Statistical analysis

In the combined analysis, safety was assessed in all eligible patients who received the study treatment and who had complete study documentation compliant with good clinical practice requirements (safety population). Efficacy was assessed in all patients who received the study treatment and who did not have inclusion/exclusion criteria violations (efficacy-evaluable population).

For the purpose of the combined analysis presented here, all statistical tests performed were two-sided at a 5% level of significance; a corresponding confidence interval (CI) was calculated when appropriate. Demographic data were examined by χ^2 test for categorical data variables and Wilcoxon test for continuous data variables. Safety and efficacy variables were analyzed by the log-rank test. The cumulative incidence of safety and efficacy endpoints was estimated by the Kaplan–Meier method and analyzed by the log-rank test. Changes over time in the cumulative incidence rate of safety variables were estimated on censored data using a competing risk model (Prentice and Kalbfleisch nonparametric estimator: cumulative incidence rate). Hazard ratios (HRs; clopidogrel versus ticlopidine, Cox proportional hazards model) and corresponding 95% CIs were determined to evaluate between-treatment differences in the incidence of vascular events.

The sample size calculation for the Phase IIIb study has been described previously [11]. The target sample size of 700 patients for the Phase IIIa study was based on the assumption that the frequency of safety events would be 4.5% in the clopidogrel group (based on earlier studies) and 10.2% in the ticlopidine group (based on published data [12, 13]).

Results

Patients

In the Phase IIIa study, 749 patients were enrolled and randomly assigned to receive treatment. Nine patients did not receive the study treatment and a further 26 were found to be ineligible for inclusion in the safety population, leaving 714 patients (clopidogrel, 366; ticlopidine, 348). A further three patients failed to meet the inclusion criteria, thus 711 patients were in the efficacy-evaluable population (clopidogrel, 366; ticlopidine, 345). In the Phase IIIb study, 1,172 patients were enrolled. In all, 17 patients withdrew prior to initiating treatment, leaving 1,155 patients in the safety population (clopidogrel, 575; ticlopidine, 580). Three patients did not meet the inclusion criteria, and one patient was incorrectly randomized, therefore 1,151 patients were in the efficacy-evaluable population (clopidogrel, 573; ticlopidine, 578).

In the combined analysis, the safety population comprised 941 patients in the clopidogrel group and 928 patients in the ticlopidine group. In total, 939 patients were included in the efficacy-evaluable population for clopidogrel and 923 patients were included in the efficacy-evaluable population for ticlopidine (Fig. 1).

Baseline characteristics for the Phase IIIa, IIIb and combined populations are shown in Table 2. In both

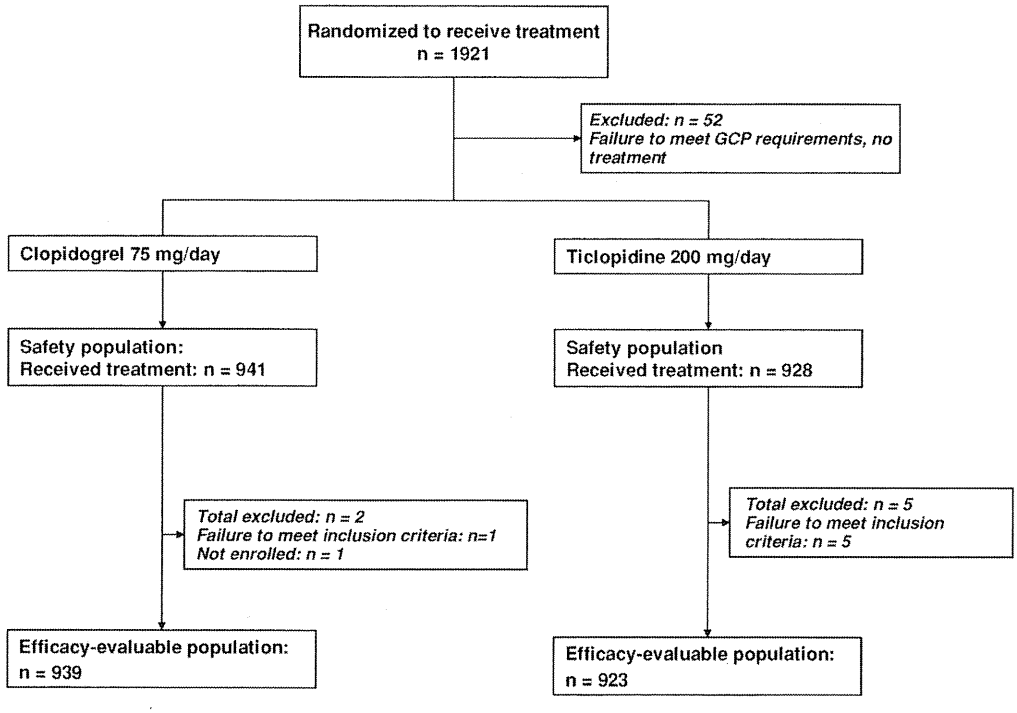


Fig. 1 Patient disposition. *GCP* good clinical practice

Table 2 Background characteristics

	Clopidogrel			Ticlopidine			*p* value[a]
	IIIa	IIIb	Total	IIIa	IIIb	Total	
No. of evaluable patients	366	575	941	348	580	928	
Male, *n* (%)	251 (68.6)	415 (72.2)	666 (70.8)	238 (68.4)	429 (74.0)	667 (71.9)	0.599[b]
Age ≥65 years, *n* (%)	211 (57.7)	321 (55.8)	532 (56.5)	203 (58.3)	329 (56.7)	532 (57.3)	
Age (years), mean ± SD	64.7 ± 8.9	64.3 ± 9.4	64.4 ± 9.2	65.1 ± 8.8	64.7 ± 9.2	64.8 ± 9.0	0.374[c]
Time from the most recent onset of cerebral infarction, *n* (%)							
<4 weeks	146 (39.9)	112 (19.5)	258 (27.4)	139 (39.9)	106 (18.3)	245 (26.4)	0.586[d]
4–12 weeks	101 (27.6)	100 (17.4)	201 (21.4)	86 (24.7)	113 (19.5)	199 (21.4)	
>12 weeks	114 (31.1)	363 (63.1)	477 (50.7)	121 (34.8)	361 (62.2)	482 (51.9)	
Type of most recent infarction, *n* (%)							
Atherothrombotic infarction	72 (19.7)	172 (29.9)	244 (25.9)	72 (20.7)	171 (29.5)	243 (26.2)	0.969[b]
Lacunar infarction	287 (78.4)	390 (67.8)	677 (71.9)	267 (76.7)	397 (68.4)	664 (71.6)	
Co-morbidities, *n* (%)							
Hypertension	253 (69.1)	411 (71.5)	664 (70.6)	247 (71.0)	393 (67.8)	640 (69.0)	0.452[b]
Diabetes	94 (25.7)	114 (19.8)	208 (22.1)	81 (23.3)	121 (20.9)	202 (21.8)	0.860[b]
Hyperlipidemia	107 (29.2)	222 (38.6)	329 (35.0)	106 (30.5)	226 (39.0)	332 (35.8)	0.713[b]
Current or ex-smoker, *n* (%)	134 (36.6)	344 (59.8)	478 (50.8)	130 (37.4)	386 (66.6)	516 (55.6)	0.113[b]

