—Regular Articles—

β-Adrenergic Blocking Agents and Intermittent Claudication: Systematic Review

Ritsuko MIYAJIMA,*[,a,b] Kazumi SANO,[b] and Hisahiro YOSHIDA[b]

Course of Clinical Pharmacy, Graduate School,[a] and Department of Drug Metabolism and Disposition,[b] Meiji Pharmaceutical University, 2–522–1 Noshio, Kiyose City Tokyo 204–8588, Japan

(Received April 16, 2004; Accepted July 14, 2004)

To clarify contradictions in past reports and the package inserts for β-adrenergic blocking agents (β-blockers) for patients with intermittent claudication (IC), we investigated the effects of β-blockers in patients with IC using the systematic review technique. Data sources were randomized, controlled trials that investigated the effects of β-blockers compared with the placebo or untreated group (controls) in patients with IC. Primary endpoints were walking distance and walking time, and secondary endpoints were ankle-brachial index (ABI) and calf blood flow. Nine trials were included in the analysis. Meta-analysis showed that there was a significant worsening in maximal walking distance and initial claudication distance in patients receiving β-blockers, with standardized mean differences of −0.31 and −0.39 (95 % confidence interval −0.58 to −0.04 and −0.73 to −0.06, P=0.03 and 0.02, respectively) compared with controls. There were no significant differences in maximal walking time (0.07, −0.24 to 0.37), time to onset of claudication (0.12, −0.23 to 0.47), ABI at rest (0.24, −0.30 to 0.78), calf blood flow at rest (0.00, −0.26 to 0.25), and calf blood flow after exercise (−0.23, −0.69 to 0.22). However, only one trial evaluated ABI, and the number of cases is increasing, suggesting that β-blockers do not worsen ABI. There was no evidence that β-blockers prescribed for patients with IC have unsuitable ''precautions'' in the package inserts. However, reluctance to administer β-blockers to patients because they have IC is not appropriate.

Key words——intermittent claudication; peripheral vascular diseases; adrenergic beta-antagonists; meta-analysis

INTRODUCTION

β-adrenergic blocking agents (β-blockers) have an important role in the pharmacotherapy of ischemic heart disease, heart failure, arrhythmia, and hypertension. For example, in the management of acute myocardial infarction, the American College of Cardiology and the American Heart Association recommend that the patients without contraindications for β-blocker therapy be treated within 12 h of the onset of infarction to reduce the magnitude of infarction, incidence of associated complications, and rate of reinfarction.[1)]

However, β-blockers induce smooth muscle spasms in vessels as a result of the compensatory reflex of sympathetic nerves and α-receptor activation by inhibiting the relaxation reaction of smooth muscle in vessels. Radack and Deck[2)] tried to clarify the effects of β-blockers in patients with intermittent claudication (IC) by performing a meta-analysis. They concluded that β-blockers did not adversely affect walking capacity or symptoms of IC in patients with peripheral arterial disease (PAD) and that they could be used safely in patients without contraindications.

When we investigated in 21 package inserts of β-blockers in Japan, most included ''precautions'' for patients with PAD. To evaluate the validity of the package inserts, we decided to perform a systematic review and reassess the use of β-blockers in patients with IC.

METHODS

Literature Search We systematically searched the MEDLINE (1966 to October 2003), Cochrane Library (Cochrane Central Register of Controlled Trials; CENTRAL) (issue 3, 2003), and Igakuchuouzasshi (1983 to October 2003) databases using the search equations show in Table 1. In MEDLINE and the Cochrane Library, we used MeSH terms because of their high specificity. To avoid oversight of the target literature, we also performed a manual search.

