□ EDITORIAL □

A Sensitive Marker for Left Atrial Dysfunction as a Risk Factor of Cardioembolic Stroke after Cessation of Paroxysmal Atrial Fibrillation

Key words: left atrial dysfunction, cardioembolic stroke, paroxysmal atrial fibrillation, transesophageal echocardiography

Not only chronic atrial fibrillation but also paroxysmal atrial fibrillation (PAF) is known to be a risk factor of cardioembolic stroke (CES). The value of transesophageal echocardiography (TEE) in addition to established clinical risk factors for stroke is controversial in patients with PAF. Altered hemostasis favoring thrombosis may contribute to formation of left atrial appendage (LAA) thrombus, but these conditions remain ill defined particularly in PAF (1). Left atrial mechanical remodeling has been established to play an important role in thrombogenesis as a potential cardiac source of embolism in patients with PAF (2), while it has not been clarified whether or not LAA dysfunction contributes to the occurrence of CES because of lack of data on the comparison of LAA function after cessation of PAF between patients with and without CES. Kaneko et al (3) compared parameters for LAA dysfunction on TEE between 17 patients with and 16 without CES after cessation of PAF.

See also p 1077.

As for parameters for LAA dysfunction on TEE, they investigated left atrial dimension, LAA area, emptying flow velocity of the LAA (LAA-eV), LAA fractional area change (LAA-FAC), and left atrial spontaneous echo contrast (LA-SEC). They did not show any significant difference in left atrial dimension (4) or LAA-eV (5), widely used indices between the two groups, while they could show significantly larger LAA area, smaller LAA-FAC, and more frequent LA-SEC in patients with CES than without CES. In addition, they showed significant improvements in these abnormalities at the second examination in the patients with CES.

According to the Stroke Prevention in Atrial Fibrillation (SPAF) investigators, left ventricular wall dyskinesia and left atrial dilatation on TEE are risk factors for stroke in patients with non-valvular atrial fibrillation (NVAF) (4). In addition, many studies have reported that decreased LAA flow velocities are predictors for stroke in patients with NVAF (5–7). SPAF III investigators have also reported that LAA peak flow velocities correlate with thromboembolic risk in NVAF patients (8, 9). However, it has not been elucidated whether left atrial dilatation or LAA flow velocities can be a marker for the risk of CES also in patients after cessation of PAF. Indeed, Kaneko et al showed that there is no significant difference in left atrial dimension or LAA-eV between the patients with and without CES after cessation of PAF (3).

In contrast, they demonstrated significantly smaller LAA-FAC in patients with CES than without CES after cessation of PAF (3). Some previous studies have reported that LAA-FAC can detect milder or earlier LAA dysfunction than LAA-eV (10, 11). Panagiotopoulos et al (11) demonstrated that patients with CES in sinus rhythm showed a significant decrease of LAA-FAC compared with control subjects, while patients with CES in atrial fibrillation showed a significant reduction of LAA-eV. In addition, they observed that patients with LA-SEC, thrombus, or both showed further reduction of LAA-FAC and LAA-eV, indicating a more advanced stage of dysfunction. If LAA-FAC is a more sensitive marker for LAA function than other markers such as LAA-eV, it could be useful to determine whether or not to continue warfarin treatment. In order to establish the value of this marker for LAA function on TEE as a sensitive and reliable predictor for CES, it may be worthwhile to evaluate in a large prospective study for stroke prevention in patients after cessation of PAF.

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Platelet Function Under Aspirin, Clopidogrel, and Both After Ischemic Stroke: A Case-Crossover Study

To the Editor:

We read with great interest the articles by Grau et al[1] and Marquardt et al,[2] which were from the same institute, concerning the platelet function under antiplatelet therapy and the course of platelet activation markers after acute ischemic stroke. Many studies have shown that activated platelets can be detected in the systemic circulation in patients with stroke, undergoing cardiopulmonary bypass surgery, peripheral artery occlusive disease, acute myocardial infarction, and other thrombotic disorders. However, which marker for activated platelets can most precisely reflect in vivo platelet activation remains uncertain. Besides, it is of great importance whether the marker is useful to predict the recurrence of vascular event and to monitor the antiplatelet therapy. We would like to compare their recent 2 studies[1,2] with previous ones including our study,[3] their previous study[4] and others.[5–10]

Platelet activation in patients with chronic phase of stroke has been observed using CD62p expression as a marker of platelet activation.[3–5] In the previous study by Grau et al,[4] the proportion of platelets expressing activation-dependent antigens (CD62p and CD63) was higher in patients with both acute and previous cerebrovascular ischemia as compared with age- and sex-matched control subjects. In addition, relatively more platelets expressed CD62p than CD63 in most patients in that study. They explained it was because the secretion of lysosomes usually require stronger stimulation than the release of α-granules. On the contrary, in the recent study by Marquardt et al,[2] CD62p expression was not significantly different on days 14 and 90 after stroke compared with control groups. We wonder why platelet activation detected by CD62p expression was not observed when compared serially. On the other hand, increased CD63 expression was observed on days 14 and 90 after stroke, which indicates continuously ongoing platelet activation. They explained that in the subacute stage after ischemic stroke, CD63 is a more sensitive marker of platelet activation than CD62p, most likely because of shedding of CD62p.[2] If so, it may be possible to detect the elevation of soluble p-selectin. Then, we would like to know if soluble p-selectin in plasma rather than CD62p on the platelet surface can be a marker of platelet activation in the subacute stage after stroke. Another question is about the course of platelet activation markers in their study.[2] It is considered that platelets are activated more strongly in the acute phase of stroke than in the chronic phase of stroke.[2,5] In the study by Marquardt et al,[2] CD62p expression declined over time after stroke, and 60% of patients showed a decrease in CD62p. However, the percentage of CD63-expressing platelets did not change between days 1 and 90 after stroke, and only 36% of patients showed a decrease in CD63 over time. Moreover, 30% of patients showed an increase in CD63, and in 34% of patients, CD63 expression did not change. If CD63 is a more sensitive marker of platelet activation than CD62p, we wonder why CD63 did not reflect the difference of platelet activation among the different phases of stroke.

In the chronic phase of stroke, CD62p and CD63 expression did not differ between patients treated with aspirin, clopidogrel, both of them, or anticoagulants in the recent articles by Grau et al[1] and Marquardt et al.[2] Other recent studies have consistently shown that aspirin does not affect the flow cytometric detection of platelet activation, neither expression of CD62p[6–9] nor CD63.[7,8] In contrast, reduction of CD62p expression has been found for the thienopyridine derivatives, clopidogrel[9] and ticlopidine.[10] Although CD62p expression stimulated with various agonists was decreased in these studies,[9,10] the expression of CD62p without stimulation was also significantly lower in patients with atherothrombotic stroke but not in those with lacunar stroke, who were treated with ticlopidine in our study.[3] It is possible that the significant difference was not detected because CD62p expression was not increased in patients with chronic phase of stroke in the study by Marquardt et al,[2] because they included patients with both subtypes of ischemic stroke. Also in the study by Grau et al,[1] CD63 expression treated with aspirin plus clopidogrel seemed slightly low, and the difference might be significant when it was assessed in a larger number of patients or in patients with a specific subtype, that is, atherothrombotic stroke, in whom stronger platelet activation occurs than in those with lacunar stroke as reported by us.[3]

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Response

We wish to thank Drs Yamazaki and Uchiyama for their interest in our studies.