SD standard deviation

[a] Test performed on the combined patients from the two studies

[b] χ^2 test

[c] *t* test

[d] Wilcoxon test

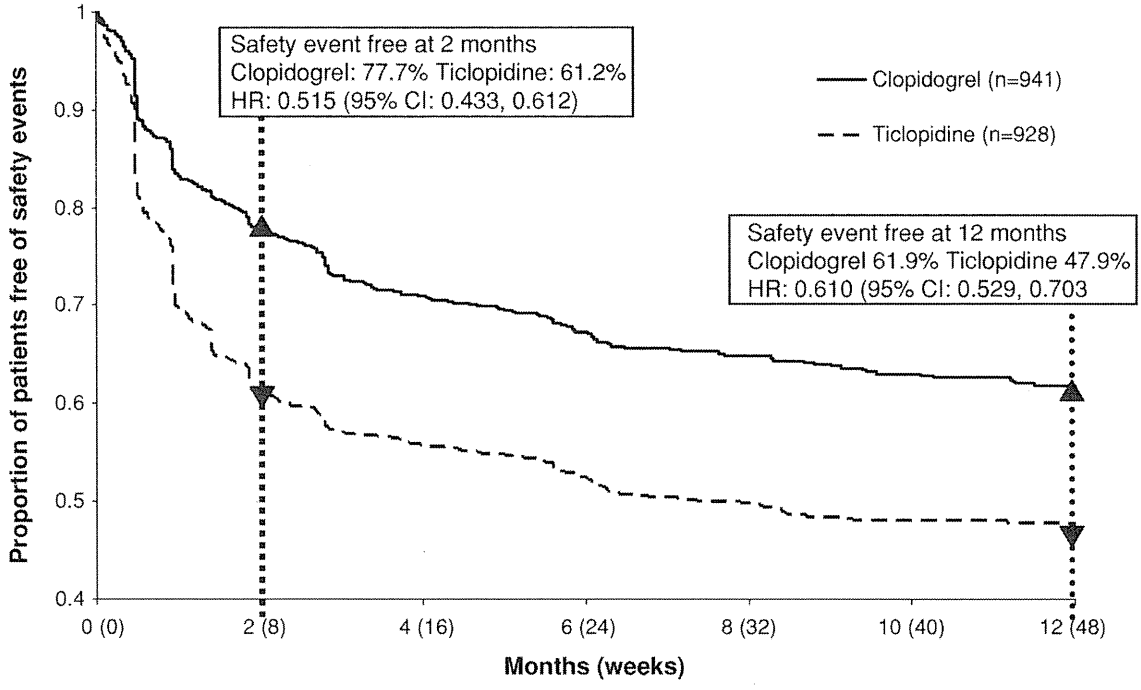
studies, there were more male than female patients and the mean age was between 64 and 65 years. In total, 240 patients in the clopidogrel group and 322 in the ticlopidine group discontinued treatment prematurely over the 52-week follow-up period. The primary reason for discontinuation was adverse events, experienced by 185 patients in the ticlopidine group compared with 134 in the clopidogrel group. Other reasons for discontinuation included refusal of medication or poor compliance (clopidogrel, 29; ticlopidine, 54), vascular events (clopidogrel, 28; ticlopidine, 28), loss to follow-up (clopidogrel, 13; ticlopidine, 14), worsening of comorbid condition (clopidogrel, 5; ticlopidine, 5), and change in treatment (clopidogrel, 2; ticlopidine, 2).

Safety and tolerability

Fewer patients in the clopidogrel group (35.0% [329/941]) experienced the combined safety endpoint of accessory symptoms and abnormal laboratory changes compared with those in the ticlopidine group (48.7% [452/928]). Using a Kaplan–Meier analysis, it was estimated that, at 1 month, 83.4% of patients in the clopidogrel group were safety event free compared with 69.9% in the ticlopidine group. At both 2 and 12 months, the estimated incidence of safety events was significantly lower in the clopidogrel group than in the ticlopidine group (Fig. 2).

It was estimated that almost twice as many patients (25.6% [238/928]) in the ticlopidine group experienced symptoms and/or abnormal laboratory findings of hepatic dysfunction compared with the clopidogrel group (13.4% [126/941]) ($p < 0.001$, log-rank test; HR, 0.455: 95% CI, 0.367, 0.565; Fig. 3). Significantly, fewer patients in the clopidogrel group had raised AST (HR, 0.435 [95% CI, 0.309, 0.612]), ALT (HR, 0.431 [95% CI, 0.318, 0.583]), γ-GTP (HR, 0.303 [95% CI, 0.229, 0.401]), or AL-P (HR, 0.426 [95% CI, 0.285, 0.638]) levels than in the ticlopidine group ($p < 0.001$, log-rank test). The cumulative incidence of patients free from leukopenia, neutropenia or hepatic dysfunction is shown in Fig. 4. In all cases, the incidence of events was estimated to be lower in the clopidogrel group than in the ticlopidine group ($p < 0.05$) and the difference in the cumulative frequency of events tended to increase after month 2. The observed difference in the incidence of safety events between the clopidogrel and ticlopidine groups was not substantially altered in a sub-analysis which included only patients with prior lacunar stroke (data not shown).

There were two deaths in each treatment group that were considered to be related to the study medication. In the



Patients, n							
Clopidogrel	941	705	623	569	350	333	321
Ticlopidine	928	535	466	427	264	244	231
Discontinued treatment prematurely, n							
Clopidogrel	0	143	177	205	221	228	234
Ticlopidine	0	239	272	290	301	311	322

Fig. 2 Safety event-free survival curve. *CI* confidence interval, *HR* hazard ratio

ticlopidine group, a 63-year-old female experienced a brainstem hemorrhage and a 61-year-old male had intracerebral bleeding. In the clopidogrel group, a 73-year-old female experienced intracerebral bleeding and a 75-year-old male died from prolonged hemorrhage following rupture of an aortic aneurysm.

Clinical efficacy

There was no difference in the incidence of the combined efficacy endpoint of cerebral infarction, MI, or vascular death in the clopidogrel (2.6%) compared with the ticlopidine (2.5%) groups (HR, 0.918 [95% CI, 0.518, 1.626]). In the defined events that made up the combined efficacy endpoint, recurrence of cerebral infarction was the only vascular event observed in either treatment group. There were no MIs or vascular deaths.

There was no difference in the total number of vascular events between the clopidogrel (3.6%) and the ticlopidine (3.7%) groups (HR, 0.878 [95% CI, 0.545, 1.412]) (Table 3; Fig. 5). The incidence of TIA, angina pectoris, peripheral arterial disease, or other events was comparable between the two treatment groups. There was no significant difference in the incidence of the combined efficacy endpoint between patients with prior lacunar stroke in the clopidogrel group (2.8% [19/677]) and in the ticlopidine group (3.3% [22/664]).

Irrespective of treatment type, predisposing risk factors for the occurrence of the primary efficacy endpoints were: previous TIA (HR, 8.5 [95% CI, 1.421, 50.0]); amaurosis fugax (HR, 30.0 [95% CI, 1.930, 464.643]); and less than 4 weeks from the most recent occurrence to treatment initiation (HR, 2.6 [95% CI, 1.242, 4.987]). The risk of the primary efficacy endpoints increased with multiple risk factors.

Discussion

In this combined analysis of two Phase III trials of the safety and efficacy of clopidogrel compared with ticlopidine in Japanese patients, clopidogrel was associated with significantly fewer adverse events but without significant difference in the incidence of secondary vascular events in patients with a history of stroke. This observation is corroborated by findings from international studies which suggest that both clopidogrel and ticlopidine are superior in efficacy to aspirin [7, 9, 14]. However, while clopidogrel

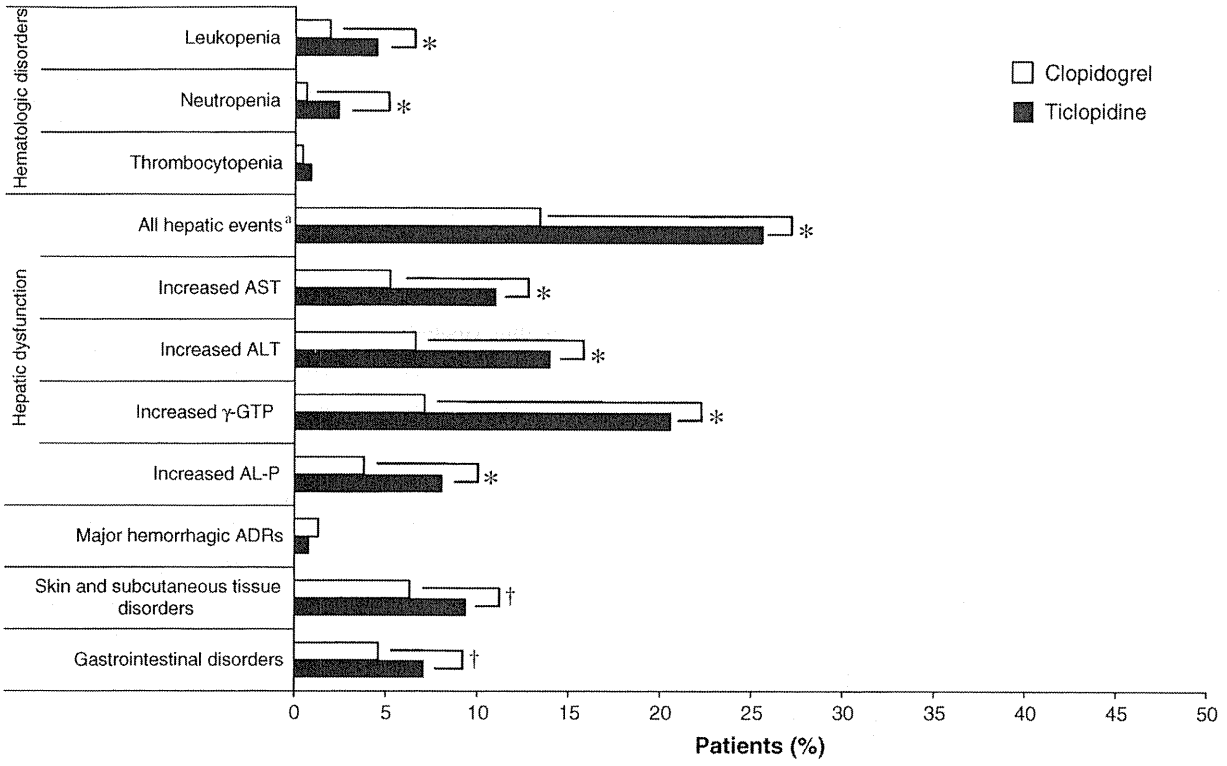


Fig. 3 Estimated frequencies of adverse events and adverse drug reactions. $^{*}p < 0.001$; $^{\dagger}p < 0.05$ (log-rank test). [a]Increased AST, increased ALT, increased serum bilirubin, increased γ-GTP, increased AL-P, increased LDH, jaundice, hepatic dysfunction, or nonicteric hepatic dysfunction. *AL-P* alkaline phosphatase, *ADR* adverse drug reaction, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *γ-GTP* γ-glutamyl transpeptidase, *LDH* lactate dehydrogenase

has a safety profile similar to that of aspirin [9, 14], ticlopidine is associated with significantly more adverse events [7, 14].