Inclusion Criteria Inclusion criteria were selected to cover randomized, controlled trials comparing β-blockers with placebo or untreated groups (controls). Medications were all that are approved in the USA or Japan. We also included trials in which patients received a diagnosis of IC, and treatment and washout periods were 2 weeks or more. Primary en-

e-mail: tu6050@std.my-pharm.ac.jp

Table 1. Search Equation

#1	Peripheral vascular diseases [MeSH]	#26	Amosulalol
#2	Intermittent claudication [MeSH]	#27	Arotinolol
#3	Arteriosclerosis obliterans [MeSH]	#28	Befunolol
#4	#1 and #2 and #3	#29	Bevantolol
#5	Adrenergic β-antagonists [MeSH]	#30	Bopindolol
#6	Acebutolol [MeSH]	#31	Bunitrolol
#7	Alprenolol [MeSH]	#32	Bucindolol
#8	Atenolol [MeSH]	#33	Carvedilol
#9	Betaxolol [MeSH]	#34	Delevalol
#10	Bisoprolol [MeSH]	#35	Esmolol
#11	Carteolol [MeSH]	#36	Indenolol
#12	Celiprolol [MeSH]	#37	Ladiolol
#13	Labetalol [MeSH]	#38	Levobetaxolol
#14	Levobunolol [MeSH]	#39	Mepindolol
#15	Metipranolol [MeSH]	#40	Nebivolol
#16	Metoprolol [MeSH]	#41	Nipradilol
#17	Nadolol [MeSH]	#42	Talinolol
#18	Oxprenolol [MeSH]	#43	Tertatolol
#19	Penbutolol [MeSH]	#44	Tilisolol
#20	Pindolol [MeSH]	#45	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44
#21	Propranolol [MeSH]		
#22	Sotalol [MeSH]		
#23	Timolol [MeSH]	#46	#25 or #45
#24	Xamoterolol [MeSH]	#47	Human [MeSH]
#25	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24	#48	#4 and #46 and #47

MeSH: Medical subject headings. MeSH terms were used by MEDLINE and the Cochrane Library.

dpoints were walking distance and walking time. Secondary endpoints were ankle-brachial index (ABI) and calf blood flow. All trials that did not fulfill these criteria were excluded. Walking distance was analyzed based on maximal walking distance and initial claudication distance (pain-free walking distance), walking time was analyzed based on maximal walking time and onset time of claudication (pain-free walking time), and calf blood flow was analyzed at rest and after exercise, respectively. In addition, in this study, only the Japanese and English literature was analyzed. The final decision on inclusion was made with the agreement of the three authors.

Validity Assessment To minimize bias and to increase the validity of the meta-analysis, the internal validity of each trial was evaluated using a scoring system.[3] Randomization, double-blinding, and withdrawals were scored for a total of 5 points. Three or more points were classified for the ''high group,'' and the others were for the ''low group.'' When these results of analyses differed, the results of the ''high group'' were adopted, and when they did not differ, the results of all trials were adopted.

Statistical Analysis The standardized mean difference (SMD) and its 95% confidence interval (CI) were calculated for each trial, and we performed the meta-analysis combining trials of β-blockers versus controls to estimate each endpoint. The study was performed as unpaired analysis as in a parallel design study, when data from the crossover design study was combined.[4] In addition, we also analyzed the test of heterogeneity ($\alpha<0.1$). When heterogeneity was not detected at the significance level of 0.1, we used the fixed-effect model (inverse variance method) since the importance of combined model selection is slight. Otherwise, we used the random-effect model (DerSimonian and Laird method) under the condition that the appropriateness of combining studies was carefully assessed. The fixed-effect model does not assume heterogeneity, and there is a tendency to overestimate the size effect more than in the random-effect model in the heterogeneous case.[5] We used the

Cochrane Collaboration's Review Manager software (RevMan 4.2) for analysis.

RESULTS

We extracted a total of 65 publications from the three databases and the manual search. Among these, nine trials satisfied the inclusion criteria (Fig. 1). Trials were excluded due to the differences in subjects (healthy volunteers), article type (case report), etc. Table 2 shows the details of these nine trials. It was estimated that six trials were in the high group. The results of the validity assessment and two combined models are shown in Table 3. The analyses of initial claudication distance and calf blood flow after exercise were adopted as the results of the ''high group.'' Heterogeneity was not found in all endpoints (Table 3), and each study was analyzed using the fixed-effect model.