The authors correctly hint to the fact that CD62p expression by platelets was increased in the subacute stage after stroke in our first[1] but not in our recently published study.[2] In contrast, both studies consistently showed that CD62p and CD63 are significantly increased over control values in the acute stage after stroke. We think that our more recent study that included serial measurements in 50 patients at 10 time points after stroke contains the more valid data. Furthermore, these results were confirmed by our case-crossover study on platelet function under aspirin, clopidogrel, and both after stroke, where we again found that CD63 but not CD62p was increased over values in control subjects in the subacute stage after stroke.[3] The first study was a pilot study and had the disadvantage that different subjects were

investigated in the acute and the chronic stage after stroke and therefore does not allow good comparability between both periods. Given our new results, it is certainly an important question whether soluble p-selectin is a marker of platelet activation in the subacute stage after stroke.

Drs Yamazaki and Uchiyama correctly state that, in fact, CD63 expression by platelets did not follow the somewhat expected course of declining values but remained elevated on an increased level for at least 3 months after stroke. We had concluded that "in the subacute stage after ischemic stroke CD63 is a more sensitive marker of platelet activation than CD62p" because CD63 but not CD62p remain increased during that period. Certainly, we must be careful when we apply our hypothetical models to empirical data. We do not sufficiently know how platelet activation "really" behaves in different stages after acute cerebral ischemia and, in particular, we cannot expect that each feature of platelet activation as a complex scenario follows the same dynamic over time. At least, we should not expect that all of these features "reflect the difference of platelet activation among the different phases of stroke" as long as we are still on our way to characterize these phases after stroke regarding platelet activation.

We agree with Yamazaki and Uchiyama that different stroke subtypes may be reflected by differences in platelet activation parameters. In our subgroup analyses, we did not find differences between lacunar and atherothrombotic stroke regarding neither CD62p nor CD63 and we found differences only with respect to CD63 and cardioembolism.[2] However, as we mention in the discussion, the focus of our study was the longitudinal assessment of platelet markers, and studies with larger numbers of patients are required to study differences between etiologic subgroups.

In our recent case-crossover study on platelet function under aspirin, clopidogrel, and both after stroke, we found barely any difference regarding CD63 expression among the 3 treatments.[3] As most of our patients had atherothrombotic stroke, we do not think that the combination therapy will be able to suppress CD63 expression efficiently. However, larger studies may be required to finally solve this issue.

We feel that the most important issue in platelet function and stroke is to identify a platelet marker that is easily and reliably assessable in clinical practice and that turns out to predict recurrent events after stroke and may thus be helpful to guide therapeutic decisions.

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□ ORIGINAL ARTICLE □

Ticlopidine Alone Versus Ticlopidine Plus Aspirin for Preventing Recurrent Stroke

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Abstract

Objective **To compare the efficacy and safety of two antiplatelet regimens, ticlopidine alone (200 mg daily) and ticlopidine (100 mg daily) plus aspirin (81 mg daily), in patients with ischemic stroke from the Tokai district of Japan.**

Methods **A randomized comparative study was performed from April 1992 until December 1995, with follow-up for an average of 1.59 years (maximum: 3 years). Statistical analysis was done on 270 eligible patients (138 treated with ticlopidine alone and 132 treated with ticlopidine plus aspirin).**

Patients **A total of 276 patients who had cerebral infarction within the previous 1 to 6 months, or one or more transient ischemic attacks within the previous 3 months.**

Results **The incidence of ischemic and hemorrhagic stroke, myocardial infarction, and other vascular events was 10.1% (n=14) in the ticlopidine group and 9.8% (n=13) in the ticlopidine plus aspirin group, showing no significant difference (p=0.933). There was also no significant difference in the event-free rate between the two groups (p=0.5003, Kaplan-Meier analysis and log-rank test). Regarding serious adverse reactions, neutropenia occurred in one patient from the ticlopidine group, while gastric ulcer and thrombocytopenia occurred in one patient each from the ticlopidine plus aspirin group.**

Conclusion **We conclude that both antiplatelet regimens are comparable in efficacy and safety for preventing the recurrence of ischemic stroke.**

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Key words: stroke, secondary prevention, ticlopidine, aspirin, combination therapy

Introduction

Antiplatelet agents are effective for the prevention of recurrent cerebral infarction and transient ischemic attacks (TIA). While aspirin and ticlopidine are widely prescribed in Japan, serious side effects of ticlopidine such as hepatotoxicity, agranulocytosis and thrombotic thrombocytopenic prupura have been reported. Thus, clopidogrel, a new and safer thienopyridine derivative which is the same class as ticlopidine, is generally administered in Western countries.

Aspirin inhibits platelet aggregation by blocking platelet cyclo-oxygenase, while ticlopidine exerts its antiplatelet activity by inhibiting platelet ADP receptors (1, 2). The efficacy of aspirin has been demonstrated in several clinical studies (3–6), but the optimum dose remains controversial. The efficacy of ticlopidine has also been demonstrated in several studies (3, 7–9). These drugs are usually administered as monotherapy, but a combination of aspirin and ticlopidine is also used with the aim of achieving a more potent antiplatelet effect (10–13). However, such combined therapy might increase the risk of major bleeding. Therefore, there is a need to determine the most appropriate doses. In a study on cerebral infarction and TIA, Uchiyama and colleagues (14) compared low-dose combination therapy with aspirin (81 mg/day) plus ticlopidine (100 mg/day) versus monotherapy with aspirin (300 mg/day) or ticlopidine (200 mg/day). They reported that combined treatment with aspirin

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and ticlopidine, which aims to inhibit all of the platelet aggregation pathways via ADP, arachidonic acid, and platelet-activating factor, might be a potent antiplatelet strategy. However, the combined treatment with aspirin and ticlopidine shows prolongation of bleeding time and more bleeding complications, a well-designed prospective study should be implemented to evaluate the usefulness of the combination therapy.

In this long-term treatment study, patients with cerebral infarction or TIA were randomized to monotherapy with a normal dose of 200 mg of ticlopidine per day or to combination therapy with both lower doses of 100 mg of ticlopidine and 81 mg of aspirin per day. The primary endpoint was the occurrence of vascular events such as cerebrovascular diseases and bleeding complications. Due to the small subject number in this study the results may not be conclusive but they are supportive.

Subjects and Methods

Study design

Between April 1992 and December 1995, patients with cerebral infarction or TIA who were treated at hospitals in the Tokai district of Japan were randomly allocated to either the ticlopidine monotherapy group (200 mg/day) or to a combination therapy group that received low-dose ticlopidine (100 mg per day) plus low-dose aspirin (81 mg/day). The subjects were followed up for an average of 1.59 years (maximum: 3 years), during which period the safety of each therapy was investigated, as well as the incidence of cerebral infarction, TIA, myocardial infarction, and other vascular events.

Patients

The subjects were patients who had suffered from non-cardiogenic cerebral infarction within the previous 1–6 months or had experienced one or more episodes of TIA within the previous 3 months. Informed consent was obtained from each patient.

Patients who had a history of cerebral hemorrhage or cardiogenic cerebral infarction, or any contraindications to treatment with ticlopidine or aspirin were excluded from the study. Also excluded were patients who had severe hepatic or renal dysfunction, a bleeding tendency, a history of hypersensitivity to ticlopidine, aspirin, or salicylic acid preparations, or previous treatment with ticlopidine or aspirin after cerebral infarction or TIA. Pregnant or breast-feeding women were also excluded.

