistical significance difference between beraprost sodium and placebo, even though there was one study that showed a tendency for improvement in walking distance. The total rate of adverse clinical events in cilostazol and beraprost sodium was higher than that for placebo, while there was no statistical significant difference between PGE_1 and placebo, although PGE_1 had a higher tendency for adverse clinical events. The literature evaluation results and the meta-analysis suggest that these two drugs (cilostazol and PGE_1) can be considered to be effective drugs for the treatment of IC. Due to current availability of only a few clinical reports, further studies are needed to clarify the efficacy of beraprost sodium in the treatment of IC.

Key words——cilostazol; prostaglandins; intermittent claudication; meta-analysis; effectiveness; safety

INTRODUCTION

Arteriosclerosis obliterans (ASO) is a chronic disease based on arteriosclerosis that occurs primarily in the extremities. The clinical classification of the severity of the disease is based on exercise limitation and symptoms and is referred to as the Fontaine classification.[1)] Most of the patients who have intermittent claudication (IC) as the main clinical symptom are classified as stage II by the Fontaine classification. IC is caused by inadequate blood supply to muscles stressed by exercise. The most common presentation in patients with IC is pain, cramping, numbness, or weakness in certain muscles that develops only during exercise. The distance a person can walk before the pain develops varies in relation to the extent and severity of the arterial occlusion. Shortness of walking distance is one of the factors that are indicative that the patients' quality of life (QOL) is decreasing. Thus increases in walking distance can be used as an objective index in calculating the amount of improvement as compared with the degree of pain.

Therapies for IC include the treatment of arteriosclerosis, peripheral vascular disease (PVD), and comorbid disease in multiple organs. The goals of therapy in patients with IC are to arrest progression of the disease, improve blood flow, relieve pain, and prevent and treat ulceration and gangrene. Therapeutic options include physical therapy, pharmacologic treatment, surgery, and nonoperative interventions. Of these options, pharmacologic treatments, especially drugs with an antiplatelet effect, are one of the best options for arresting progression of the underlying disease and prevention of further claudication. Unfortunately, there are few drugs that directly improve the conditions of the targeted diseased artery. Accordingly, current pharmacological intervention is based on ''antiartheriosclerosis'', ''improvement of microvascular circulation'', ''reduction of spasm'', and ''development of collateral vessels''.

e-mail: k-kato@my-pharm.ac.jp

Aspirin, ticlopidine, eicosapentaenoic acid, sarpogrelate hydrochloride, dipyridamole, cilostazol, limaprost alfadex, beraprost sodium (beraprost), alprostadil, alprostadil alfadex, argatroban, etc., have been approved for the treatment of ASO in Japan. Based on their pharmacological characteristics, they have been classified into two categories, drugs that only have antiplatelet action and drugs that have antiplatelet action combined with vasodilation. Aspirin and ticlopidine belong to the former category. Although there has been a paucity of studies directly addressing the effects of aspirin on IC symptoms, aspirin reduces the risk of adverse cardiovascular events including cardiac death in patients with peripheral arteriosclerosis, and is the overwhelming antiplatelet drug of choice in patients with vascular disease of any origin, which includes stroke, myocardiac infarction, PVD, and angina.[2] In contrast, ticlopidine has been shown to increase pain-free walking distance (PFWD) and absolute walking distance, as compared with placebo in patients with PVD,[3,4] decrease the risk of death from cardiovascular causes by approximately 30%[5] and decrease the need for revascularization surgery over a 5-year treatment period in this patient population.[6] However, ticlopidine is well known to cause severe adverse drug reactions such as thrombogenic thrombocytopenia purpurea, hepatic impairment, etc. The Ministry of Health, Labour and Welfare in Japan is currently appealing to health care providers to be aware of the occurrence of these adverse drug reactions in the publication ''Dissemination of emergency safety information''.[7]

Cilostazol, which is a selective phosphodiesterase inhibitor (type III) and beraprost, which is prostaglandin I_2 (PGI_2) analogue, are both oral formulations, while prostaglandin E_1 (PGE_1) is an injectable formulation. All three of these compounds belong to the latter category of drugs, i.e., having an antiplatelet action with vasodilation. These drugs are considered to be advantageous for the prophylaxis and treatment of ASO owing to their pharmacological characteristics. In 1999, the Food and Drug Administration (FDA) approved cilostazol for the treatment of IC.[8] However, in spite of the many cases where pharmacological intervention was started at the stage II Fontaine classification, there have been no large clinical trials that specifically investigated improvement of IC.

The objective of this study was to use a systemic review of literature and meta-analysis to investigate the effectiveness and safety of cilostazol, beraprost, and PGE_1 in the treatment of IC from the viewpoint of improved walking distance.

METHODS

Literature Search A comprehensive literature search on the effectiveness and safety of cilostazol, beraprost, and PGE_1 for IC was conducted using the MEDLINE database (PubMed). A search for all randomized controlled trials published in both the English and Japanese languages on MEDLINE between January 1966 and May 2001 was conducted. On MEDLINE we combined a search of studies containing the keyword ''cilostazol'', ''beraprost sodium'', and ''prostaglandins'' with a search using the Medical Subject Heading (MeSH) ''intermittent claudication''. In addition to the electronic database search, manual searches were carried out using reference lists from retrieved articles. We also consulted several content experts and pharmaceutical companies for information about the existence of any unpublished or current trials.

Inclusion Criteria Two investigators (MH, RS) examined each paper's title and abstract, and then the full paper if necessary. To be included in this meta-analysis, the studies had to meet the following criteria: a randomized, double-blind, placebo-controlled trial of adults, ASO patients with a chief complaint of IC (stage II as determined by the Fontaine classification), effectiveness evaluation of the maximum walking distance (MWD) or PFWD by using a treadmill test.