Waking Distance Table 4 shows that maximal walking distance (SMD: −0.31, 95% CI: −0.58 to −0.04, $P=0.03$) and initial claudication distance (−0.39, −0.73 to −0.06, $P=0.02$) worsened significantly in patients receiving β-blockers. We also performed subanalysis based on β_1-receptor selectivi-

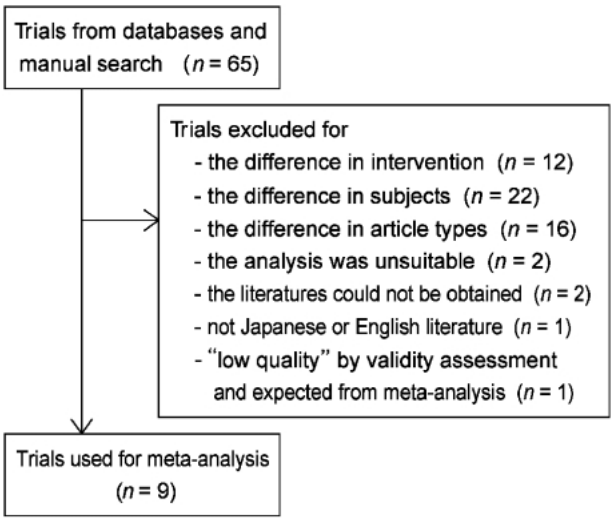


Fig. 1. Progress through the Stages of a Meta-analysis
n=number of trials.

Table 2. Details of Trials Included in the Analysis

Trial	Study design	Regimen	No. of subjects	Treatment period	Jadad's score
Roberts *et al.*[19]	Crossover	Atenolol, 100 mg/day	23	1 month	4
		Labetalol, 400 mg/day	23	1 month	
		Pindolol, 20 mg/day	23	1 month	
		run-in	23	1 month	
Svendsen *et al.*[14]	Crossover	Acebutolol, 400 mg/day	7	2 months	2
		Metoprolol, 200 mg/day	7	2 months	
		run-in	14	10 weeks	
Lepatalo and von Knorring[12]	Crossover	Metoprolol, 100—200 mg/day	14	3 weeks	3
		placebo	14	3 weeks	
Hiatt *et al.*[16]	Crossover	Propranolol, 120 mg/day	19	3 weeks	4
		Metoprolol, 150 mg/day	19	3 weeks	
		placebo	19	3 weeks	
Bogaert and Clement[17]	Crossover	Propranolol, 160 mg/day	10	2 months	3
		Metoprolol, 200 mg/day	10	2 months	
		placebo	10	1 month	
Clement[20]	Crossover	Propranolol, 160 mg/day	10	2 months	3
		Metoprolol, 200 mg/day	10	2 months	
		placebo	10	2 months	
Reichert *et al.*[18]	Crossover	Propranolol, 240—1600 mg/day	5	2 weeks	4
		placebo	5	2 weeks	
Svendsen *et al.*[15]	Crossover	Acebutolol, 400 mg/day	11	2 months	2
		Metoprolol, 200 mg/day	14	2 months	
		run-in	14	10 weeks	
Lepatalo[13]	Crossover	Metoprolol, 100—200 mg/day	14	3 weeks	2
		run-in	14	3 weeks	