The two populations studied in this trial were very similar. The treatment period was different for the Phase IIIa trial (26 weeks) compared with the Phase IIIb trial (52 weeks), but there were no procedural differences between the clopidogrel and ticlopidine groups in either trial. As the populations were well matched between trials and between treatment groups within each trial, it was considered that the increased population size available in a combined analysis would have greater statistical power.

Liver dysfunction (all laboratory measures) was observed significantly more frequently in the ticlopidine group than in the clopidogrel group. The incidences of raised AST and AL-P levels were approximately doubled and the incidence of raised γ-GTP levels almost trebled in the ticlopidine group compared with the clopidogrel group. Previously, a much higher risk of liver damage during ticlopidine treatment has been observed in Japan than in populations from the rest of the world and liver function tests are recommended when commencing ticlopidine treatment [8]. Recent evidence has linked this increased liver dysfunction susceptibility to certain human leukocyte antigen types in the Japanese population [15]. In the present study, the differences in measures of liver dysfunction were higher in the ticlopidine group at 2 months, indicating that clopidogrel had a more favorable liver safety profile than ticlopidine at the commencement of treatment. This difference in the rate of liver dysfunction between clopidogrel and ticlopidine was even greater at 12 months. Overall, the HR suggested that the risk of hepatic dysfunction was halved in the clopidogrel group compared with the ticlopidine group.

It was estimated that neutropenia occurred more frequently in the ticlopidine group (2.4%) than in the clopidogrel group (0.6%). These rates were both higher than those reported in previous international trials which showed that ticlopidine had a higher frequency of neutropenia (<1%) than both clopidogrel and aspirin (~0.2%) [7, 10]. Furthermore, in a systematic review of four randomized, controlled trials that enrolled 22,656 predominantly white patients at high risk of vascular disease, the neutropenia event rate was 0.1% (10/9,599) in those patients who received clopidogrel and 2.3% (35/1,529) in those who received ticlopidine over 1–3 years [14]. Although the absolute rates of neutropenia associated with the use of thienopyridines remain equivocal, it is clear that neutropenia is less likely to occur with clopidogrel than with ticlopidine in all patient populations evaluated to date. The reason for the potentially higher frequency of neutropenia in our combined analysis is unclear, although no cases of

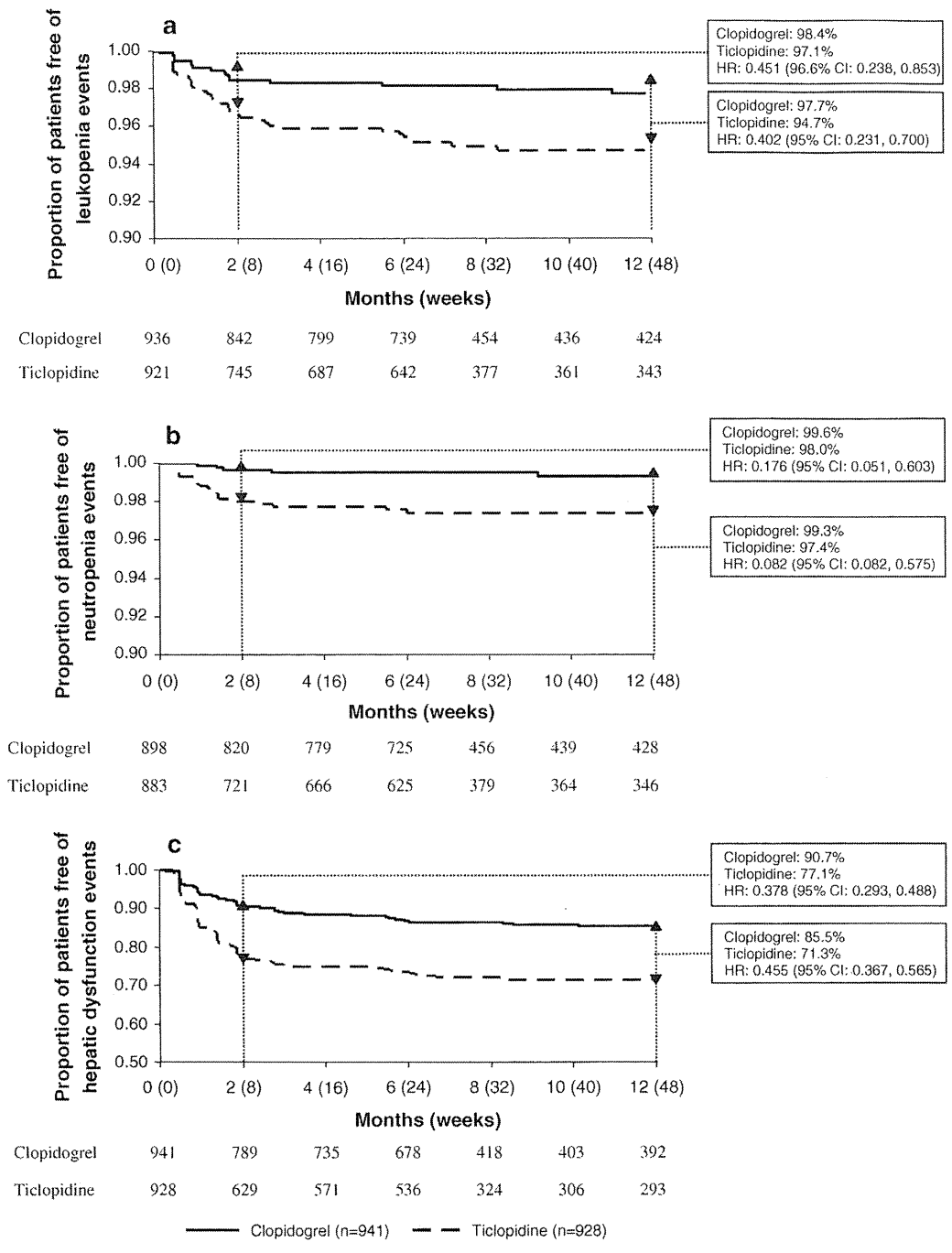


Fig. 4 Cumulative frequency of patients free of **a** leukopenia **b** neutropenia and **c** hepatic dysfunction. *CI* confidence interval, *HR* hazard ratio

severe neutropenia were observed. Leukopenia was also more common and significantly worse in the ticlopidine group. The differences between the incidences of leukopenia and neutropenia were significant at 2 months and increased with the duration of treatment up to 12 months. Given the potential for long-term therapy with either agent, the reduced frequency of hematologic disorders in the clopidogrel group may be a significant factor in treatment choice.

There was no significant between-group difference in the frequency of major hemorrhagic ADRs. This observation is supported by international meta-analysis data ($n = 22{,}656$) which revealed no discernible differences between clopidogrel and ticlopidine therapy on either intracranial or extracranial hemorrhage event rates [14]. The incidences observed in our study for both agents were similar to those observed in Japanese stroke patients receiving placebo [16] and in Western patients receiving clopidogrel [17]. The increased risk of bleeding because of clopidogrel or ticlopidine therapy would therefore appear to be minimal and similar to the risk observed in international clinical trials.

In this combined analysis of two Phase III trials, no difference was observed between the efficacy of clopidogrel and ticlopidine in the combined efficacy endpoint of cerebral infarction, MI, and vascular death up to 52 weeks.