Outcomes

The endpoints of this study were the recurrence of cerebrovascular events and the occurrence of myocardial infarction or other vascular events. The following combinations of these events were selected as outcomes for evaluation: recurrent cerebral infarction, cerebral hemorrhage, recurrent cerebral infarction, TIA, or cerebral hemorrhage, and recurrent cerebral infarction, TIA, cerebral hemorrhage, and myocardial infarction or other vascular events.

Statistical analysis

The baseline characteristics of the patients were analyzed by the χ^2 test and the Wilcoxon rank-sum test, and the recurrence rate or incidence of cerebrovascular events, myocardial infarction, or other vascular events, as well as data on adverse reactions, were analyzed by the χ^2 test. The event-free rate for cerebrovascular events, myocardial infarction, and other vascular events was compared between the two groups by Kaplan-Meier analysis and the log-rank test. The level of significance was set at $p<0.05$ (two-tailed).

Results

Enrollment of patients

Between April 1992 and December 1995, 276 patients were enrolled at 25 institutions participating in this trial. Seven patients were excluded from the study, comprising 3 patients who did not take the study drug at all despite being instructed to do so, 2 patients who were not actually treated with the study drug after enrollment, and 1 patient who was treated outside the study period. As a result, 270 patients (138 from the TIC group and 132 from the TIC+ASA group) were eligible for analysis (Fig. 1).

Clinical profile

The baseline characteristics of the 270 subjects are shown in Table 1. Men accounted for 67.4% of the TIC group and 62.1% of the TIC+ASA group, with the mean age of each group being 67.2±9.4 (SD) years and 67.0±9.7 years, respectively. Inpatients accounted for 33.3% of the TIC group and 32.6% of the TIC+ASA group, and 39.1% of the TIC group had a smoking history compared with 27.3% of the TIC+ASA group. There were no significant differences be-

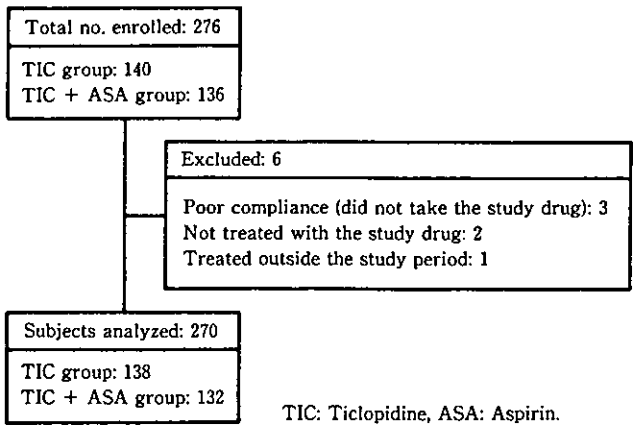

Figure 1. Flowchart showing the disposition of patients.

Table 1. Demographic and Clinical Characteristics of the Subjects

Characteristic		TIC group	TIC+ASA group	p value (χ^2-test)
No. of patients analyzed		138	132	
Sex	M	93 (67.4)	82 (62.1)	p=0.365
	F	45 (32.6)	50 (37.9)	
Age	mean±SD	67.2±9.4	67.0±9.7	p=0.946 (Wilcoxon-test)
	<40	1 (0.7)	1 (0.8)	
	≥40	3 (2.2)	6 (4.5)	
	≥50	25 (18.1)	22 (16.7)	
	≥60	49 (35.5)	44 (33.3)	
	≥70	60 (43.5)	58 (43.9)	
Admission status	Inpatient	46 (33.3)	43 (32.6)	p=0.977
	Outpatient	79 (57.2)	78 (59.1)	
	Inpatient/Outpatient	8 (5.8)	8 (6.1)	
Smoking history	Yes	54 (39.1)	36 (27.3)	p=0.053
	No	77 (55.8)	92 (69.7)	
	Unknown	1 (0.7)	0 (0.0)	
Diagnosis	Cerebral infarction	117 (84.8)	116 (87.9)	p=0.345
	TIA	19 (13.8)	16 (12.1)	
	Cerebral Infarction plus TIA	2 (1.4)	0 (0.0)	
Clinical category of cerebral infarction	Lacunar	69 (50.0)	72 (54.5)	p=0.234
	Atherothrombotic	43 (31.2)	32 (24.2)	
	Unknown	26 (18.8)	28 (21.2)	
Arterial system involved	Internal carotid	107 (77.5)	103 (78.0)	p=0.381
	Vertebrobasilar	31 (22.5)	28 (21.2)	
	Other	2 (1.4)	0 (0.0)	
	Unknown	3 (2.2)	2 (1.5)	
Complications	Yes	94 (68.1)	94 (71.2)	p=0.395
	No	44 (31.9)	35 (26.5)	
	Hypertension	62 (44.9)	66 (50.0)	p=0.893
	Diabetes mellitus	29 (21.0)	32 (24.2)	
	Ischemic heart disease	13 (9.4)	11 (8.3)	
	Hyperlipidemia	11 (8.0)	16 (12.1)	
	Arrhythmia	5 (3.6)	3 (2.3)	
	Other	19 (13.8)	22 (16.7)	

( ): %

tween the two groups with respect to these characteristics.

In the TIC group, 84.8% of the patients had cerebral infarction, 13.8% had TIA, and 1.4% had cerebral infarction plus TIA. In the TIC+ASA group, 87.9% had cerebral infarction and 12.1% had TIA. The internal carotid territory was involved in 77.5% of the TIC group and 78.0% of the TIC+ASA group, with predominance of this region in both groups. Complications were present in 68.1% of the TIC group and 71.2% of the TIC+ASA group. Hypertension was the most common complication (44.9% and 50.0%, respectively), followed by diabetes mellitus (21.0% and 24.2%), ischemic heart disease (9.4% and 8.3%), and hyperlipidemia (8.0% and 12.1%). There were no significant differences between the two groups with respect to these complications.

Arrhythmia (not confirmed to be atrial fibrillation or another type) was detected in five patients (3.6%) of the TIC group and three patients (2.3%) of the TIC+ASA group, but none of them had a new stroke. The subtypes of cerebral infarction were determined on the basis of the clinical features and the site of the infarct focus, and were well matched between the 2 groups.

Outcome events

The incidence of outcome events (cerebral infarction,

Table 2. Number of Patients with Events Over Time

Duration of study	TIC group		TIC+ASA group	
	Patients with events	All patients	Patients with events	All patients
2 weeks	1	138	1	132
4 weeks	1	136	1	132
6 weeks	0	136	0	132
8 weeks	0	136	0	131
6 months	2	135	1	129
12 months	3	125	4	123
18 months	5	119	2	115
24 months	2	107	3	102
30 months	0	100	1	95
36 months	0	96	0	93

TIA, myocardial infarction, or other vascular events) during the follow-up period is shown in Table 2. The incidence of events was not significantly different (p=0.935) between the TIC group [10.1% (n=14)] and the TIC+ASA group [9.8% (n=13)]. The mean follow-up period was 1.79 years in the TIC group and 1.39 years in the TIC+ASA group, with the annual incidence of events being 5.7/100 person-years in the TIC group and 7.1/100 person-years in the TIC+ASA group (Table 3). The difference between the two groups was not statistically significant. The event-free rates for each group calculated by Kaplan-Meier analysis are shown in Fig. 2. The log-rank test showed no significant difference between the two groups (p=0.5003).