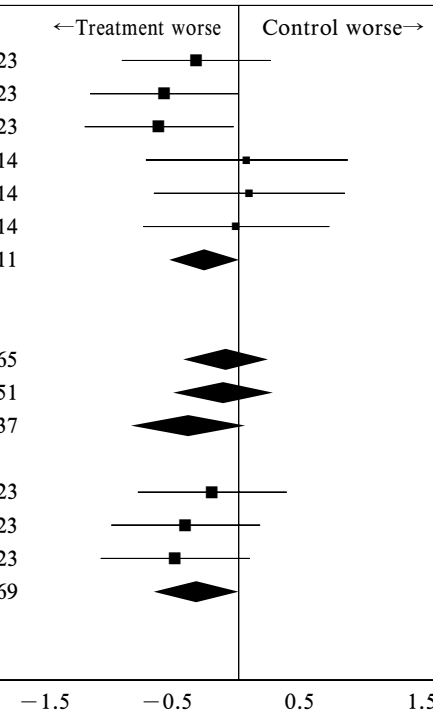
Table 3. Results of the Validity Assessment and Two Combined Models

Comparison/endpoint	Validity assessment				Combined model		
	High+low group		High group		Fixed effect		Random effect
	SMD [95% CI]	No. of studies	SMD [95% CI]	No. of studies	SMD [95% CI]	Test of heterogeneity	SMD [95% CI]
Walking distance							
Maximal walking distance	−0.31 [−0.58, −0.04]	3	−0.37 [−0.68, −0.06]	2	−0.31 [−0.58, −0.04]	P=0.44	−0.31 [−0.58, −0.04]
Initial claudicaiton distance	−0.27 [−0.55, 0.02]	2	−0.39 [−0.73, −0.06]	1	−0.27 [−0.55, 0.02]	P=0.63	−0.27 [−0.55, 0.02]
Walking time							
Maximal walking time	0.07 [−0.24, 0.37]	4	0.07 [−0.24, 0.37]	4	0.07 [−0.24, 0.37]	P=1.00	0.07 [−0.24, 0.37]
Onset of claudication	0.12 [−0.23, 0.47]	3	0.12 [−0.23, 0.47]	3	0.12 [−0.23, 0.47]	P=0.96	0.12 [−0.23, 0.47]
ABI							
ABI at rest	0.24 [−0.30, 0.78]	1	No data		0.24 [−0.30, 0.78]	P=0.75	0.24 [−0.30, 0.78]
Calf blood flow							
Calf blood flow at rest	0.00 [−0.26, 0.25]	3	0.04 [−0.23, 0.30]	2	0.00 [−0.26, 0.25]	P=0.77	0.00 [−0.26, 0.25]
Calf blood flow after exercise	−0.58 [−0.95, −0.21]	2	−0.23 [−0.69, 0.22]	1	−0.23 [−0.69, 0.22]	P=0.90	−0.23 [−0.69, 0.22]

ABI: ankle-brachial-index, SMD: standardized mean difference, CI: confidence interval.

Table 4. Results of Walking Distance: Maximal Walking Distance and Initial Claudication Distance

Study	Treatment drug	Treatment n	Control n	SMD (fixed) (95% CI)	Weight (%)	SMD (fixed) (95% CI)
Maximal walking distance				←Treatment worse Control worse→		
Roberts *et al.*[19]	Atenolol	23	23		21.21	−0.35 (−0.93 to 0.23)
Roberts *et al.*[19]	Labetalol	23	23		20.56	−0.60 (−1.19 to −0.01)
Roberts *et al.*[19]	Pindolol	23	23		20.44	−0.64 (−1.23 to −0.04)
Svendsen *et al.*[14]	Acebutolol	11	14		11.55	0.06 (−0.73 to 0.85)
Svendsen *et al.*[14]	Metoprolol	14	14		13.11	0.09 (−0.66 to 0.83)
Lepatalo and von Knorring[12]	Metoprolol	14	14		13.13	−0.02 (−0.76 to 0.72)
Total		108	111		100.00	−0.31 (−0.58 to −0.04)
Test for hetrogeneity: chi^2=4.78, df=5 (P=0.44)						
Test for overall effect: Z=2.24 (P=0.03)						
β_1-receptor-selective drugs		62	65		—	−0.09 (−0.44 to 0.26)
ISA (−) drugs		51	51		—	−0.14 (−0.53 to 0.25)
ISA (+) drugs		34	37		—	−0.38 (−0.86 to 0.09)
Initial claudication distance						
Roberts *et al.*[19]	Atenolol	23	23		33.88	−0.22 (−0.80 to 0.36)
Roberts *et al.*[19]	Labetalol	23	23		33.26	−0.43 (−1.02 to 0.15)
Roberts *et al.*[19]	Pindolol	23	23		32.87	−0.53 (−1.11 to 0.06)
Total		69	69		100.00	−0.39 (−0.73 to −0.06)
Test for hetrogeneity: chi^2=0.54, df=2 (P=0.76)						
Test for overall effect: Z=2.28 (P=0.02)						