Assessment of Quality of Literature We evaluated the quality of the literature using the score system developed by Chalmers.[9] The major items evaluated for each study were: study hypothesis, patient selection, patient characteristics, number of study patients, randomization and blinding, measurements and definition of outcome, and the statistical method. Quality was graded for each of the 30 items on a scale of 0—15 (total maximum score=100). Due to the specific nature of each item, maximal score differed for each item. Three investigators (MH, KO, and RS) independently evaluated the studies and total scores for each study were compared to evaluate the overall quality. Differences were resolved by consensus. The quality of the studies was classified as fol-

lows; high (greater than 70 points), moderate (40 to 69 points), low (less than 40 points). We used only high or moderate studies for the final data analysis.

Data Extraction We extracted the data for clinical study design used, patient characteristics, test drug, dose or dosage, and duration of drug administration. The outcome measures assessed were 1) the number of patients during analysis, 2) mean and standard deviation for the MWD; which included the increase from baseline of MWD at the end of drug administration, the increase from baseline of MWD at 4 weeks after the commencement of drug administration, the decrease in MWD at the end of the follow-up periods after drug discontinuation, 3) mean and standard deviation for PFWD; which included the increase from baseline of PFWD at the end of drug administration, the increase from baseline of PFWD at 4 weeks after the commencement of drug administration, the decrease in PFWD at the end of the follow-up periods after drug discontinuation, and 4) the number of patients who had adverse clinical events during the study.

Statistical Analysis The data was subjected to meta-analysis by a fixed effects model. This model assumes a common treatment effect across the studies being pooled, with differences primarily due to sampling variations. Using this model, study size was the major determinant of the statistical weight given to individual study results.

For examination of the results related to the effectiveness (MWD and PFWD) on IC by the drugs, we estimated the mean difference and 95% confidence interval (CI) for each study. We used the general variance based method[10] for combining the data to estimate the effectiveness of each drug in the improvement of walking distance. Statistical significance was judged by using the weighted mean difference (WMD) and 95% CI. Thus there was statistical significance if the 95% CI did not include zero.

For examination of the results related to the safety of the drugs, we estimated the odds ratio (OR) for each of the clinical adverse events and the 95% CI for each study. We used the Mantel-Haenszel method[10] for combining the data to estimate the safety of each drug. Statistical significance was judged by using the OR and 95% CI. Thus there was statistical significance if the 95% CI did not include one. For the studies in which one treatment arm had no events, 0.5 was added to each cell of the corresponding 2 by 2 table before calculating the statistics.

A test for homogeneity of the pooled estimates of the data was carried out using a Q statistic, which is referred to as a chi-square distribution with the degree of freedom equal to the number of studies minus 1. Statistical significance was expressed at a level of $p < 0.05$. A finding of significant heterogeneity indicated that the variation in the effectiveness or safety among studies exceeded that expected from random variation, possibly due to fundamental differences in the intervention, study samples, or designs. Pooled estimates of the effectiveness or safety may be inappropriate in cases of significant heterogeneity.[10] If homogeneity of the data of pooled estimates was rejected, the weight given to each study consisted of the reciprocal of the sum of the variance for each study and the variance across all studies using a random effects model (DerSimonian-Laird method).[10] Meta-analytical calculations were performed using Excel 2000 software (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Of the clinical studies we reviewed, there were 28 related reports (7 for cilostazol, 2 for beraprost, 19 for PGE_1). Six of 7 studies for cilostazol met our criteria with 5 of them dealing with MWD, 3 with PFWD, and 5 with documented adverse clinical events. All 2 studies for beraprost met our criteria with 1 study dealing with MWD and PFWD, and both studies documenting adverse clinical events. Nine of 19 studies for PGE_1 used intravenous administration, and three of them met our inclusion criteria. All of these 3 studies dealt with MWD, PFWD, and adverse clinical events.

The results for the quality score for the literature were as follows. All 6 papers studied for cilostazol scored moderate quality (40—69 points); Beebe et al.[11] (66 points), Dawson et al.[12] (57 points), Dawson et al.[13] (54 points), Dawson et al.[14] (66 points), Elam et al.[15] (58 points), and Money et al.[16] (54 points). The two beraprost studies scored moderate quality (40—69 points); Lievre et al.[17] (62 points), and Lievre et al.[18] (59 points). The three PGE_1 studies scored moderate quality (40—69 points); Diehm et al.[19] (66 points), Mangiafico et al.[20] (64 points), and Mangiafico et al.[21] (65 points). All of the studies used in the meta-analysis were judged as being of appropriate literature quality

for data combination.

Table 1 shows a summary of the clinical studies included in the meta-analysis. Total number of patients for the meta-analysis included 686 drug-treated and 666 placebos for the cilostazol group, 251 drug-treated and 254 placebos for the beraprost group, and 139 drug-treated and 135 placebos for the PGE_1 group. Figure 1 shows the increased MWD and PFWD at the end of drug administration in the study for the 3 drugs, cilostazol, beraprost, and PGE_1. Except for Dawson et al.,[13] the four cilostazol studies showed a statistical significant difference between the cilostazol and placebo group. The pooled result of WMD [95% CI] of MWD was 52.19 m [32.08, 72.31] (with the fixed effects model) for cilostazol and showed a statistical significant difference between the 2 groups. For beraprost, there was a tendency for an increased MWD as compared with placebo [WMD, 95% CI: 119.00 m, −5.48, 243.48], even though there was only one study and the difference was not statistically significant. For PGE_1, the pooled result of WMD [95% CI] of MWD was 100.27 m [15.76, 184.78] (with the random effects model) for PGE_1 and showed a statistical significant difference between the 2 groups.

With regard to the increased PFWD at the end of drug administration in the study for the 3 drugs, all 3 studies for cilostazol showed statistical significant difference between the cilostazol and placebo group. The pooled result of WMD [95% CI] of PFWD was 39.75 m [23.39, 56.10] (with the fixed effects model) and showed a statistical significant difference between the 2 groups. For beraprost, there was a tendency for an increase in PFWD as compared with placebo [WMD, 95% CI: 69.00 m, −10.39, 148.39], even though there was only one study and it did not show a statistical significant difference. For PGE_1, all 3 studies showed statistical significant differences between the PGE_1 and placebo group. The pooled result of WMD [95% CI] of PFWD was 55.73 m [21.54, 89.92] (with the random effects model) and showed a statistical significant difference between the 2 groups.