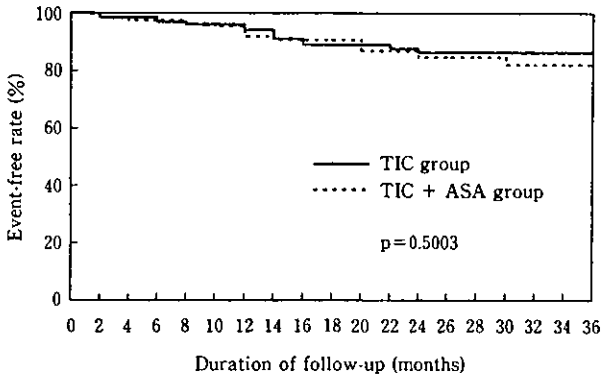

Figure 2. Kaplan-Meier curves of the event-free rate for stroke/TIA, myocardial infarction, and other vascular events.

Stratified analysis of events

The events that occurred in the TIC group consisted of cerebral infarction in 7 patients, TIA in 4 patients, myocardial infarction in 2 patients, and arteriosclerosis obliterans (ASO) in 1 patient. The events occurring in the TIC+ASA group consisted of cerebral infarction in 7 patients, cerebral hemorrhage in 2 patients, TIA in 3 patients, and ASO in 1 patient. While comparison of the annual incidence of events showed no significant differences between the two groups, cerebral hemorrhage was reported in only two patients from the TIC+ASA group (Table 4).

Safety

During the study period, adverse reactions were reported in 15 patients (10.9%) of the TIC group and 17 patients (12.9%) of the TIC+ASA group, with the difference between the two groups not being significant (p=0.610). A list of the adverse reactions is shown in Table 5. Serious adverse reactions included leukopenia in 1 patient of the TIC group, as well as gastric ulcer, nausea, and thrombocytopenia in one each of the TIC+ASA group (a total of 3 patients).

Follow-up of these adverse events showed that nausea (TIC+ASA group) persisted, but the other symptoms subsided or were relieved. Gastrointestinal symptoms were reported in 7 patients of the TIC+ASA group, and vomiting was reported in 1 patient of the TIC group.

Table 3. Number of Patients with Events and Annual Incidence

	No.	Patients with events (%)	p value (χ^2-test)	Mean follow-up period (y)	Annual incidence (100 persons-year)
TIC group	138	14 (10.1%)	p=0.935	1.79	5.7
TIC+ASA group	132	13 (9.8%)		1.39	7.1

Table 4. Annual Incidence Stratified by the Type of Event

Type of event	TIC group	TIC+ASA group	p value (χ^2-test)
	Annual incidence (% per year)	Annual incidence (% per year)	
Cerebral infarction (CI)	2.9 (7)	3.8 (7)	p=0.611
Cerebral hemorrhage (CH)	0	0.8 (2)	p=0.849
CI+TIA	4.5 (11)	5.5 (10)	p=0.846
CI+TIA+CH	4.5 (11)	6.5 (12)	p=0.813
CI+TIA+MI+CH+Other vascular events	5.7 (14)	7.1 (13)	p=0.457

( ): No. of patients with events. TIA: transient ischemic attack, MI: myocardial infarction.

Table 5. Adverse Reactions in Each Treatment Group

	TIC group	TIC+ASA group
Number of patients	138	132
Number of patients with reactions	15 (10.9)	17 (12.9)
Number of adverse reactions	16 (11.6)	17 (12.9)
Major bleeding	6 (4.3)	6 (4.5)
Gastrointestinal symptoms	1 (0.7)	7 (5.3)
Hepatic dysfunction	2 (1.5)	2 (1.5)
Leukopenia	1 (0.7)	0
Thrombocytopenia	0	1 (0.8)
Rash	3 (2.2)	0
Fatigue	0	1 (0.8)
Facial flushing	1 (0.7)	0
Hypertension	2 (1.5)	0

( ): %

Leukopenia occurred in a 58-year-old female patient with a WBC of 4,000/mm^3 before administration. The WBC decreased to 3,300/mm^3 during the 4th week of ticlopidine therapy and administration was immediately discontinued. The WBC recovered to 4,000/mm^3 after 4 weeks of follow-up, so ticlopidine therapy was resumed. The WBC did not change thereafter and administration was continued.

Thrombocytopenia occurred in a 63-year-old male patient with a platelet count of 27.6×10^4/mm^3 before administration. During the 4th week after the start of coadministration of ticlopidine and aspirin, the platelet count decreased to 4.9×10^4/mm^3, and ticlopidine administration was immediately discontinued. The patient was followed up and the platelet count recovered to 11.9×10^4/mm^3 at 8 weeks after the discontinuation of ticlopidine therapy. Neither this patient nor any of the other patients developed thrombotic thrombocytopenic purpura.

Discussion

In this study, the recurrence of cerebrovascular events and the occurrence of myocardial infarction and other vascular events were assessed as a combined endpoint. Fourteen patients (10.1%) of the TIC group and 13 patients (9.9%) of the TIC+ASA group reached the endpoint, with no significant difference being seen between the two groups (p=0.935). Kaplan-Meier analysis of the event reduction rate (i.e., the decrease in the occurrence of cerebral infarction, TIA, myocardial infarction, cerebral hemorrhage, and other vascular events) revealed no significant difference between the two groups (p=0.5003, log-rank test). Comparison of the annual incidence of events showed that it was 5.7/100 person-years in the TIC group and 7.1/100 person-years in the TIC+ASA group. The type of events that occurred generally showed a similar pattern in both groups. However, despite the fact that there was no significant difference in the annual incidence of vascular events, it was noteworthy that cerebral hemorrhage occurred only in the TIC+ASA group.

Cerebral hemorrhage occurred in 2 men aged 82 and 68 years with a history of cerebral infarction. The 82-year-old patient also had a history of severe hypertension, which had been well controlled. Moderate bleeding into the right putamen was observed at 2 years and 7 months after the start of combination therapy, and administration was discontinued. There was a possibility that this therapy led to enlargement of the hematoma. The 68-year-old patient did not have

hypertension and was followed up on combined therapy for 1 year and 6 months. Thereafter, he did not return to hospital for review. It was confirmed by telephone that cerebral hemorrhage had occurred one month later and he had been admitted to another hospital. According to his family, the patient had hemiplegia caused by a major cerebral hemorrhage. Uchiyama and colleagues (14) also reported that hemorrhagic complications were more frequent among patients receiving aspirin plus ticlopidine compared with those receiving aspirin alone or ticlopidine alone.