Table 3 Vascular events up to 52 weeks

Vascular event	Clopidogrel ($n = 939$)	Ticlopidine ($n = 923$)	Hazard ratio (95% CI)[a]	p value[b]
Primary vascular endpoints, no. of patients (%)	24 (2.6)	23 (2.5)	0.92 (0.52, 1.63)	0.769
Cerebral infarction	24	23		
Myocardial infarction	0	0		
Vascular death	0	0		
Other vascular events, n (%)	10 (1.1)	11 (1.2)		
Transient ischemic attack	3	6[c]		
Angina pectoris	3	4		
Peripheral arterial occlusion	2	1		
Others	2	1		
All vascular events, n (%)	34 (3.6)	34 (3.7)	0.88 (0.55, 1.41)	0.591

CI confidence interval

[a] Estimated using the Cox proportional hazards ratio (95% CI: Wald CI)

[b] Log-rank test

[c] One patient had two transient ischemic attacks

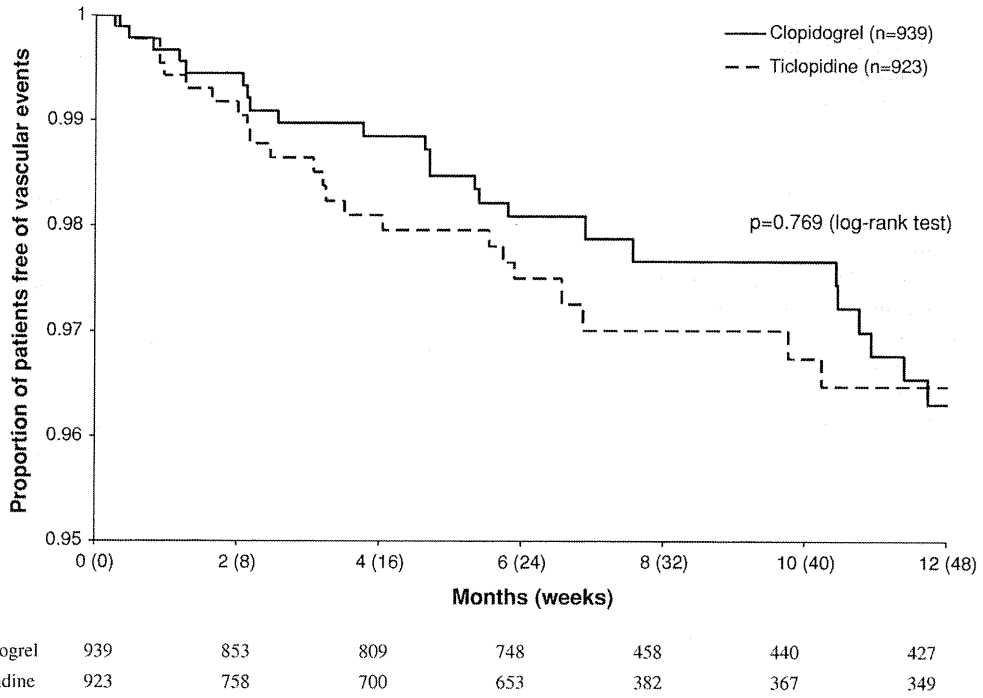


Fig. 5 Vascular event-free survival curve

A number of factors are likely to contribute to this finding. Vascular events in our studies were relatively infrequent compared with other nonJapanese studies [9, 14]. For example, the vascular event rate for this composite endpoint was more than three times higher (12%) in mostly white patients who received either clopidogrel or ticlopidine over 1–3 years [14]. It had been expected that approximately a third of Japanese stroke patients would experience a noncerebral, recurrent event; however, this was not the case in the current analysis. Indeed, the 1-year follow-up results from the REACH Registry suggest that the recurrence of MI is lower in patients in Japan than in the rest of the world [18] and therefore many thousands of patients would be required to detect any differences in the efficacy between clopidogrel and ticlopidine in the Japanese population.

This combined analysis of two Phase III studies suggests that clopidogrel is not significantly different from ticlopidine in efficacy, but the frequency of adverse events—and in particular measures of hepatic toxicity—is lower in patients treated with clopidogrel than in those treated with ticlopidine.

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Stroke Prevention by Cilostazol in Patients with Atherothrombosis: Meta-analysis of Placebo-controlled Randomized Trials

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Background: Cilostazol is an antiplatelet agent that inhibits phosphodiesterase III in platelets and vascular endothelium. Previous randomized controlled trials of cilostazol for prevention of cerebrovascular events have garnered mixed results. We performed a systematic review and meta-analysis of the randomized clinical trials in patients with atherothrombotic diseases to determine the effects of cilostazol on cerebrovascular, cardiac, and all vascular events, and on all major hemorrhagic events. *Methods:* Relevant trials were identified by searching MEDLINE, EMBASE, and the Cochrane Controlled Trial Registry for titles and abstracts. Data from 12 randomized controlled trials, involving 5674 patients, were analyzed for end points of cerebrovascular, cardiac, and major bleeding events. Searching, determination of eligibility, data extraction, and meta-analyses were conducted by multiple independent investigators. *Results:* Data were available in 3782, 1187, and 705 patients with peripheral arterial disease, cerebrovascular disease, and coronary stenting, respectively. Incidence of total vascular events was significantly lower in the cilostazol group compared with the placebo group (relative risk [RR], 0.86; 95% confidence interval [CI], 0.74-0.99; P=.038). This was particularly influenced by a significant decrease of incidence of cerebrovascular events in the cilostazol group (RR, 0.58; 95% CI, 0.43-0.78; $P < .001$). There was no significant intergroup difference in incidence of cardiac events (RR, 0.99; 95% CI, 0.83-1.17; P=.908) and serious bleeding complications (RR, 1.00; 95% CI, 0.66-1.51; P=.996). *Conclusions:* This first meta-analysis of cilostazol in patients with atherothrombosis demonstrated a significant risk reduction for cerebrovascular events, with no associated increase of bleeding risk. **Key Words:** Meta-analysis—cilostazol—stroke—cerebrovascular disorders—prevention—atherothrombosis—phosphodiesterase inhibitor—vascular endothelium—platelet aggregation inhibitor.

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Atherothrombosis, including ischemic cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral artery disease (PAD), is reported as a leading cause of morbidity and mortality on a worldwide scale.[1] Atherosclerotic plaque disruption leading to platelet activation and thrombus formation is considered as a common underlying condition of these atherothrombotic diseases.[2] The REACH Registry, an international database of patients with atherothrombosis, showed 15.9% of those with symptomatic atherothrombosis had symptomatic polyvascular disease at baseline.[3] In the 1-year follow-up, one of 6 patients with CAD, CVD, or PAD had symptomatic involvement of one or two other arterial beds, and multiple disease locations increased the risk of vascular events, suggesting atherothrombosis should be treated as a systemic disease.[4]

Various antiplatelet agents have been shown to exert protective effects in patients with occlusive CVD and improve long-term effects of ischemic stroke and transient ischemic attack (TIA).[5]

Cilostazol is an antiplatelet agent indicated for the treatment of intermittent claudication (IC) with peripheral artery occlusion worldwide and for the prevention of ischemic stroke in Japan and some other Asian countries. It is a potent inhibitor of type III phosphodiesterase whose effects include vasodilatation,[6] inhibition of vascular smooth muscle cell growth,[7] prevention of thrombosis,[8] and increase of blood flow[9] in the limb arteries. It has also been shown to improve serum lipid profile by lowering triglycerides and increasing high-density lipoprotein cholesterol.[10]

In Western countries, antiplatelet therapy for stroke prevention includes aspirin, clopidogrel, and dipyridamole, alone or in combination.[3,11] In Japan, cilostazol is approved for stroke prevention,[12-14] and its use is recommended in the Japanese stroke treatment guidelines.[15] Cilostazol is used as a direct and indirect antiplatelet agent through inhibiting platelet activation by various stimuli and by improving overall vascular endothelial function.[16]

Randomized controlled trials (RCTs) of cilostazol have been conducted in patients with atherothrombotic diseases such as PAD/IC, coronary stenting, and cerebrovascular events. However, the data taken individually from such studies are limited and have not provided conclusive evidence for effects. According to the latest Cochrane review, 8 RCTs comparing cilostazol versus placebo in patients with stable IC demonstrated a significant improvement in walking distance and no increase of major adverse events including cardiovascular events and mortality in the cilostazol group.[17] In the current study, we conducted a systematic review and meta-analysis of cilostazol RCTs with a view to evaluating the effects of cilostazol on ischemic and hemorrhagic events. The aim of this meta-analysis was to establish the potential benefit of cilostazol in the prevention of cerebrovascular and cardiac events, and to investigate the role of cilostazol in bleeding complications.