Figure 2 shows the increased MWD and PFWD at 4 weeks after the commencement of cilostazol and PGE_1 administration. With the exception of Dawson et al.,[11] the two cilostazol studies did not show any statistical significant differences between the cilostazol and placebo group. The pooled result of WMD [95% CI] of MWD was 19.52 m [6.66, 32.37] (with the fixed effects model) and showed a statistical significant difference between the 2 groups. For PGE_1, all 3 stu-

Table 1. Summary of Clinical Trials Included in the Meta–analysis

Source	Daily dose	Duration	No. of patients (drug/placebo)	Disease status	Treadmill condition (speed, slope)
Cilsotazol, p.o					
Beebe 1999[11]	200 mg	24 weeks	175/170	IC	3.2 km/hr, 12.5%
Dawson 1998[12]	200 mg	12 weeks	54/27	IC	3.2 km/hr, 12.5%
Dawson 1999[13]	① 200 mg	24 weeks	16/16	Stable, moderate	3.2 km/hr, ↑3.5%/3 min
	② P	6 weeks		-severe IC	
Dawson 2000[14]	200 mg	24 weeks	227/239	Stable, moderate	3.2 km/hr, ↑3.5%/3 min
				-severe IC	
Elam 1998[15]	200 mg	12 weeks	95/94	Stable, IC	Not mentioned
Money 1998[16]	200 mg	16 weeks	119/120	IC	3.2 km/hr, ↑3.5%/3 min
Beraprost, p.o					
Lievre 1996[17]	120 μg	12 weeks	42/41	Stage II	3.2 km/hr, 10%
Lievre 2000[18]	120 μg	6 months	209/213	IC	3.0 km/hr, 10%
PGE_1, i.v					
Diehm 1997[19]	① 60 μg or P	① 5 day/1 week×4 weeks	106/102	Stage II	3 km/hr, 12%
	② 60 μg or P	② 2 day/1 week×4 weeks			
	③ P	③ 12 weeks			
Mangiafico 1999[20]	60 μg or P	4 weeks	12/12	Stage II	3 km/hr, 5%
Mangiafico 2000[21]	① 60 μg or P	① 4 weeks	21/21	IC	3 km/hr, 5%
	② P	② 8 weeks			

p.o: oral administration, i.v: intravenous administration, P: placebo, IC: intermittent claudication

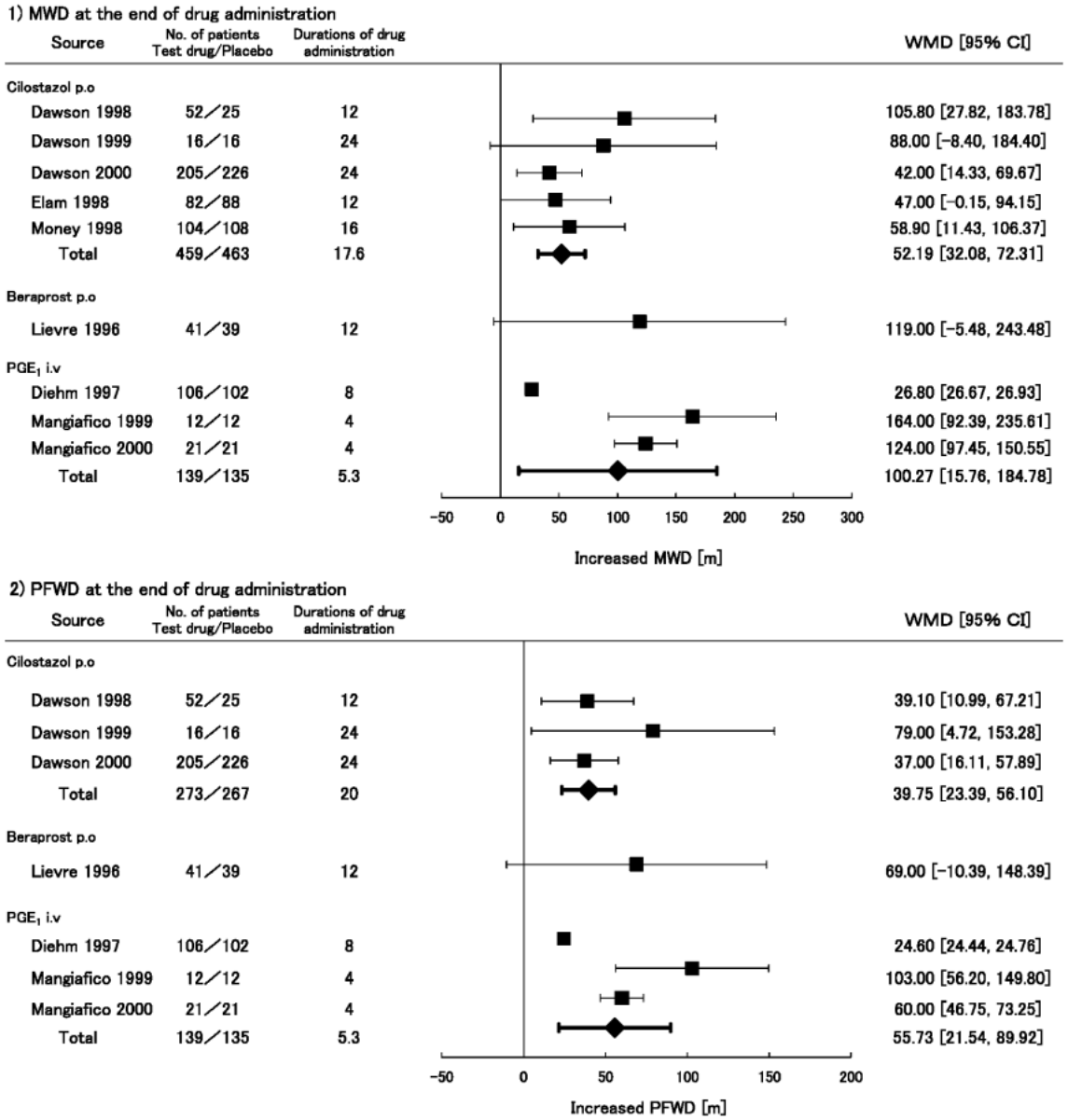

Fig. 1. Effect of Cilostazol, Beraprost, and PGE_1 on Maximum Walking Distance and Pain-Free Walking Distance at the End of Drug Administration in Patients with Arteriosclerosis Obliterans