The serious adverse reactions noted in our study consisted of leukopenia in 1 patient from the TIC group, as well as gastric ulcer, nausea, and thrombocytopenia in 1 patient each from the TIC+ASA group. Among the serious adverse reactions experienced by patients receiving combined therapy, it seems likely that gastric ulcer and nausea were associated with administration of aspirin, while leukopenia and thrombocytopenia were associated with administration of ticlopidine.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial (CURE) (15) was a randomized comparative study of the prevention of recurrent events by aspirin monotherapy or combined therapy with aspirin and clopidogrel (another thienopyridine) in 12,500 patients with acute coronary syndrome and no ST elevation. The relative risk of recurrent events was significantly lower in the combination therapy group (reduced by 20%). There were significantly more patients with major bleeding in the combination therapy group than in the monotherapy group, but there was no significant difference in episodes of life-threatening bleeding or hemorrhagic stroke (15). Since the subjects of that study had coronary artery diseases, the results cannot be directly compared with data on the efficacy and safety of combined therapy for patients with cerebral infarction (16). However, bleeding complications caused by antithrombotic therapy tend to be more common in patients with cerebrovascular disease than in those with heart disease (17). In the present study, it is particularly noteworthy that no cerebral hemorrhage occurred in the TIC group, while it occurred in two patients from the TIC+ASA group. In conclusion, the present comparison of the preventive effect of ticlopidine alone (200 mg/day) with that of aspirin (81 mg/day) plus ticlopidine (100 mg/day) on vascular events (stroke, TIA, myocardial infarction, and other vascular events) in patients with cerebral infarction or TIA showed no difference between the two treatment strategies with respect to the event rate. However, the present study population was rather small, so further exploration of this issue by a large-scale clinical study is necessary. In this context, the Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) (18) study is currently in progress. MATCH has enrolled 7,600 patients with a high risk of cerebral infarction or TIA and complications such as previous myocardial infarction, and it aims to compare subsequent stroke and other important vascular events between clopidogrel monotherapy and combined therapy with clopidogrel and aspirin. The results of MATCH will provide further information on the efficacy and safety of combination therapy with a thienopyridine and aspirin.

Appendix

This study was performed with the cooperation of the doctors and staff of the following hospitals: Chukyo Social Insurance Hospital (S. Riku), Tsushima Municipal Hospital (K. Takatsuki), Suzuka Central General Hospital (M. Katou, S. Nakayama), First Nagoya Red Cross Hospital (H. Watanabe), Enshu General Hospital (K. Nokura), Higashi Nagoya National Sanatorium Hospital (S. Okuda), Nagai Hospital (M. Kawanishi), Meitetsu Hospital (S. Miyao), Shinshiro Municipal Hospital (F. Sofue), Anjo Kosei Hospital (M. Hashizume), Tosei General Hospital (M. Uchida), Jyosei Municipal Hospital (S. Takagi), Kasugai Municipal Hospital (T. Indou), Nagoya National Hospital (A. Takeda), Higashi Municipal Hospital of Nagoya City (T. Usui), Moriyama Municipal Hospital (S. Shibata), Nagoya Ekisaikai Hospital (C. Mabuchi), Matuzaka Municipal Hospital (M. Matsuyama), Okada Clinic (T. Okada), Chubu Rosai Hospital (T. Sakakibara), Toki General Hospital (N. Takahashi), Fujita University Hospital (H. Yamamoto), Second Nagoya Red Cross Hospital (T. Yanagi), Teramoto Neurology Clinic (J. Teramoto), and Kawamura Hospital (Y. Kawamura).

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Articles

Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial

*Executive Steering Committee on behalf of the SPORTIF III Investigators**

Summary

Background Warfarin prevents ischaemic stroke in patients with non-valvular atrial fibrillation, but dose adjustment, coagulation monitoring, and bleeding risk limit its use. The oral direct thrombin inhibitor ximelagatran represents a potential alternative. We aimed to establish whether ximelagatran is non-inferior to warfarin, within a margin of 2% per year, for prevention of stroke and systemic embolism.

Methods We randomised 3410 patients with atrial fibrillation and one or more stroke risk factors to open-label warfarin (adjusted-dose, international normalised ratio [INR] 2·0–3·0) or ximelagatran (fixed-dose, 36 mg twice daily); patients were recruited from 259 hospitals, doctor's offices, or health-care clinics. Primary analysis was based on masked event assessment and was by intention to treat. Primary endpoint was stroke or systemic embolism.

Findings During 4941 patient-years of exposure (mean 17·4 months, SD 4·1), 96 patients had primary events (56 in the warfarin group *vs* 40 in the ximelagatran group). The primary event rate by intention to treat was 2·3% per year with warfarin and 1·6% per year with ximelagatran (absolute risk reduction 0·7% [95% CI −0·1 to 1·4], p=0·10; relative risk reduction 29% [95% CI −6·5 to 52]). Rates of disabling or fatal stroke, mortality, and major bleeding were similar between groups, but combined minor and major haemorrhages were lower with ximelagatran than with warfarin (29·8% *vs* 25·8% per year; relative risk reduction 14% [4 to 22]; p=0·007). Raised serum alanine aminotransferase was more common with ximelagatran.

Interpretation In high-risk patients with atrial fibrillation, fixed-dose oral ximelagatran was at least as effective as well-controlled warfarin for prevention of stroke and systemic embolism.

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Introduction

Non-valvular atrial fibrillation carries a substantial risk of ischaemic stroke and systemic embolism.[1] Results of several randomised trials have shown that adjusted-dose warfarin provides highly effective prophylaxis,[2] reducing stroke by 62% compared with placebo in a meta-analysis. Benefit is tempered, however, by a 7–10-fold increase in intracranial haemorrhage, particularly in elderly patients.[2–4] Interactions of vitamin K antagonists with food, drugs,[7] and other factors require dose adjustments and regular monitoring of anticoagulation. Expense and inconvenience[8–10] associated with this unpredictability contribute to under-treatment of patients with atrial fibrillation at high risk for stroke,[11,12] creating a need for easily administered safe alternatives.

Ximelagatran is an oral direct thrombin inhibitor under investigation as an anticoagulant for prevention and treatment of thromboembolism.[13] Its pharmacokinetic profile is predictable and stable over time,[14,15] and unaffected by bodyweight, age, sex, or ethnic origin.[15–17] With a rapid onset of action and metabolism independent of the hepatic cytochrome P450 enzyme system, ximelagatran has a low potential for drug interactions and no known food interactions,[14,15,18] making coagulation monitoring and dose adjustments unnecessary.[15–17]

In this report, we describe the main results of SPORTIF III (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation), one of two long-term phase III studies comparing safety and efficacy of ximelagatran with warfarin in patients with atrial fibrillation at risk for ischaemic stroke.[19]

Methods

The rationale and design of SPORTIF III have been described.[19] In brief, this study was a randomised, multicentre, open-label, parallel-group trial comparing oral ximelagatran with adjusted-dose warfarin for prevention of stroke and systemic embolism in high-risk patients with atrial fibrillation.

Administrative organisation

The Executive Steering Committee developed the protocol and oversaw all aspects of study implementation, while masked to treatment outcomes, and prepared results for publication with unrestricted access to data. The sponsor supported the work of the Committee, providing two of eight voting members. An independent data safety monitoring board oversaw treatment safety.