SMD: standardized mean difference, CI: confidence interval, ISA: intrinsic sympathomimetic activity, n: number of subjects. Closed squares show the SMD of each trial, and the size expresses the weight of each trial. Horizontal bars denote 95% CIs. Lozenges express SMD and 95% CI as combined in each trial. ISA (−) means that β-adrenergic blocking drugs do not have ISA. ISA (+) means that β-adrenergic blocking drugs have ISA.

ty or intrinsic sympathomimetic activity (ISA) of maximum walking distance. Although a worsening tendency with ISA accompanying β-blockers occurred (−0.38, −0.86 to 0.09, $P=0.11$), it was not significant (Table 4). The analysis of initial claudication distance adopted the results of the ''high group'' based on the validity assessment (Table 3).

Walking Time The SMD of maximal walking time was 0.07 (−0.24 to 0.37, $P=0.67$), and there was no significant difference among trials in the results of subanalysis by β_1-receptor selectivity (Table 5). Similarly, onset time of claudication was 0.12 (−0.23 to 0.47, $P=0.51$), and there was no significance by the existence of β_1-receptor selectivity (Table 5).

ABI Table 6 shows the results for ABI, and there was no significance difference among trials (0.24, −0.30 to 0.78, $P=0.39$). However, only one trial evaluated ABI, and it had few enrollees as compared with another endpoints (β-blocker group, $n=25$; control group, $n=28$).

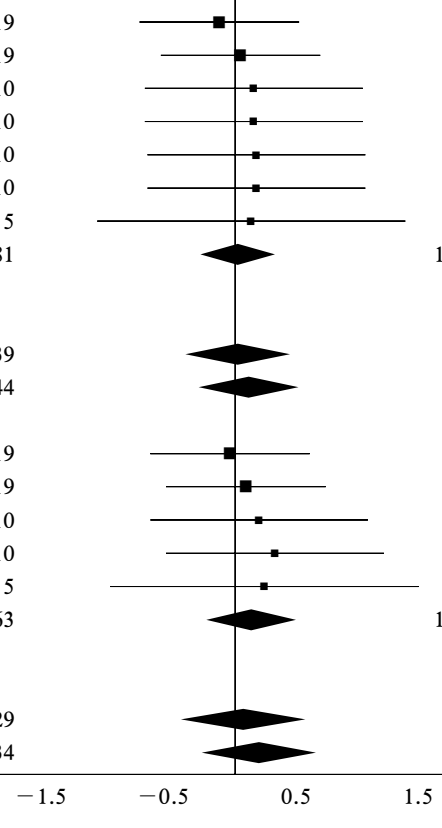
Calf Blood Flow The SMD of calf blood flow at rest was 0.00 (−0.26 to 0.25, $P=0.97$), and there was no significant difference in the results of subanalysis based on β_1-receptor selectivity (Table 7). Similarly, there was no significant difference after exercise. However, a tendency to decrease compared with the values at rest was seen. The analysis of calf blood flow after exercise adopted the results of the ''high group'' in the validity assessment (Table 3).