MWD=maximum walking distance, PFWD=pain-free walking distance, WMD=weighted mean difference, 95% CI=95% confidence interval.

dies showed statistical significant differences between the PGE_1 and placebo group. The pooled result of WMD [95% CI] of MWD was 98.94 m [10.76, 187.12] (with the random effects model) and showed a statistical significant difference between the 2 groups.

With regard to the increased PFWD at 4 weeks after the commencement of drug administration, there were no statistical significant differences in all 3 cilostazol studies between the cilostazol group and placebo group. The pooled result of WMD [95% CI] of PFWD was 12.15 m [2.93, 21.37] (with the fixed effects model) and showed a statistical significant difference between the 2 groups. For PGE_1 administration, all 3 studies showed statistical significant differences between the PGE_1 and placebo group. The pooled result of WMD [95% CI] of PFWD was 54.83 m [16.77, 92.90] (with the random effects model) and showed a statistical significant difference between the 2 groups.

Figure 3 shows the MWD and PFWD at the end of the follow-up periods for the cilostazol and PGE_1 groups. For cilostazol, there was only one study, and there was a tendency for a decrease in MWD (WMD

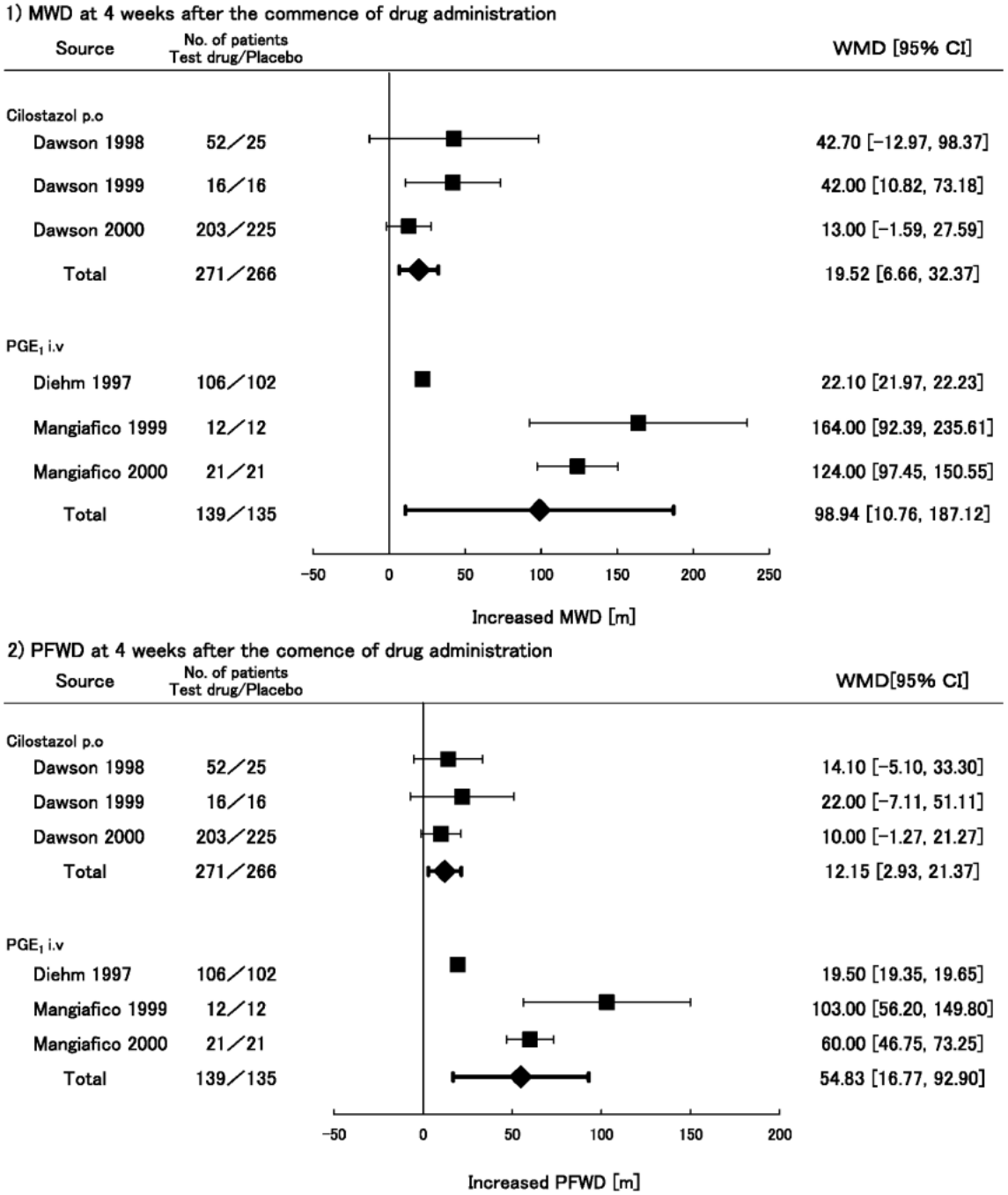

Fig. 2. Effect of Cilostazol and PGE_1 on Maximum Walking Distance and Pain-free Walking Distance at 4 Weeks after Commencement of Drug Administration in Patients with Arteriosclerosis Obliterans

MWD=maximum walking distance, PFWD=pain-free walking distance, WMD=weighted mean difference, 95% CI=95% confidence interval.