Patients

Between August, 2000, and September, 2001, high-risk patients were enrolled at 259 hospitals, doctor's offices, or health-care clinics in 23 countries in Europe, Asia, and Australasia. Criteria for inclusion, summarised in panel 1, were based on present clinical indications for anticoagulant treatment.[5] Signed informed consent was

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Panel 1: Principle inclusion and exclusion criteria

Inclusion criteria

1 Age 18 years or older
2 Persistent or paroxysmal non-valvular atrial fibrillation verified by at least two electrocardiogram recordings, one of which was made within 2 weeks before randomisation
3 One or more of the following risk factors for stroke:
- Hypertension (raised blood pressure needing antihypertensive treatment but <180/100 mm Hg)
- Age 75 years or older
- Previous stroke, transient ischaemic attack, or systemic embolism
- Left ventricular dysfunction (left-ventricular ejection fraction <40% or symptomatic congestive heart failure)
- Age 65 years or older and coronary artery disease
- Age 65 years or older and diabetes mellitus

Exclusion criteria

1 Mitral stenosis or previous valvular heart surgery
2 Transient atrial fibrillation caused by reversible disorders
3 Stroke within the previous 30 days or transient ischaemic attack within 3 days
4 Conditions associated with increased risk of bleeding:
- History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding
- Overt gastrointestinal bleed in the previous year
- Endoscopically verified ulcer disease in the previous 30 days
- Major surgical procedure or trauma in the previous 30 days
- Persistent blood pressure 180/100 mm Hg or greater with or without antihypertensive treatment
- Haemorrhagic disorder

5 Active infective endocarditis
6 Current atrial myxoma or left ventricular thrombus
7 Admission for acute coronary syndrome or percutaneous coronary intervention within 30 days
8 Requirement for chronic anticoagulant treatment for disorders other than atrial fibrillation
9 Planned cardioversion
10 Planned major surgery
11 Treatment with platelet-inhibitor drugs, other than aspirin 100 mg/day or less, within 10 days, or with fibrinolytic agents within 30 days before randomisation
12 Regular use of non-steroidal anti-inflammatory drugs
13 Renal insufficiency (calculated creatinine clearance <30 mL/min)
14 Active liver disease or persistent elevation of liver enzymes two or more times the upper limit of normal
15 Childbearing potential, pregnancy, or lactation
16 Drug addiction, alcohol abuse, or both
17 Anaemia (haemoglobin <100 g/L or platelet count $<100\times10^9$/L)

required from every participant according to a protocol approved by local ethics committees and in accordance with the Declaration of Helsinki.

Treatment allocation

Patients were randomised to either treatment with a fixed dose of ximelagatran (36 mg twice daily) or warfarin dose-adjusted to maintain the international normalised ratio (INR) between 2·0 and 3·0. Treatment was allocated with a masked, interactive voice-response system according to an adaptive algorithm balanced by country, aspirin treatment at entry, and history of stroke or transient ischaemic attack. Anticoagulants were administered in an open-label fashion. For patients randomised to warfarin, doses were titrated according to local clinical practice based on INR measurements done at least every 31 days. Concomitant treatment with aspirin was permitted in doses up to 100 mg daily, but other antithrombotic drugs were prohibited.

Endpoints and assessments

The primary objective was to compare the efficacy of ximelagatran with that of warfarin for prevention of all stroke (ischaemic or haemorrhagic) and systemic embolic events. Secondary endpoints included composites of (1) major and minor bleeding; (2) treatment discontinuation; (3) ischaemic stroke, transient ischaemic attack, and systemic embolism; and (4) death, stroke, systemic embolism, and acute myocardial infarction. Stroke was defined as abrupt onset of a focal neurological deficit in the distribution of a brain artery persisting more than 24 h or due to intracerebral haemorrhage. When the neurological deficit lasted less than 24 h, the event was classified as a transient ischaemic attack. Fatal stroke was defined as death from any cause within 30 days of stroke. Systemic embolism was defined as abrupt vascular insufficiency associated with clinical and radiological evidence of arterial occlusion in the absence of another probable mechanism. In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism needed angiographic demonstration of acute arterial occlusion.

The medical history, findings on physical examination, and results of a standard 12-lead electrocardiogram were recorded for every participant at baseline. After randomisation, patients were seen at 1, 4, and 6 weeks, then at 2, 3, 4, 5, 6, 8, 10, and 12 months, and every 3 months thereafter. Primary event detection was enhanced by administration of a standard stroke-symptom questionnaire; positive responses prompted additional evaluation. Local study-affiliated neurologists or stroke specialists, masked to treatment, assessed all possible primary events and transient ischaemic attacks as early after onset as feasible, based on clinical findings and results of CT or MRI of the brain. An independent, masked, Central Event Adjudication Committee then reviewed the reports. Severity of stroke was assessed 3 months after the event, according to the modified Rankin scale[20] and Barthel index of activities of daily living.[21] Bleeding was categorised as major when

Panel 2: Classification of haemorrhagic events

Major bleeding

- Fatal bleeding
- Clinically overt bleeding associated with a reduction in haemoglobin 20 g/L or greater
- Clinically overt blood loss needing transfusion 2 U or more of whole blood or erythrocytes
- Bleeding involving critical anatomical sites
  - Intracranial haemorrhage*
  - Intraspinal haemorrhage
  - Intraocular haemorrhage
  - Retroperitoneal haemorrhage
  - Pericardial haemorrhage
  - Atraumatic intra-articular haemorrhage

Minor bleeding

- Other bleeding, including that causing treatment cessation

*Included in primary analysis as haemorrhagic stroke.

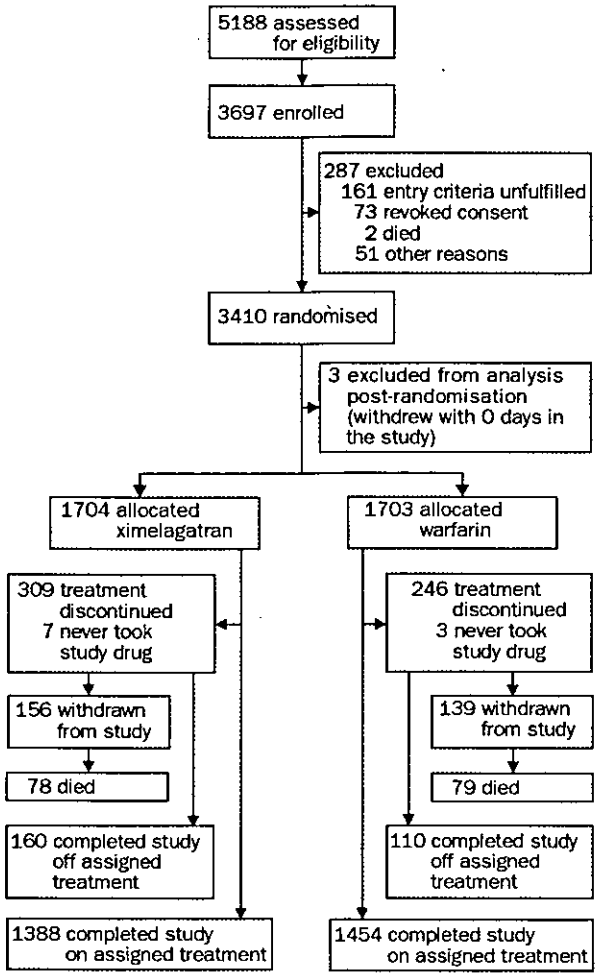


Figure 1: **Trial profile**

associated with a functional deficit, haemoglobin fell by 20 g/L, transfusion was administered, or an important anatomical site was involved (panel 2). All clinically overt bleeding that did not satisfy criteria for major haemorrhage was classified as minor.

Blood chemistry, haematology, urinary erythrocytes, faecal haemoglobin, and serum concentrations of hepatic transaminases, alkaline phosphatase, and bilirubin were measured monthly for the first 6 months and every 2 months during year 1, and every 3 months thereafter. By October, 2001, after more than 10 000 patients had been exposed to ximelagatran in clinical trials involving various thromboembolic disease states, increases in liver enzymes were noted in 5–6% of patients, usually within 2–6 months after starting treatment. These changes were typically reversible, whether or not treatment was stopped, and not associated with symptoms. To assure the safety of trial participants, the protocol was amended to provide additional surveillance of liver function. When any of these laboratory values increased beyond three times the upper limit of normal, testing once a week was done until values returned to baseline or normal concentrations, or an alternative cause of the abnormalities was found. Study treatment was stopped if indices of liver function rose above five times the upper limit of normal, if a rise between three and five times the upper limit of normal persisted for 8 weeks, or if clinical signs of hepatotoxicity developed.