Methods

A search of trials involving cilostazol was conducted in Ovid MEDLINE 1950 to August Week 4, 2007; Ovid EMBASE 1947-August Week 4, 2007; and the Cochrane Central Register of Controlled Trials. Since cilostazol does not have a Medical Subject Heading (MeSH), the terms "clz," "cilostazol," "pletal," and "pletaal" were combined using the Boolean "or" and searched in all fields (.af.) of the MEDLINE record. MeSH terms for atherothrombotic disease were similarly identified and combined using the Boolean "or". The resulting two data sets were combined using the Boolean "and" and limited to humans studies. All languages were included. The retrieval was limited to the publication types (.pt.) of RCT or meta-analysis and further defined by the text words "double blind" and "placebo." The same basic search was conducted in EMBASE; however, cilostazol is a subject heading in EMBASE. The EMBASE search yielded one relevant article that was not indexed in MEDLINE. Eligibility criteria included adult patients with vascular risk factors and at least one cardiac event, CVD, or PAD. Eligible interventions included oral cilostazol given at any dosage versus placebo (with allowance of any concomitant antithrombotic agents) for a minimum duration of 12 weeks. The eligible outcomes included any cardiac, cerebrovascular, and adverse hemorrhagic events. Study methodology was limited to prospective RCTs versus placebo. Multiple reviewers independently searched the literature, applied eligibility criteria, screened titles and abstracts, selected relevant articles for appraisal, determined quality, and extracted the necessary data. Any disagreements among reviewers were resolved by consensus discussion.

Quality of the included RCTs was assessed by applying the Jadad scale.[18,19]

The Jadad scale, sometimes described as Jadad scoring or Oxford quality scoring system, is the most widely used scale to assess the methodological quality of a clinical trial. Articles reporting a clinical trial may receive scores ranging from a minimum of 0 (lowest quality) to a maximum of 5 (highest quality). The Jadad scale includes questions concerning randomization and its description, blinding and its description, and dropouts.

The primary efficacy end points of the meta-analysis were frequencies of cerebrovascular events including stroke, TIA, and carotid intervention; cardiac events including myocardial infarction, unstable angina, sudden cardiac death, and coronary intervention; and all vascular events (cardiac and cerebrovascular). Safety end points examined were numbers of bleeding events that were fatal or life threatening, and/or required hospitalization.

Statistical Analysis

The relative risk (RR), 95% confidence intervals (CI), *P* values, and risk reduction of cilostazol versus placebo for

Table 1. *Summary of demographic characteristics and medical history*

Trial	Treatment	Randomized patients, n	Duration (wk)	Patient inclusion criteria	Male, n (%)	Age (y) mean ± SD	Caucasian, n (%)	Diabetes, n (%)	Hypertension, n (%)	Stroke, n (%) (including TIA)	CV (MI), n (%)	Smoker (current), n (%)	Reference
21-90-201	Cilostazol 100 mg bid	54	12	PAD/IC	38 (70.4)	65.7 ± 1.1	53 (98.2)	14 (25.9)	NA	NA	NA	22 (40.7)	Thompson[23] 2002
	Placebo	27			24 (88.9)	67.2 ± 2.0	27 (100)	4 (14.8)	NA	NA	NA	15 (55.6)	
21-92-202	Cilostazol 50 mg bid	171	24	PAD/IC	131 (76.6)	64.5 ± 9.9	152 (88.9)	51 (29.8)	NA	14 (8.2)	49 (28.6)	62 (36.3)	Thompson[23] 2002
		175			130 (74.3)	64.3 ± 8.5	154 (88.0)	46 (26.3)	NA	9 (5.1)	39 (22.3)	61 (34.9)	
	Cilostazol 100 mg bid	170			131 (77.1)	65.1 ± 9.3	151 (88.8)	48 (28.2)	NA	12 (7.1)	42 (24.7)	75 (44.1)	
	Placebo												
21-93-201	Cilostazol 100 mg bid	95	12	PAD/IC	83 (87.4)	66.7 ± 9.0	84 (88.4)	18 (18.9)	NA	10 (10.5)	11 (11.6)	37 (38.9)	Thompson[23] 2002
	Placebo	94			76 (80.9)	65.8 ± 8.5	77 (81.9)	19 (20.2)	NA	16 (17.0)	14 (14.9)	42 (44.7)	
21-94-201	Cilostazol 50 mg bid	132	24	PAD/IC	98 (74.2)	63.9 ± 8.7	105 (79.5)	38 (28.8)	NA	NA	NA	63 (47.7)	Thompson[23] 2002
		133			102 (76.7)	63.1 ± 10.2	120 (90.2)	31 (23.3)	NA	NA	NA	67 (50.4)	
	Cilostazol 100 mg bid	129			100 (77.5)	64.4 ± 10.2	115 (89.1)	22 (17.1)	NA	NA	NA	62 (48.1)	
	Placebo												
21-94-203	Cilostazol 100 mg bid	119	16	PAD/IC	90 (75.6)	64.8 ± 9.4	106 (89.1)	30 (25.2)	NA	10 (8.4)	25 (21.0)	43 (36.1)	Thompson[23] 2002
	Placebo	120			90 (75.0)	64.5 ± 8.8	102 (85.0)	37 (30.8)	NA	13 (10.8)	20 (16.7)	48 (40.0)	
21-94-301	Cilostazol 100 mg bid	123	24	PAD/IC	86 (69.9)	66 ± 8.3	123 (100)	15 (12.2)	NA	8 (6.5)	18 (12.9)	48 (39.0)	Thompson[23] 2002
	Placebo	124			91 (73.4)	65.9 ± 8.8	123 (99.2)	15 (12.1)	NA	15 (12.1)	16 (14.6)	44 (35.5)	
21-95-201	Cilostazol 100 mg bid	72	12	PAD/IC	54 (75.0)	67.6 ± 8.8	66 (91.7)	22 (30.6)	44 (61.1)	7 (9.7)	19 (26.4)	26 (36.1)	Thompson[23] 2002
		73			59 (80.8)	65.3 ± 9.9	61 (83.6)	25 (34.2)	47 (64.4)	10 (13.7)	20 (27.4)	24 (32.9)	
	Cilostazol 150 mg bid	70			57 (81.4)	65.6 ± 7.4	59 (84.3)	24 (34.3)	41 (58.6)	7 (10.0)	17 (24.3)	27 (38.6)	
	Placebo												
21-96-202	Cilostazol 100 mg bid	227	24	PAD/IC	172 (75.8)	65.5 ± 9.3	201 (88.5)	72 (31.7)	166 (73.1)	37 (16.3)	54 (23.8)	94 (41.4)	Thompson[23] 2002
	Placebo	239			176 (73.6)	65.9 ± 9.4	212 (88.7)	75 (31.4)	172 (72.0)	38 (15.9)	70 (29.3)	90 (37.7)	
CASTLE	Cilostazol 100 mg bid	717	144	PAD/IC	483 (67.4)	66.6	566 (78.9)	271 (37.8)	591 (82.4)	74 (10.3)	210 (29.3)	205 (28.6)	Stone[24] 2008
	Placebo	718			474 (66.0)	65.9	570 (79.4)	242 (33.7)	582 (81.1)	76 (10.6)	208 (28.9)	225 (31.3)	

(Continued)

Table 1. *Summary of demographic characteristics and medical history (Continued)*

Trial	Treatment	Randomized patients, n	Duration (wk)	Patient inclusion criteria	Male, n (%)	Age (y) mean ± SD	Caucasian, n (%)	Diabetes, n (%)	Hypertension, n (%)	Stroke, n (%) (including TIA)	CV (MI), n (%)	Smoker (current), n (%)	Reference
CREST	Cilostazol	354	24	Coronary	271 (76)	60 ± 11	NA	82 (23)	230 (66)	9 (3)†	75 (21.2)	122 (35)	Douglas[26]
	100 mg bid	351		stenting	252 (72)	60 ± 10	NA	99 (28)	230 (66)	18 (5)†	80 (22.8)	137 (39)	2005
	Placebo												
CSPS	Cilostazol	526	90.3*	Cerebro-	340 (64.7)	65.7 ± 8.7	NA	141 (36.5)	326 (61.2)	526 (100)	42 (7.9)	NA	Gotoh[12]
	100 mg bid	526		vascular	350 (66.5)	65.1 ± 8.8	NA	123 (23.0)	322 (60.3)	526 (100)	44 (8.2)	NA	2000
	Placebo			event									
TOSS	Cilostazol	67	24	Cerebro-	41 (61.2)	61.18 ± 10.42	NA	26 (38.8)	35 (52.2)	67 (100)	5 (7.5)‡	31 (46.3)	Kwon[25]
	100 mg bid	68		vascular	41 (60.3)	62.54 ± 8.97	NA	28 (41.2)	43 (63.2)	68 (100)	6 (8.8)‡	29 (42.6)	2005
	Placebo			event									

Abbreviations: bid, twice a day; CASTLE, cilostazol, A study in long-term effects; CREST, cilostazol for RESTenosis trial; CSPS, cilostazol stroke prevention study; CV, coronary vascular events; IC, intermittent claudication; MI, myocardial infarction; NA, data not available; PAD, peripheral arterial disease; TIA, transient ischemic attack; TOSS, Trial of cilostazol in symptomatic intracranial arterial stenosis.

*Mean duration of drug intake.

†Including carotid artery stenosis>78%.

‡Coronary artery disease.

the risk of cerebrovascular events, cardiac events, overall vascular events, and serious bleeding for each study, and integrated results of all studies, were displayed. The data from each study were plotted in figures in descending order (funnel plot).