DISCUSSION

When the reasons for the ''precaution'' in β-blocker package inserts were investigated, ''information on adverse drug reactions (no. 45)'' released in 1980 seemed to be the beginning. The information was based on a report from a hospital on pindolol administration and peripheral circulatory disturbance. In 1988, the Ministry of Health and Welfare (current-

Table 5. Results of Walking Time: Maximal Walking Time and Time of Onset of Claudication

Study	Treatment drug	Treatment *n*	Control *n*	SMD (fixed) (95% CI)	Weight (%)	SMD (fixed) (95% CI)
Maximal walking time				←Treatment worse Control worse→		
Hiatt *et al.*[16]	Metoprolol	19	19		22.9	−0.13 (−0.77 to 0.50)
Hiatt *et al.*[16]	Propranolol	19	19		22.95	0.04 (−0.60 to 0.68)
Bogaert and Clement[17]	Metoprolol	10	10		12.04	0.16 (−0.72 to 1.03)
Bogaert and Clement[17]	Propranolol	10	10		12.03	0.16 (−0.72 to 1.04)
Clement[20]	Metoprolol	10	10		12.03	0.18 (−0.70 to 1.05)
Clement[20]	Propranolol	10	10		12.03	0.17 (−0.71 to 1.05)
Reichert *et al.*[18]	Propranolol	5	5		6.02	0.12 (−1.12 to 1.36)
Total		81	81		100.00	0.07 (−0.24 to 0.37)
Test for hetrogeneity: $chi^2=0.59$, df=6 ($P=1.00$)						
Test for overall effect: Z=0.43 ($P=0.67$)						
β_1-receptor-selective drugs		39	39		—	0.02 (−0.42 to 0.46)
Nonselective drugs		44	44		—	0.11 (−0.31 to 0.53)
Onset of claudication						
Hiatt *et al.*[16]	Metoprolol	19	19		30.30	−0.06 (−0.69 to 0.58)
Hiatt *et al.*[16]	Propranolol	19	19		30.28	0.10 (−0.54 to 0.74)
Clement[20]	Metoprolol	10	10		15.86	0.20 (−0.68 to 1.08)
Clement[20]	Propranolol	10	10		15.67	0.34 (−0.54 to 1.22)
Reichert *et al.*[18]	Propranolol	5	5		7.89	0.23 (−1.01 to 1.48)
Total		63	63		100.00	0.12 (−0.23 to 0.47)
Test for hetrogeneity: $chi^2=0.61$, df=4 ($P=0.96$)						
Test for overall effect: Z=0.65 ($P=0.51$)						
β_1-receptor-selective drugs		29	29		—	0.03 (−0.48 to 0.55)
Nonselective drugs		34	34		—	0.19 (−0.29 to 0.67)



SMD: standardized mean difference, CI; confidence interval, *n*; number of subjects. Closed squares show the SMD of each trial, and the size expresses the weight of each trial. Horizontal bars denote 95% CIs. Lozenges express SMD and 95% CI as combined in each trial.

Table 6. Results of ABI: ABI at Rest

Study	Treatment drug	Treatment *n*	Control *n*	SMD (fixed) (95% CI)	Weight (%)	SMD (fixed) (95% CI)
ABI at rest				←Treatment worse Control worse→		
Svendsen *et al.*[15]	Acebutolol	11	14		47.11	0.14 (−0.65 to 0.94)
Svendsen *et al.*[15]	Metoprolol	14	14		52.89	0.32 (−0.42 to 1.07)
Total		25	28		100.00	0.24 (−0.30 to 0.78)
Test for hetrogeneity: chi^2=0.10, df=1 (P=0.75)						
Test for overall effect: Z=0.86 (P=0.39)						

−1.5 −0.5 0.5 1.5

ABI: ankle-brachial-index, SMD: standardized mean difference, CI: confidence interval, ISA: intrinsic sympathomimetic activity, *n*: number of subjects. Closed squares show the SMD of each trial, and the size expresses the weight of each trial. Horizontal bars denote 95% CIs. Lozenges express SMD and 95% CI as combined in each trial.