Statistical analyses

The primary analysis compared treatment efficacy for the first occurrence of any stroke or systemic embolic event among all randomised patients according to intention to treat. The objective was to establish whether ximelagatran was non-inferior[22] to warfarin within a prespecified absolute margin (Δ) of 2% per year for the difference in rates of primary events.[19,23] The proportion of all patients having primary events and the associated one-sided 97·5% CI for the difference between treatment groups was estimated with the time to first event, assuming a constant event rate. A confirmatory efficacy analysis included the same endpoints but was done as randomised with an on-treatment approach. This approach included the same number of patients as the intention-to-treat analysis, but duration of exposure was censored from the 31st consecutive day or 61st cumulative day off study drug. Patients were analysed as treated for adverse events.

To obtain at least 90% power, the protocol mandated a minimum per-patient exposure of 12 months, more than 4000 patient-years of follow-up in aggregate, and accumulation of at least 80 primary events.[19] All patients were included in the intention-to-treat analysis, irrespective of whether study treatment was continued or prematurely stopped. Patients in whom follow-up was incomplete were included in the intention-to-treat analyses, with exposure truncated at the time of study withdrawl. Interim analyses were scheduled at 12·5%, 25%, 50%, and 75% of total exposure; actual percentages differed slightly. A predefined group-sequential stopping rule was applied only for negative trends along prespecified safety parameters. The study was not stopped early and reached a planned termination.

All patients were followed up for occurrences of primary events and mortality until study closure. All remaining endpoints were recorded during the on-treatment period. Hence, unless otherwise stated, composite endpoints confined to stroke, systemic embolic event, and death were analysed according to intention to treat, and assessments of all other endpoints, composite endpoints, and exploratory analyses used the on-treatment approach. The proportions of patients in each treatment group having major and minor bleeding were calculated, accounting for length of individual exposure. All other adverse events and laboratory variables were summarised with descriptive statistics. No patient was counted more than once for a given composite endpoint.

Role of the funding source

AstraZeneca employed five members of the Executive Steering Committee (L Frison, M Grind, J Horrow, M Nevinson, and S Partridge), who provided input into the study through membership of the Committee and of whom two were voting members (see Contributors), and paid expenses to the other members.

Results

Patients and follow-up

The outcome of all participants over the course of the trial is shown in figure 1. Of the 3410 randomised patients, three withdrew by their baseline visit and never received study drug. These were excluded from all analyses; hence the study population consisted of 3407 patients and subsequent references to all patients in the trial refer to this cohort. Five patients in each treatment group did not have the qualifying additional risk factors. Three of these patients terminated study drug within 1 month and seven continued assigned treatment; one in the ximelagatran group developed a secondary endpoint event (myocardial

	Ximelagatran (n=1704)	Warfarin (n=1703)
Characteristic		
Men	1158 (68%)	1196 (70%)
Age (years, mean [SD])	70·3 (8·6)	70·1 (8·6)
Bodyweight (kg, mean [SD])	80·7 (16·8)	81·7 (16·9)
Ethnic origin		
White	1494 (88%)	1500 (88%)
Asian	201 (12%)	196 (12%)
Other	9 (1%)	7 (1%)
Aspirin at entry	345 (20%)	359 (21%)
Vitamin K antagonist at entry	1267 (74%)	1235 (73%)
Systolic blood pressure (mm Hg, mean [SD])	139 (18)	139 (18)
Atrial fibrillation onset less than 1 year	368 (22%)	347 (20%)
Paroxysmal atrial fibrillation	160 (9%)	124 (7%)
Risk factors		
One*	511 (30%)	545 (32%)
Two	614 (36%)	579 (34%)
Three or more	579 (34%)	579 (34%)
Previous stroke, TIA, or both	417 (24%)	405 (24%)
Previous non-CNS embolism	74 (4%)	77 (5%)
Age 75 years or older	581 (34%)	565 (33%)
Hypertension	1229 (72%)	1230 (72%)
Left ventricular dysfunction	574 (34%)	584 (34%)
Age 65 years or older and coronary artery disease	581 (34%)	558 (33%)
Age 65 years or older and diabetes mellitus	288 (17%)	290 (17%)

Data are number of patients (%) unless otherwise stated. TIA=transient ischaemic attack. *Includes five patients in each group incorrectly randomised without risk factors.

Table 1: **Characteristics of randomised patients**

infarction); all were included in the analyses. Three patients assigned to warfarin and seven assigned to ximelagatran took no study drug, and one patient randomised to the warfarin group erroneously received ximelagatran instead, but no endpoint events arose in these patients.

Clinical characteristics of randomised patients are summarised in table 1. Key demographic features were evenly distributed between treatment groups and were similar to cohorts of patients with atrial fibrillation enrolled in previous trials showing the superiority of warfarin over placebo for prevention of stroke and systemic embolism.[24–27] Randomised patients were predominantly white men (mean age 70 years [SD 9]). Duration of atrial fibrillation was 1 year or more in 2679 (79%) patients; dysrhythmia was persistent in 3123 (92%) cases. A history of stroke or transient ischaemic attack was present in 822 (24%) participants, hypertension in 2459 (72%), and left-ventricular dysfunction in 1158 (34%). 2345 (69%) patients in the cohort had more than one additional risk factor for thromboembolism. Before entry, 2501 (73%) were receiving anticoagulant drugs, and 704 (21%) were taking aspirin. 337 patients assigned to ximelagatran (20%) and 290 taking warfarin (17%) also took aspirin at some point during the trial (p=0·042). Aspirin was used concurrently for at least half the period on study drug by 222 patients assigned to ximelagatran (13%) and 173 (10%) on warfarin (p=0·010).

In patients assigned to warfarin, the mean INR was 2·5 (SE 0·7) across all measurements over the course of the study. Values were within the therapeutic range of 2·0–3·0 for 66% of the entire follow-up period and within the extended range of 1·8–3·2 for 81%. In patients assigned to ximelagatran, adherence estimated by pill counts was 94%.

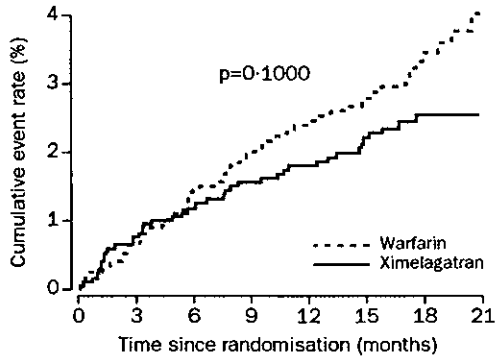
Patients' follow-up was completed by the end of September, 2002, after accumulation of 4941 patient-years at risk. Mean duration of follow-up was 17·4 months (SD 4·1). 138 patients (4%) were withdrawn from the study for reasons other than death and their follow-up was thus truncated for the analyses presented in this report. Attempts to ascertain vital status on all patients with incomplete follow-up resulted in subsequent contact with all but 25 of 78 such patients assigned to ximelagatran (seven of whom had died) and all but 20 of the 60 such patients in the warfarin group (three of whom had died). Mean follow-up while taking assigned treatment was 16·3 months (SD 4·8) for the warfarin group and 15·8 months (5·7) in the ximelagatran group. Premature termination of study treatment happened in 246 (14%) patients in the warfarin group and 309 (18%) in the ximelagatran group (p=0·003). This occurrence was the result of study endpoints in 61 (4%) patients in the warfarin group and 52 (3%) in the ximelagatran group. 61 patients (4%) stopped warfarin because of adverse events compared with 132 (8%) on ximelagatran; this difference was mainly related to elevation of serum concentrations of transaminases in some patients treated with ximelagatran.