In cases such as the current analysis, it is usual practice to analyze data by hazard ratio over time, however, since the holders of the databases for each study are different and it is difficult to obtain data for individual patients, the data were analyzed using RR based on numerical values in a 2×2 contingency table. The RR of each study was extremely close to the hazard ratio, because the risk of onset in each study was low, even though the observation periods were different among the studies.

It was assumed that the population RRs are constant for all studies (fixed-effect model), because the RRs across studies were not very different.

Assessments of publication bias were conducted with funnel plot,[20] fail-safe N,[21] and file drawer test.[22] Publication bias may arise from the tendency for researchers, editors, and pharmaceutical companies to handle experimental results that are positive differently from results that are negative or inconclusive.

The integrated RRs were calculated using asymptotic variance method: the weighted mean of log RRs was calculated by 1/[asymptotic variance of log RR] = 1/[1/n11−1/(n11+n12)+1/n21−1/(n21+n22)], and logarithmic back-transformation (using the exponent) of the weighted mean. The 95% CI, corresponding P values, and heterogeneity were also calculated using asymptotic variance of log RRs. Two-tailed tests were performed with a 5% level of significance.

Results

Our search yielded 33 potentially eligible published studies. Of these 33, we identified 12 double-blind, placebo-controlled trials. The clinical trials, from Japan, Korea, and the United States, included 9 trials in patients with PAD/IC (n = 3782, 66.7%),[23,24] two in patients with cerebrovascular events (n = 1187, 20.9%),[12,25] and one in patients after coronary stenting (n = 705, 12.4%).[26] A list of the 12 RCTs and events relevant to the end points that were examined in the trials is presented in Table 1. A total of 5674 patients were included in the meta-analysis. The baseline demographic characteristics are summarized in Table 1 and concomitant use of antiplatelet agents is stated in Table 2. Overall, patients in the cilostazol and placebo arms were evenly matched in terms of sex, age, and medical background.

The results of heterogeneity were as follows: P = .11 for all vascular events; P = .27 for cerebrovascular events; P = .92 for cardiac events; and P = .68 for serious bleeding; no statistically significant differences were seen among the RRs of trials. Since no significant heterogeneity between trials existed, pooling of results was justified.

Table 2. *Concomitant use of antithrombotic agents*

	Cilostazol			Placebo		
	ASA	Clo	ASA + Clo	ASA	Clo	ASA + Clo
21-90-201	0	0	0	0	0	0
21-92-202	0	0	0	0	0	0
21-93-201	0	0	0	0	0	0
21-94-201	0	0	0	0	0	0
21-94-203	0	0	0	0	0	0
21-94-301	0	0	0	0	0	0
21-95-201	0	0	0	0	0	0
21-96-202	145 (63.9%)	0	0	154 (64.4%)	0	0
CASTLE	366	37	156	355	49	149
CREST	354 (100%)	354 (100%)	354 (100%)	351 (100%)	351 (100%)	351 (100%)
CSPS	0	0	0	0	0	0
TOSS	67	0	0	68	0	0
Total	932	391	510	928	400	500

Abbreviations: ASA, acetylsalicylic acid; CASTLE, cilostazol, A study in long-term effects; Clo, clopidogrel; CREST, cilostazol for RESTenosis trial; CSPS, cilostazol stroke prevention study; TOSS, trial of cilostazol in symptomatic intracranial arterial stenosis.

All 12 RCTs had maximal Jadad scores of 5, revealing uniformly high methodological quality.

Funnel plot examinations indicated only a very small probability of the existence of publication bias. Given the remote likelihood that publication bias had influenced the pooled meta-analysis estimates, no further statistical tests for publication bias were considered necessary.

Table 3 details the total numbers of vascular events, cerebrovascular events, and cardiac events that occurred in each treatment arm in the trials, together with the number

Table 3. *Summary of meta-analysis results in 12 trials*

Trial	Treatment	Randomized patients, n	Vascular events n (%)	Coronary vascular events n (%)	Cerebral vascular events n (%)	Serious bleeding n (%)	Reference
21-90-201	Cilostazol	54	2 (3.7)	2 (3.7)	0	1 (1.9)	Thompson[23] 2002
	Placebo	27	1 (3.7)	1 (3.7)	0	1 (3.7)	
21-92-202	Cilostazol	346	9 (2.6)	7 (2.0)	2 (0.6)	3 (0.9)	Thompson[23] 2002
	Placebo	170	6 (3.5)	3 (1.8)	3 (1.8)	0	
21-93-201	Cilostazol	95	0	0	0	1 (1.1)	Thompson[23] 2002
	Placebo	94	0	0	0	1 (1.1)	
21-94-201	Cilostazol	265	6 (2.3)	6 (2.3)	0	1 (0.4)	Thompson[23] 2002
	Placebo	129	4 (3.1)	2 (1.6)	2 (1.6)	0	
21-94-203	Cilostazol	119	1 (0.8)	1 (0.8)	0	0	Thompson[23] 2002
	Placebo	120	1 (0.8)	1 (0.8)	0	0	
21-94-301	Cilostazol	123	4 (3.3)	2 (1.6)	2 (1.6)	1 (0.8)	Thompson[23] 2002
	Placebo	124	3 (2.4)	3 (2.4)	0	0	
21-95-201	Cilostazol	145	3 (2.1)	3 (2.1)	0	0	Thompson[23] 2002
	Placebo	70	2 (2.9)	1 (1.4)	1 (1.4)	0	
21-96-202	Cilostazol	227	5 (2.2)	2 (0.9)	3 (1.3)	0	Thompson[23] 2002
	Placebo	239	2 (0.8)	2 (0.8)	0	0	
CASTLE	Cilostazol	717	144 (20.1)	126 (17.6)	18 (2.5)	18 (2.5)	Stone[24] 2008
	Placebo	718	166 (23.1)	132 (18.4)	34 (4.7)	22 (3.1)	
CREST	Cilostazol	354	73 (20.6)	68 (19.2)	5 (1.4)	10 (2.8)	Douglas[26] 2005
	Placebo	351	69 (19.7)	67 (19.1)	2 (0.6)	11 (3.1)	
CSPS	Cilostazol	526	40 (7.6)	3 (0.6)	37 (7.0)	11 (2.1)	Gotoh[12] 2000
	Placebo	526	72 (13.7)	3 (0.6)	69 (13.1)	7 (1.3)	
TOSS	Cilostazol	67	2 (3.0)	2 (3.0)	0	0	Kwon[25] 2005
	Placebo	68	2 (2.9)	2 (2.9)	0	2 (2.9)	

Abbreviations: CASTLE, cilostazol, A study in long-term effects; CREST, cilostazol for RESTenosis trial; CSPS, cilostazol stroke prevention study; TOSS, trial of cilostazol in symptomatic intracranial arterial stenosis.