[95% CI]; −76.00 m [−183.79, 31.79]) even though it did not show a statistical significant difference between the cilostazol and placebo group. For PGE_1, in both studies there were statistical significant differences between the PGE_1 and placebo group. The pooled result of MWD (WMD [95% CI]) showed a decreased MWD of −16.45 m [−44.12, 11.21] (with the random effects model), even though it did not show a statistical significant difference between the 2 groups. For the PFWD at the end of follow-up periods, there was only one cilostazol study, and there was a tendency for PFWD to decrease (WMD [95% CI]; −76.00 m [−183.79, 31.79]) even though it did not show a statistical significant difference between

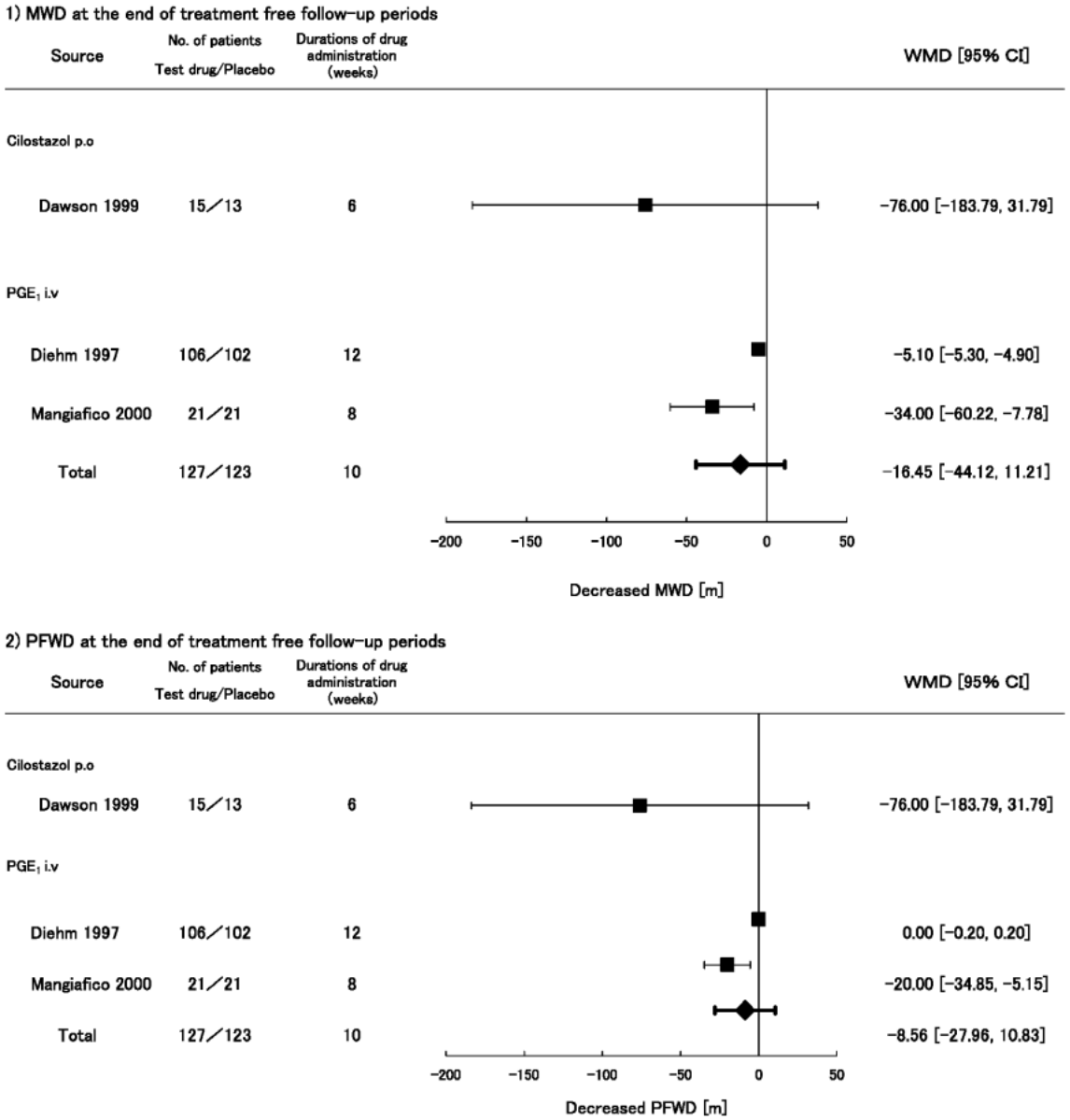

Fig. 3. Effect of Cilostazol and PGE_1 on Maximum Walking Distance and Pain-free Walking Distance at the End of the Follow-up Periods after the Termination of Drug Administration in Patients with Arteriosclerosis Obliterans
MWD=maximum walking distance, PFWD=pain-free walking distance, WMD=weighted mean difference, 95% CI=95% confidence interval.

the cilostazol and placebo group. For PGE_1, the study of Mangiafico et al.[21] documented a statistical significant difference between the PGE_1 and placebo group. The pooled result of PFWD (WMD [95% CI]) exhibited a slight decrease in PFWD of −8.56 m [−27.96, 10.83] (with the random effects model), although it did not show a statistical significant difference between the 2 groups.

Figure 4 shows the OR for death and dropout between the cilostazol and placebo group. The meta-analysis for death or dropout did not exhibit a statistical significant difference between the 2 groups. However with the fixed effects model for total death and dropout events, there was a statistical significant difference between the 2 groups (OR [95% CI]; 1.98 [1.27, 3.07].