Table 7. Results of Calf Blood Flow: Calf Blood Flow at Rest and after Exercise

Study	Treatment drug	Treatment *n*	Control *n*	SMD (fixed) (95% CI)	Weight (%)	SMD (fixed) (95% CI)
Calf blood flow at rest				←Treatment worse Control worse→		
Roberts *et al.*[19]	Atenolol	23	23		18.98	0.23 (−0.35 to 0.81)
Roberts *et al.*[19]	Labetalol	23	23		19.07	0.13 (−0.45 to 0.71)
Roberts *et al.*[19]	Pindolol	23	23		19.07	0.13 (−0.45 to 0.71)
Hiatt *et al.*[16]	Metoprolol	19	19		15.76	−0.13 (−0.77 to 0.51)
Hiatt *et al.*[16]	Propranolol	19	19		15.64	−0.27 (−0.91 to 0.37)
Lepatalo[13]	Metoprolol	14	14		11.47	−0.32 (−1.06 to 0.43)
Total		121	121		100.00	0.00 (−0.26 to 0.25)
Test for hetrogeneity: chi^2=2.52, df=5 (P=0.77)						
Test for overall effect: Z=0.04 (P=0.97)						
β_1-receptor-selective drugs		56	56		—	−0.03 (−0.40 to 0.34)
Nonselective drugs		42	42		—	−0.05 (−0.48 to 0.38)
ISA (−) drugs		75	75			−0.09 (−0.41 to 0.23)
Calf blood flow after exercise						
Hiatt *et al.*[16]	Metoprolol	19	19		49.90	−0.26 (−0.90 to 0.38)
Hiatt *et al.*[16]	Propranolol	19	19		50.10	−0.21 (−0.84 to 0.43)
Total		38	38		100.00	−0.23 (−0.69 to 0.22)
Test for hetrogeneity: chi^2=0.02, df=1 (P=0.90)						
Test for overall effect: Z=1.02 (P=0.31)						

−1.5 −0.5 0.5 1.5

SMD: standardized mean difference, CI: confidence interval, ISA: intrinsic sympathomimetic activity, *n*: number of subjects. Closed squares show the SMD of each trial: and the size expresses the weight of each trial. Horizontal bars denote 95% confidence intervals. Lozenges express SMDs and 95% confidence intervals as combined in each trial. ISA (−) means that β-adrenergic blocking drugs do not have ISA. ISA (+) means that β-adrenergic blocking drugs have ISA.

ly the Ministry of Health, Labor and Welfare) directed that the ''precaution'' be included in package inserts for all β-blockers as a result of a drug efficacy review. Most studies added to the analysis were reported around the same time. However, there were too few objective, randomized clinical trials in those days. It would be difficult to perform any more randomized, controlled trials for ethical reasons, i.e., IC may progress in patients not receiving β-blockers. It is therefore meaningful to reassess β-blocker use in IC using the technique of a systematic review.

The analysis showed that only the ''reproducible walking distance'' in IC patients decreased significantly with β-blockers. Our study differed from the results of Radack *et al.*[2] in this, although there was no other publication in the extracted trials after their report. The difference probably was due to different inclusion criteria or evaluation method. We used the technique of systematic review in this study and meta-analysis for the statistical analysis. This has

the advantage of accuracy or reproducibility by showing selection criteria clearly as compared with a narrative review. However, we could not reproduce Radack *et al.*'s results because their data were not given in detail. We consider that is also a reason for the difference in the results.

In the analysis of calf blood flow, a tendency to worsen after exercise as compared with at rest was seen, and this was due to the presence of IC. However, continuing exercise may improve oxygenation in the legs,[6] walking distance,[7] and the quality of life.[8] Therefore suitable exercise under the supervision of a specialist (e.g., physiotherapist) may be useful to delay the progression of IC.

In this study, subanalysis was performed based on β_1-receptor selectivity and ISA. Nonselective β-blockers may attenuate epinephrine-induced vasodilation during exercise by blocking β_2-receptors in peripheral vessels. This result was not seen, although it is expected that the difference in β_1-receptor selectivity influenced the endpoints. It appears that the occurrence of ISA is unrelated to the clinical condition in IC. Further investigation will be required to confirm this.