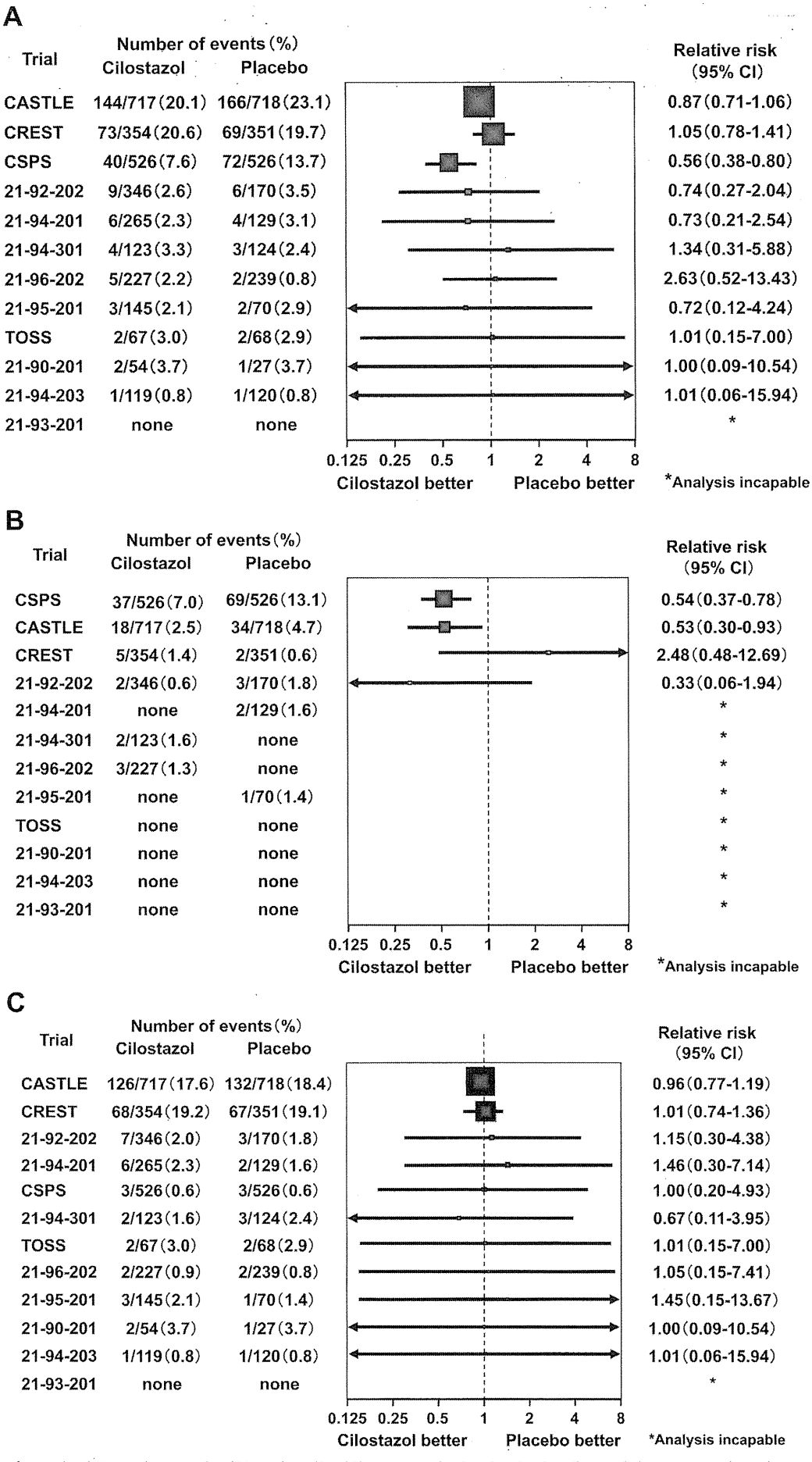

Figure 1. *Number of vascular (A), cerebrovascular (B), and cardiac (C) events and RR reduction by cilostazol therapy in each study. Size of square represents estimate accuracy of logarithmic risk ratio.*

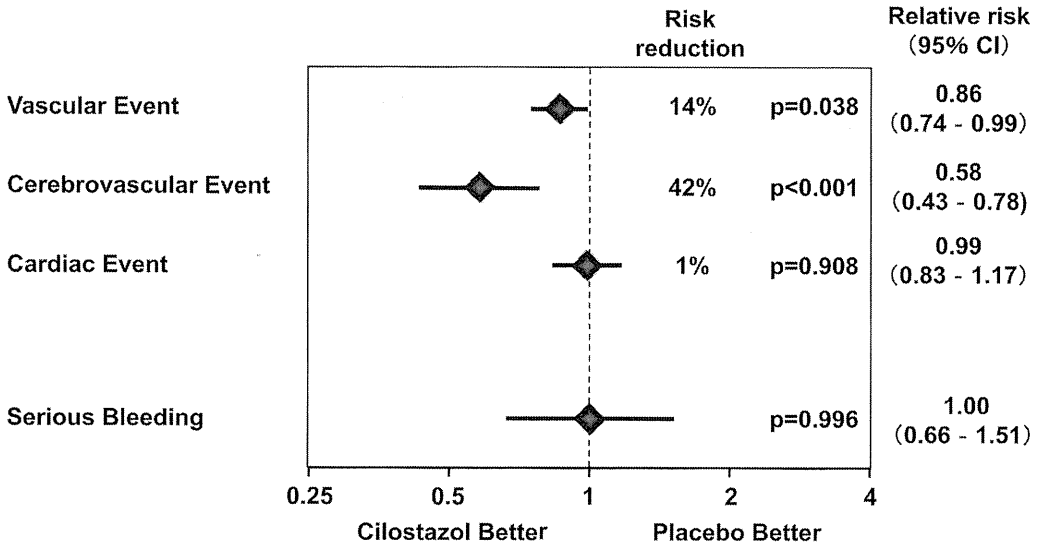

Figure 2. *Meta-analysis of total, cerebrovascular, and cardiac events, and serious bleeding observed in total population from all RCTs.*

of serious bleeding events. As shown in Fig 1, the risk reduction for any vascular event was variable between the trials analyzed. However, when the total population from the trials was assessed in the meta-analysis (Fig 2), there was a significant reduction in the occurrence of all vascular events in the cilostazol group compared with the placebo group (RR, 0.86; 95% CI, 0.74-0.99; $P = .038$). The decrease in RR for all vascular events was mainly due to a large reduction of the incidence of cerebrovascular events in the cilostazol group compared with the placebo group (RR, 0.58; 95% CI, 0.43-0.78; $P < .001$). The reduction of the incidence of cardiac events between the two groups was only 1% and was not statistically significant (RR, 0.99; 95% CI, 0.83-1.17; $P = .908$). There was no significant difference in the incidence of serious bleeding complications between the cilostazol and placebo groups (RR, 1.00; 95% CI, 0.66-1.51; $P = .996$).

Discussion

The results from this meta-analysis, including 5674 patients in total, provide definitive evidence that cilostazol had a significant protective effect against the recurrence of vascular events in patients with atherothrombosis. There was a significant 14% and highly significant 42% reduction of vascular and cerebrovascular events, respectively, in patients taking cilostazol. This effect was not associated with any increase of bleeding events in patients on cilostazol. The pathological conditions of atherothrombosis are characterized by vascular endothelial dysfunction, platelet activation, and thrombus formation. Cilostazol has not only antiplatelet properties but also improves vascular endothelial function and exerts anti-inflammatory effects, which may be prophylactic against bleeding.[14,16,26,27] In contrast, aspirin and clopidogrel, which act exclusively on platelets, have limited effects on cerebrovascular events with 20% to 25% reduction[5,28] and can increase risk of serious bleeding even in monotherapy and especially in combination.[29-31] Drugs that have dual effects on platelets and endothelial function, although not increasing bleeding risk, are obviously preferable for prevention of cerebrovascular events, making cilostazol a good candidate.

Cilostazol reduced mortality and/or morbidity associated with cardiac events, although only by 1% and this was not statistically significant. The reason for this finding is not clear. It is possible that where occlusion occurs in small coronary vessels, it is difficult to perceive that as a symptomatic event, as opposed to the same occurrence in brain resulting in symptomatic ischemic stroke and TIA. Moreover, distinct mechanisms between the formation of thrombi in large and small vessels might discriminate various antiplatelet agents. In smaller vessels, not only platelets but also leukocyte plugging can cause ischemic events, such as shown in no-reflow phenomena.[32] On the other hand, the role of leukocyte plugging, which can specifically be prevented by cilostazol, in the formation of symptomatic occlusive thrombus formation in larger vessels might be less important than that in smaller vessels. In this context, agents such as aspirin and clopidogrel, which inhibit platelet-derived procoagulant activity by adenosine diphosphae (ADP) receptor antagonists, may be more effective in prevention of events in larger vessels such as coronary artery occlusion.[33] This in fact is the major strategy for preventing cardiac events; therefore, with cilostazol's involvement, the effect could be diminished (or masked) from that of other agents.

One limitation of this meta-analysis was the nonuniformity of patients participating in the trials examined. The patients differed in medical history with regard to IC, ischemic stroke, and CAD, with some trials favoring recruitment of patients with one disease over another. Drouet et al[34] stated that secondary prevention of an ischemic event in the index territory provides primary

prevention for other arterial territories that are still clinically silent, and antiplatelet therapy is mandatory for optimal prevention of ischemic events in atherothrombotic patients. The current results demonstrating significant preventive effects of cilostazol support this statement and the notion that cilostazol can prevent cerebrovascular events without increasing the risk of bleeding in a range of patients with various atherothrombotic diseases.

We wish to acknowledge assistance from Kay E. Wellik, MLS, AHIP, Mayo Clinic Arizona, for assistance with search strategies and biomedical literature informatics.