Figure 5 shows the OR for the 11 adverse clinical events between the cilostazol and placebo group. The meta-analysis for each of the items, headache, dizziness, palpitation, diarrhea, and abnormal stool exhibited statistical significant differences between the 2 groups. Gastrointestinal complication (diarrhea, loose stools, flatulence, nausea, etc.) showed a statistical significant difference, but there was only

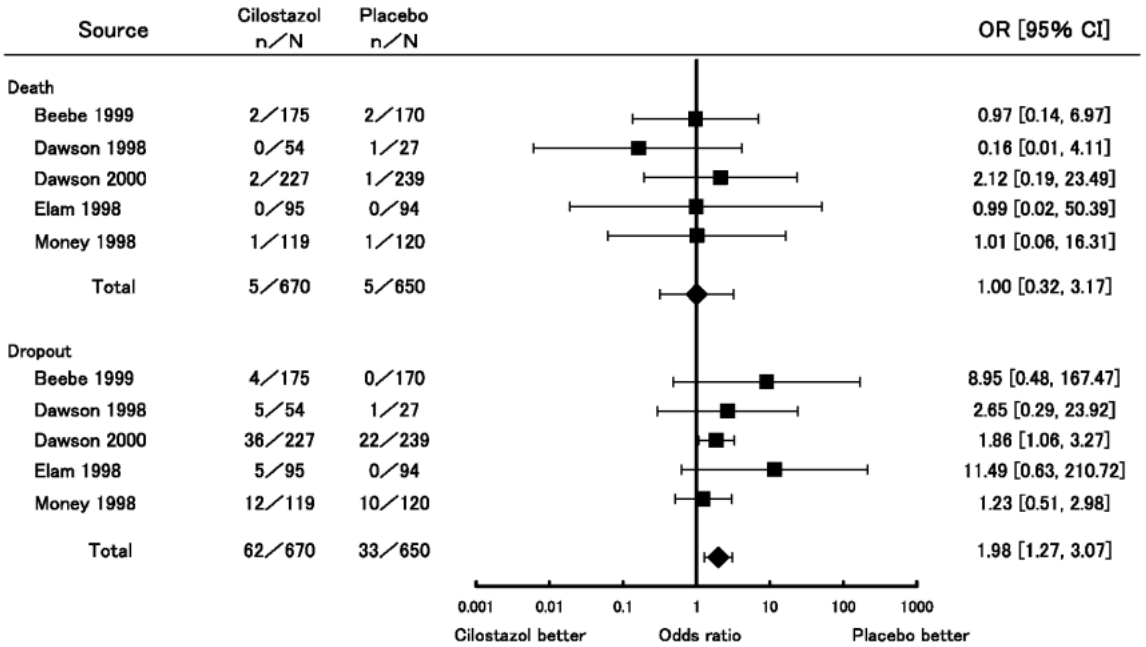

Fig. 4. Effect of Cilostazol on Death and Dropout in Patients with Arteriosclerosis Obliterans
OR=odds ratio, 95% CI=95% confidence interval.

one study analyzed. The pooled result obtained by combining all items showed a statistical significant difference between the 2 groups (OR [95% CI]; 2.34 [1.75, 3.11] with the random effects model).

Figure 6 shows the OR for the adverse clinical events between the test drug and placebo group for beraprost and PGE_1. There was a statistical significant difference between the beraprost and placebo group for the OR for headache, flushes, and vasodilation, although there was only one study concerning flushes and vasodilation. The pooled result obtained by combining all items showed a statistical significant difference between the 2 groups (OR [95% CI]; 3.78 [2.05, 6.96] with the fixed effects model). For PGE_1, the pooled result obtained by combining all items did not show a statistical significant difference between the PGE_1 and placebo group (OR [95% CI]; 2.34 [0.60, 9.14] with the fixed effects model). Although there was only one study concerning infusion vein reddening, hypotension, dizziness and nausea, PGE_1 had a tendency to increase these adverse events.

DISCUSSION

Using a systemic review of literature and meta-analysis we studied the effectiveness and safety of three IC therapeutic drugs with an antiplatelet effect (cilostazol, beraprost, and PGE_1). Our study documented a statistically significant increase of MWD and PFWD in patients with IC only in the cilostazol group when compared with placebos during study periods (difference from the baseline during the study periods). Comparisons of increases of WMD from the baseline versus the placebo for both parameters (MWD and PFWD) among the 3 drugs found that changes for beraprost and PGE_1 were larger than those seen for cilostazol. Although MWD is known to be superior in reproducibility compared to PFWD,[22] we consider PFWD to be the more important parameter than MWD because PFWD increases are directly connected to the patients' QOL. For averages in the increased PFWD throughout the study periods, there were large differences in the increased PFWD among the 3 drugs (cilostazol 39.8 m in 20 weeks, beraprost 69.0 m in 12 weeks, PGE_1 55.7 m in 5.3 weeks). At the end of drug administration, beraprost showed the greatest increase in PFWD among the 3 drugs. PGE_1 was ranked second despite the very short administration duration (5.3 weeks). Comparison between cilostazol and PGE_1 after 4 weeks of drug administration, which was almost equal to the total duration of PGE_1 administration, found that there was a four-fold increase in both MWD and PFWD in the PGE_1 group when compared to the cilostazol group. There was no data available for the beraprost group at this time point.