Evaluation of true endpoints, such as the progression of disease (e.g., in the Fontaine classification or Rutherford classification), was also planned in addition to surrogate endpoints such as walking distance. However, no suitable trials were found in our search and thus that was not possible. New findings may allow the evaluation of ABI, the simplest and most widely used citation[9] noninvasively and it may become the index for diagnosis and the degree of severity of IC[9,10] because it correlates fairly well with physical activity.[11] There was no significant difference in ABI in our review because only one trial evaluated it. It was suggested that ABI may improve with β-blockers if the number of cases increased.

We did not find a basis for excluding the precaution on β-blocker use for patients with IC in package inserts in Japan. Moreover, the studies included in this review were performed in Finland,[12,13] Denmark,[14,15] Belgium,[16,17] Israel,[18] and the USA.[16,19] Investigation of racial differences and α-receptor sensitivity in patients with IC is necessary.

CONCLUSION

It may not be appropriate to hesitate to prescribeβ-blockers to patients with IC. However, monitoring is required when β-blockers are administered to those patients.

REFERENCES

1) Ryan T. J., Anderson J. L., Antman E. M., Braniff B. A., Brooks N. H., Califf R. M., Hillis L. D., Hiratzka L. F., Rapaport E., Riegel B. J., Russell R. O., Smith Jr. E. E., Weaver W. D., *J. Am. Coll. Cardiol.*, **28**, 1328–1428 (1996).
2) Radack K., Deck C., *Arch. Intern. Med.*, **151**, 1769–1776 (1991).
3) Jadad A. R., Moore R. A., Carroll D. C., Reynolds D. J., Gavaghan D. J., McQuay H. J., *Control. Clin. Trials*, **17**, 1–12 (1996).
4) Elbourne D. R., Altman D. G., Higgins J. P., Curtin F., Worthington H. V., Vail A., *Int. J. Epidemiol.*, **31**, 140–149 (2002).
5) Field A. P., *Psychol. Methods*, **6**, 161–180 (2001).
6) Zetterquist S., *Scand. J. Clin. Lab. Invest.*, **25**, 101–111 (1970).
7) Leng G. C., Fowler B., Emst E., *Cochrane Database Syst. Rev.*, **2**, CD000990 (2000).
8) Regensteiner J. G., Steiner J. F., Hiatt W. R., *J. Vasc. Surg.*, **23**, 104–115 (1996).
9) Ouriel K., *Lancet*, **358**, 1257–1264 (2001).
10) Hiatt W. R., *N. Engl. J. Med.*, **344**, 1608–1621 (2001).
11) Montgomery P. S., Gardner A. W., *J. Am. Geriatr. Soc.*, **46**, 706–711 (1998).
12) Lepantalo M., von Knorring J., *Clin. Physiol.*, **4**, 275–282 (1984).
13) Lepantalo M., *Br. J. Clin. Pharmacol.*, **18**, 90–93 (1984).
14) Svendsen T. L., Jelnes R., Tonnesen K. H., *Acta Med. Scand.*, **219**, 161–165 (1986).
15) Svendsen T. L., Jelnes R., Tonnesen K. H., *Acta Med. Scand.* (Suppl.), **693**, 129–132 (1985).
16) Hiatt W. R., Stoll S., Nies A. S., *Circulation*, **72**, 1226–1231 (1985).
17) Bogaert M. G., Clement D. L., *Eur. Heart J.*, **4**, 203–204 (1983).
18) Reichert N., Shibolet S., Adar R., Gafni J., *Clin. Pharmacol. Ther.*, **17**, 612–615 (1975).
19) Roberts D. H., Tsao Y., McLoughlin G. A., *Lancet*, **2**, 650–653 (1987).
20) Clement D. L., *Verh. K. Acad. Geneeskd. Belg.*, **42**, 164–214 (1980).