Appendix 1. Literature search strategy

Database: Ovid MEDLINE(R) <1950 to May Week 3 2008>
Search Strategy:

1	(clz or cilostazol or pletal or pletaal).af. (676)
2	exp vascular diseases/ (1054726)
3	exp coronary stenosis/ (7132)
4	exp arterial occlusive diseases/ (136888)
5	Intermittent Claudication/ (6102)
6	exp stroke/ (47823)
7	exp peripheral vascular diseases/ (38293)
8	Coronary Artery Disease/ (19056)
9	exp carotid artery diseases/ (29097)
10	exp cerebral arterial diseases/ (7448)
11	exp cardiovascular diseases/ (1462403)
12	exp myocardial infarction/ (118964)
13	exp intracranial arterial diseases/ (37524)
14	vascular.af. (452827)
15	vascular death.af. (321)
16	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (1725936)
17	1 and 16 (415)
18	limit 17 to humans (341)
19	limit 18 to (meta analysis or randomized controlled trial) (79)
20	double blind$.mp. (117129)
21	placebo.mp. (110531)
22	20 and 21 (64125)
23	19 and 22 (31)
24	from 23 keep 1-31 (31)

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第6回

脳血管障害に関する現在進行中の試験と今後の展望

解説
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クロピドグレルはすでに脳梗塞の亜急性期や慢性期，頸動脈狭窄，アテローム血栓症に有効であることが示され，エビデンスが蓄積されている．さらに，心原性脳塞栓症やラクナ梗塞など，その他の脳血管障害に対する効果を確認するために，現在いくつかの試験が進行中あるいは計画中である．ここでは現在進行中ならびに計画中のトライアルについて紹介する．

心原性脳塞栓症を対象としたACTIVE A / W

ACTIVE（Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events）は，脳卒中の危険因子を有する高リスクの心房細動患者14,500例を対象に，抗血栓療法による血管イベント抑制効果を検討した大規模な多施設国際共同試験である．

デザインはやや複雑で，ACTIVE W，ACTIVE AとACTIVE Iのarmがある（図1）．ACTIVE Wではガイドラインでワルファリンの適応となる患者に対して，アスピリン・クロピドグレル併用療法とINR2.0-3.0のワルファリン療法を比較している．一方，ACTIVE Aはガイドラインで抗血小板療法でもよいとされている患者に対して，アスピリン・クロピドグレル併用療法とアスピリン単独療法を比較している．

さらに，ARB併用による上乗せ効果をみるACTIVE Iというarmもある．ARBには心房細動新規発症の予防効果があるというエビデンスが蓄積されている．そのため抗血栓療法にARB療法を併用した場合のイベント発症についても検討されている．

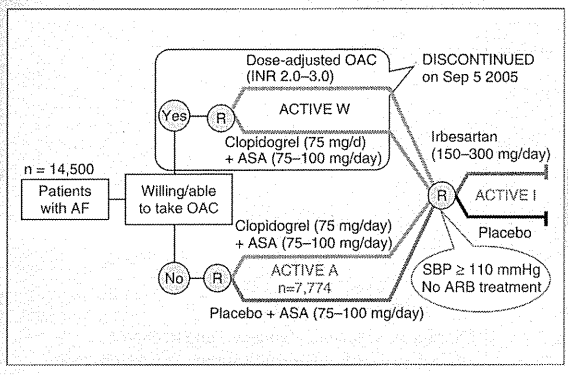

図1　ACTIVE A: Study design
Principal investigator: Connolly S.

ところが，ACTIVE Wは，アスピリン・クロピドグレル併用療法ではワルファリン療法に比し，脳卒中発症頻度が明らかに高かったため，試験は中止された．心臓内にできる血栓はフィブリン血栓が主とされており，心原性脳塞栓症は強力な抗血小板療法であっても予防できないであろうということを如実に示す結果ではないかと思われる．この結果は2005年に*Lancet*に報告されている．

ACTIVE AやACTIVE Iは現在も進行中で，2009年に海外の主要学会でキーオープンされ，結果が発表される予定である．アスピリン・クロピドグレル併用療法とアスピリン単独療法の効果の相違，およびARB併用による効果に関して，どのような結果が出るか非常に興味のあるところである．

TIAおよびMinor strokeを対象としたFASTER 2

FASTER(Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence)は，発症後24時間以内の一過性脳虚血発作(TIA)または軽症脳梗塞患者を対象に，アスピリン・クロピドグレル併用療法とアスピリン単独療法を比較したpilot studyである．併用療法はアスピリン単独療法よりも90日以内の脳卒中発症が少ない傾向があった．ただし，出血性合併症(特に無症候性)の頻度も併用療法の方が単独療法よりも高い傾向があった．症例数が少なく，有意差が出なかったため，大規模な国際共同研究FASTER 2が計画されており，2009年早々に開始予定となっている．

FASTER 2は，発症12時間以内のTIAまたは軽症脳梗塞で，NIHSS(National Institutes of Health Stroke Scale)が3点以下の患者を対象とし，目標登録症例数は5,600例，100施設の協力を得て，3年

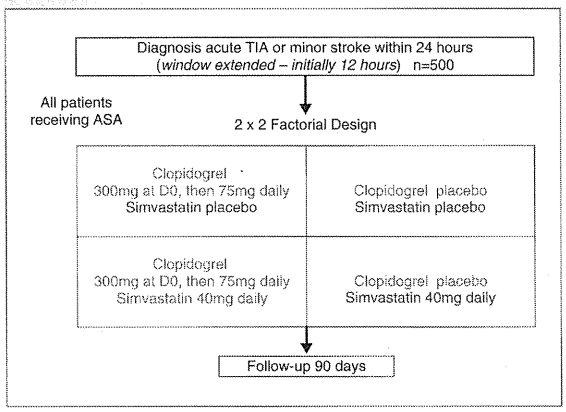

図2 FASTER 2: Study design
Principal investigators: Kennedy J and Buchan A.
International multicenter double-blind randomized study.
Kennedy J, et al; FASTER Investigators. *Lancet Neurol* 2007; 6: 941-3.

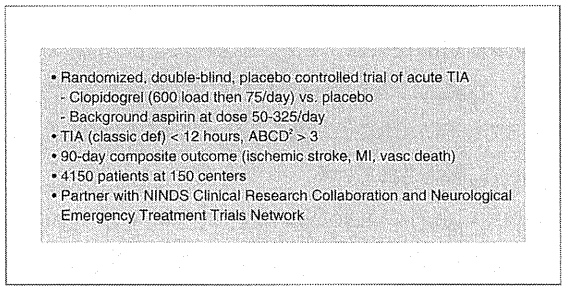

図3 POINT: Study design
Principal investigator: Johnston SC.

間の登録期間を予定している(図2).

発症直後のTIAは脳卒中発症リスクが非常に高いため，早期から強力な抗血小板療法を行うことによって，脳卒中発症が予防できる可能性がある．しかし，併用療法は出血性合併症のリスクが危惧されることから，リスクとベネフィットのプロファイルを検討するという意味で，臨床的に非常に意義のある試験ではないかと思う．

またFASTER 2にきわめてデザインが似た試験としてPOINT(Platelet-Oriented Inhibition in New TIA)がある．発症12時間以内のTIAまたは軽症脳梗塞でNIHSSが2点以下のより軽症の患者を対象として，アスピリン・クロピドグレル併用療法とアスピリン単独療法を比較することになっている(図3)．1次エンドポイントは，90日間の心血管死，脳卒中および心筋梗塞で，安全性も検討される．米国国内の150施設で，目標症例数5,000例として，2009年に開始される予定である．

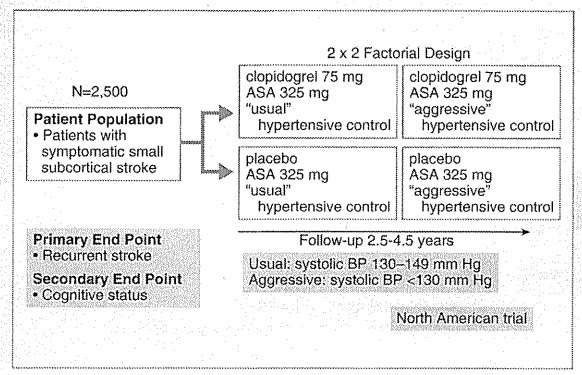

図4 SPS3: Study design
Principal investigators: Benavente O and Hart R.
ClinicalTrials.gov (http://clinicaltrials.gov/ct2/home)

なお，FASTER 2もPOINTも，クロピドグレルはloading doseとして300mgを初回投与し，その後は75mgを投与するというデザインとなっている．両試験ともに結果が出るのは数年後になるだろうが，発症直後のTIAまたは軽症脳梗塞の患者に対する抗血小板療法の有効性と安全性を検討するという意味では，非常に興味ある臨床試験と言える．

ラクナ梗塞を対象としたSPS3

現在進行中のSPS3（Secondary Prevention of Small Subcortical Strokes）は，ラクナ梗塞（皮質下小梗塞）に対する抗血小板療法を検討する試験である．アスピリン・クロピドグレル併用療法とアスピリン単独療法を，2×2 factorial designにより比較する試験で，2つの抗血小板療法を比較するとともに，目標収縮期血圧を130-149mmHgとした通常の降圧療法と，130mmHg未満という積極的な降圧療法を比較している（図4）．

Primary outcomeは脳卒中再発，およびその他の血管イベント，認知機能，およびMRI画像における白質の異常所見である．またsecondary outcomeは，頭蓋内出血やその他の出血性合併症などが挙げられている．目標症例数は2,500例，観察期間は2.5-4.5年となっている．現在，症例登録中であり，この試験も結果が出るのはまだ先の予定である．ラクナ梗塞に対する抗血小板療法については，有効性と安全性の面でさまざまな議論がなされていることから，きわめて注目すべき臨床試験であると思われる．