PGE_1 has a strong vasodilation effect, while

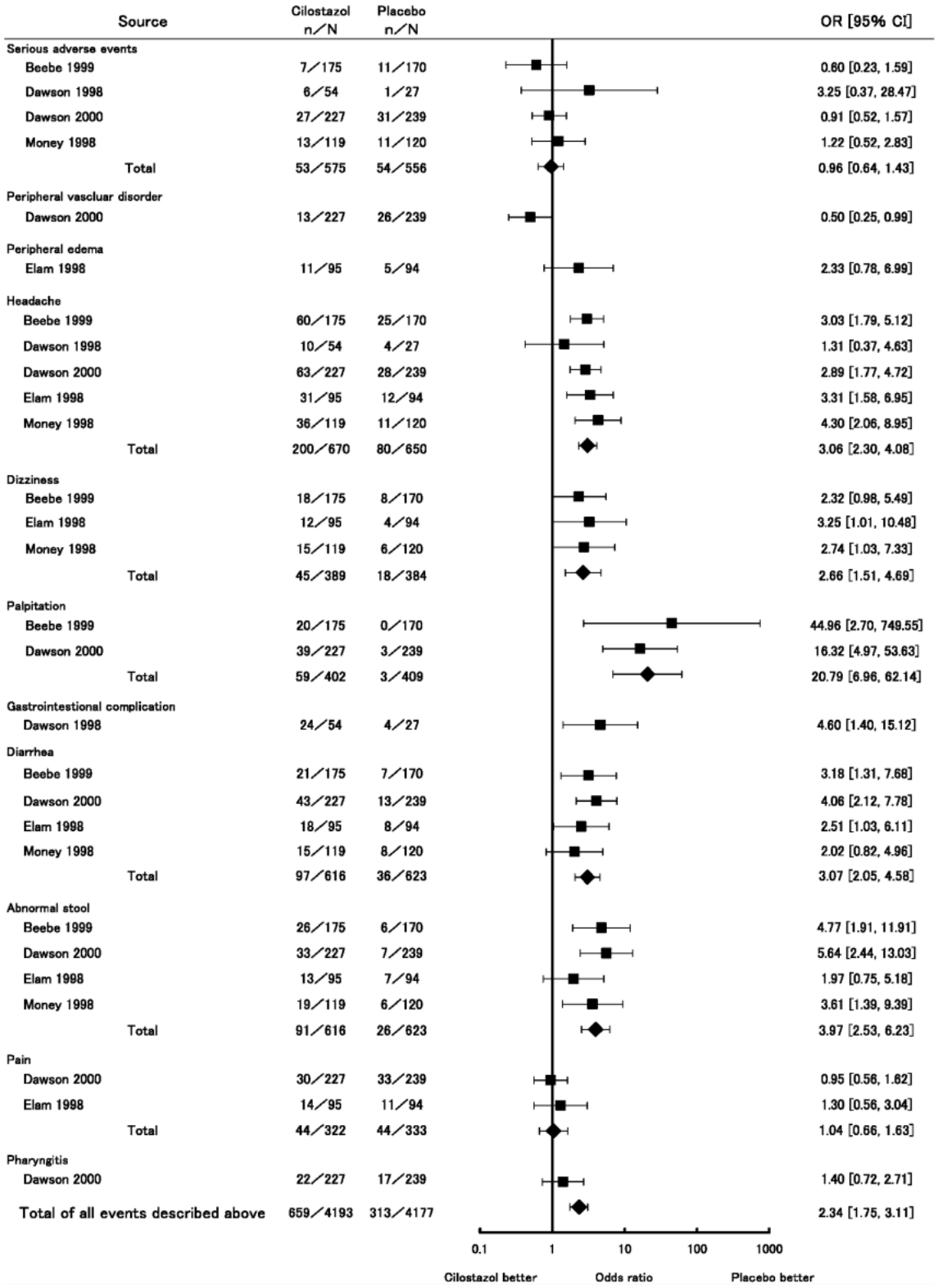

Fig. 5. Effect of Cilostazol on Adverse Clinical Events in Patients with Arteriosclerosis Obliterans
OR=odds ratio, 95% CI=95% confidence interval.

cilostazol and beraprost have a strong antiplatelet effect, which might be the reason from a pharmacological standpoint why the onset of the effect of PGE_1 is faster than that for cilostazol. PGE_1 increases blood flow by directly acting on peripheral vessels and dilating blood vessels. This effect appears about 5

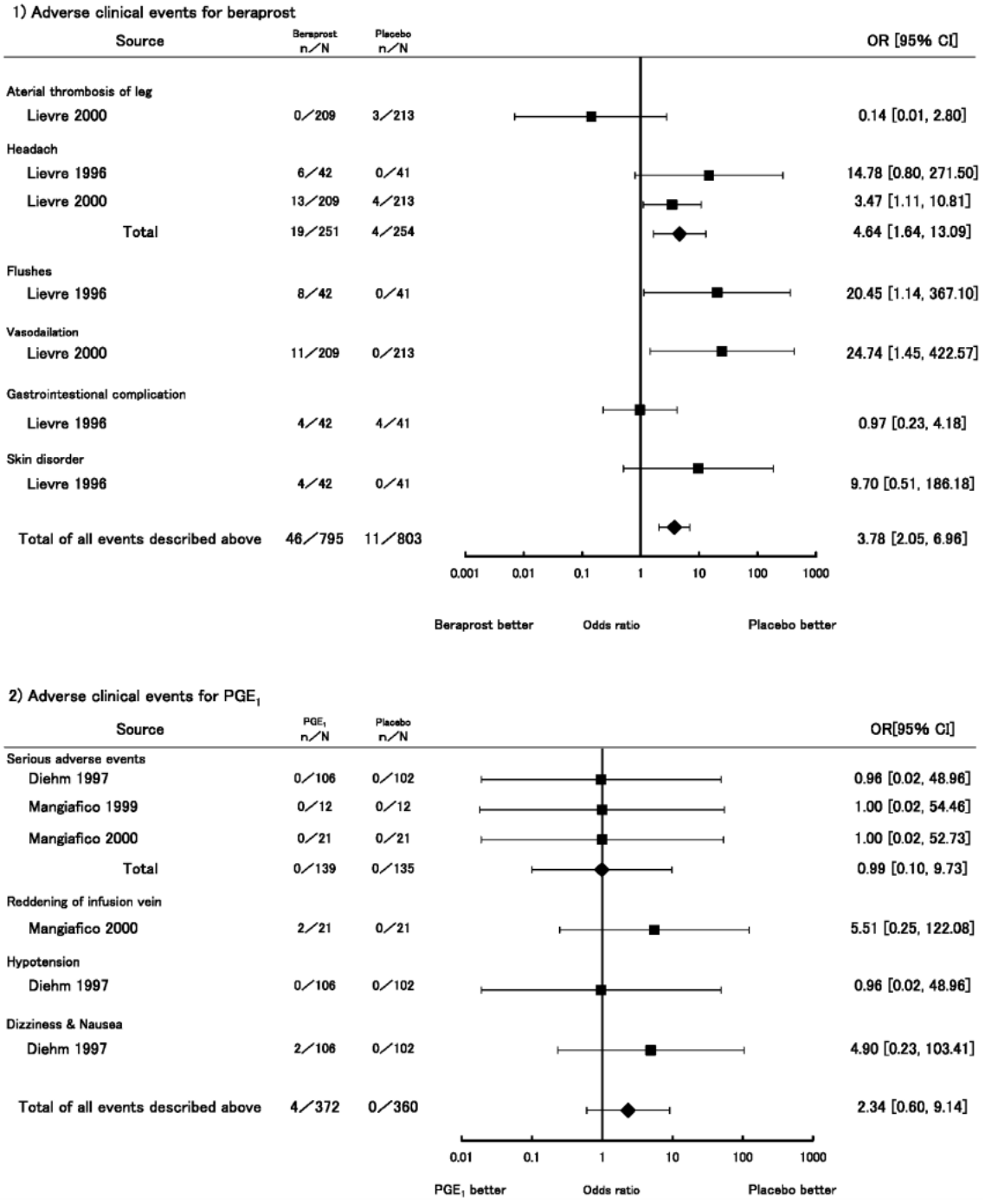

Fig. 6. Effect of Beraprost and PGE_1 on Adverse Clinical Events in Patients with Arteriosclerosis Obliterans
OR=odds ratio, 95% CI=95% confidence interval.

minutes after intravenous administration of PGE_1.[22] On the other hand, the drugs with an antiplatelet effect have a gradual action on intrinsic factors related to platelet coagulation, thus giving the appearance of exerting their pharmacological effect slowly. The duration until the pharmacological effect appears in IC treatments is 2—4 weeks for cilostazol,[24] and 1 week in beraprost.[25] For PGE_1 there are no reports that have documented the exact time of onset but it seems to be considerably faster. Data does indicate that the PGE_1 effect persists for a long time after drug administration is discontinued, in spite of the short half-life.[23] Comparing cilostazol to PGE_1, 6 weeks after cilostazol was discontinued, there was a decrease of 76 m as compared to placebo, while the PGE_1 group decreased only 9—17 m in spite of an average

of 10 weeks elapsing after the drug was discontinued. These results suggest that patients need to continue to take cilostazol for a long time after the commencement of drug administration in contrast to being able to inject PGE_1 intermittently to maintain the drug effect.

Comparison of safety and the OR of pooled results obtained by combining all adverse clinical events found that there are many studies that have been done and many kinds of adverse clinical events that have been documented for cilostazol. However the OR of cilostazol was almost same as that for PGE_1, although there was no statistical significant difference found between PGE_1 and placebo. For the rate of dropout by patients due to adverse drug reactions, cilostazol also had the highest numbers, whereas there were no patient dropouts in the PGE_1 group. As the number of studies for beraprost and PGE_1 were fewer than cilostazol and as there was only short-term administration for PGE_1, more studies on the long-term administration of PGE_1 are needed in order to clarify the rate of adverse clinical events for beraprost and PGE_1.

The results of this study suggest that these 2 drugs (cilostazol, PGE_1) are effective for the treatment of IC from the viewpoint of the improvement in walking distance.

The conclusions drawn from this meta-analysis might be subject to some limitations. First, we could only find a few beraprost and PGE_1 studies as compared to cilostazol in patients with IC, even though we consulted the manufacturers and companies marketing both of these drugs about unpublished data. Therefore, there is the possibility that our conclusions could have been affected by a limited publication bias. Second, the study periods, disease status, and treadmill conditions were not always the same in each of the studies, which may make direct comparisons of questionable value.

In a comparison of the direct drug cost, assuming that the patient must go to a hospital or clinic for PGE_1 injections from Monday to Friday, or in the case of cilostazol or beraprost take oral doses everyday at home, the three month total drug costs will be ¥44,694 (Japanese yen) for cilostazol, ¥51,732 for beraprost, and ¥447,840 for PGE_1, respectively.[26] This is an approximate ten-fold increase in the cost for PGE_1 compared to cilostazol.

If we calculate the drug cost for each 1 m increase of PFWD by using the average study period and each PFWD at the end of study, the drug cost per 1 m increase of PFWD is ¥1,124 for cilostazol, ¥750 for beraprost (although there was no statistical significant difference between beraprost and placebo for the PFWD), and ¥8,036 for PGE_1. This makes the differences in drug cost for PGE_1 about 11 times higher than beraprost (the cheapest drug), and about 7 times higher than cilostazol. Thus when prescribing medication for IC, we need to not only look at drug effect but also take into consideration the cost to the patient/health insurance programs to ensure we choose the best regimen for each patient. Additionally, with regard to PGE_1, while the rapid therapeutic onset is very beneficial, we also have to take into consideration the inconvenience for patients, as the intravenous formulation requires frequent trips by patients to hospitals or clinics.

Presently, limaprost alfadex, an oral formulation of the PGE_1 derivative, is available for the treatment of ASO in Japan. The price/day (when taken three times per day) is almost the same price/day as cilostazol and beraprost. This formulation has been reported to show a 56% improvement in the symptoms of pain, psychroesthesia, and ulcer in 138 patients with thromboangiitis obliterans.[27] The reported efficacy for IC has not been documented yet, however, we can expect the effectiveness of the oral formulation of PGE_1 in IC to be similar to the injectable results that found PGE_1 useful in the treatment of IC. Presently, limaprost alfadex is available locally in Japan and Korea. And as there are no large clinical studies being undertaken at the moment or any papers found by our literature survey, a large clinical study is needed in the future to clarify the effectiveness for IC treatment.

CONCLUSION

Three drugs with antiplatelet effects (cilostazol, beraprost, PGE_1) were studied. These drugs have different pharmacological characteristics and dosage formulation. Using a systemic review of literature and meta-analysis and comparison with placebo, we examined the effectiveness and safety of the drugs in the treatment of patients with IC. This study suggests that these 2 drugs (cilostazol and PGE_1) can be considered to be effective for the treatment of IC.

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