Outcomes analysis

Treatment efficacy

56 patients had primary events in the warfarin group during 2440 patient-years at risk, a yearly rate of 2·3%. 40 patients had events in the ximelagatran group during 2446 patient-years, a yearly rate of 1·6%. Absolute risk reduction was 0·7% per year (95% CI −0·1 to 1·4; p=0·1000) and relative risk reduction 29% (95% CI −6·5 to 52). Figure 2 shows the cumulative proportions of patients having primary endpoints over 24 months according to intention to treat.

By intention to treat, all-cause mortality was 79 patients in the warfarin-assigned group (3·2% per year) and 78 patients in the ximelagatran group (3·2% per year). 33 vascular deaths occurred in patients assigned to warfarin and 40 in those on ximelagatran (p=0·478). Nine fatal strokes happened in the warfarin group and ten in the ximelagatran group. Non-fatal disabling stroke (modified Rankin severity score ≥3 or Barthel function index <60) occurred in eight patients in the warfarin group and five in the ximelagatran group. In patients assigned to warfarin, 67 cases of ischaemic stroke, transient ischaemic stroke, or systemic embolism arose (a composite rate of 2·9% per year) compared with 48 in patients assigned to ximelagatran (2·1% per year), an absolute risk reduction with ximelagatran of 0·8% per year (95% CI −0·2 to 1·7; p=0·1086). INRs at the time of these events were below



Patients at risk

Warfarin	1703	1633	1576	864	318
Ximelagatran	1704	1630	1575	865	358

Figure 2: **Cumulative rate of primary events (all stroke and systemic thromboembolism) according to assigned treatment and intention to treat**

	Number of patients (event rates [% per patient-year])		Difference (95% CI)	p
	Ximelagatran (n=1704)	Warfarin (n=1703)		
Primary events (ITT)	40 (1·6%)	56 (2·3%)	−0·7% (−1·4 to 0·1)	0·1000
Ischaemic stroke	32 (1·3%)	46 (1·9%)	..	..
Haemorrhagic stroke	4 (0·2%)	9 (0·4%)*	..	..
Systemic embolism	4 (0·2%)	2 (0·1%)	..	..
Primary events (OT)	29 (1·3%)	52 (2·2%)	−0·9% (−1·7 to −0·2)	0·0180
Primary event or death (ITT)	103 (4·2%)	124 (5·1%)	−0·9% (−2·1 to 0·3)	0·1538
Mortality†	78 (3·2%)	79 (3·2%)	..	..
Fatal stroke or fatal systemic embolism	12 (0·5%)	9 (0·4%)	..	..
Fatal stroke	10 (0·4%)	9 (0·4%)	..	..
Fatal haemorrhagic stroke	3 (0·2%)	5 (0·3%)	..	..
Fatal or disabling stroke‡	15 (0·6%)	16 (0·7%)	−0·0% (−0·5 to 0·4)	1·0
Non-fatal disabling stroke	5 (0·2%)	8 (0·3%)	..	..
Transient ischaemic attack§	23 (1·0%)	23 (1·0%)	..	..
Myocardial infarction	24 (1·1%)	13 (0·6%)	..	..
Composite of mortality, stroke, systemic embolism, and myocardial infarction (OT)	96 (4·2%)	116 (4·9%)	−0·7% (−1·9 to 0·5)	0·2606
Composite of ischaemic stroke, systemic embolism, and transient ischaemic attack (OT)	48 (2·1%)	67 (2·9%)	−0·8% (−1·7 to 0·2)	0·1086
Major bleeding (OT)	29 (1·3%)	41 (1·8%)	−0·5% (−1·2 to 0·2)	0·2281
Major or minor bleeding (OT)¶	478 (25·8%)	547 (29·8%)	−4·0% (−6·9 to −1·1)	0·0065

Differences were not calculated for endpoints that were not among the prespecified objectives. No patient was counted more than once for each composite endpoint. ITT=intention-to-treat analysis. OT=on-treatment analysis. *One patient had both initial ischaemic and subsequent haemorrhagic strokes. †Ten additional deaths, seven from the ximelagatran group and three from the warfarin group, were reported in patients who had already terminated the study. They are not accounted for in any analyses. ‡Strokes followed by death within 30 days or resulting in functional disability (modified Rankin score ≥3 or a decrease in the Barthel index <60 at 3 months after stroke), §Rates given refer to those in patients without primary events. ¶Not all deaths associated with bleeding met criteria for major bleeding.

Table 2: **Rates of primary and secondary events according to assigned treatment**

2·0 in 17 (25%) warfarin-treated patients. No difference was recorded in rates of the composite endpoint of death, stroke, systemic embolism, and definite myocardial infarction (table 2, figure 3). Of the 822 patients with stroke or transient ischaemic attack before entry, rates of primary events were 5·1% per year on warfarin and 3·8% per year on ximelagatran (p=0·313). For primary prevention, the corresponding figures were 1·5% per year for warfarin and 1·0% per year for ximelagatran (p=0·1816).

By on-treatment analysis of the primary endpoint cluster (all stroke and systemic embolic events), 52 patients had events during 2352 patient-years at risk in the warfarin group, an average rate of 2·2% per year. 29 patients had during 2286 patient-years in the ximelagatran group, an average rate of 1·3% per year. The absolute risk reduction was 0·9% per year (0·2 to 1·7; p=0·0180) with ximelagatran and the relative risk reduction was 43% (10 to 63).

Haemorrhage

Haemorrhagic stroke occurred in nine patients (0·4% per year) in the warfarin group and four (0·2% per year) in the ximelagatran group (p=0·266; table 2), which proved fatal in five and three patients, respectively. Major haemorrhagic events other than stroke occurred in 41 patients in the warfarin group (1·8% per year), of whom 44% had an INR greater than 3·0, and treatment was permanently stopped in 15 of these patients. 29 participants receiving ximelagatran had major bleeding (1·3% per year), and 17 of these stopped treatment (p=0·228). Of these patients with major bleeds, other than haemorrhagic stroke, three were fatal (one of 29 assigned to ximelagatran *vs* two of 41 assigned to warfarin). Major bleeding most often involved the gastrointestinal tract (15 patients in each group), subdural haematoma (four in the warfarin group *vs* six in the ximelagatran group), or intra-ocular bleeding (four in the warfarin group *vs* three in the ximelagatran group). Pericardial, retroperitoneal, articular, or spinal bleeding was noted only in warfarin-treated patients. When minor and major haemorrhages were counted, significantly more bleeding was reported in patients randomised to warfarin (n=547, 29·8% per year) than in those assigned to ximelagatran (n=478, 25·8% per year; relative risk reduction 14% [95% CI 4 to 22]; p=0·0065). Of the 627 patients (18%) taking aspirin (≤100 mg/day) concurrently with assigned treatment at any point during the trial, overall rates of bleeding (major and minor) were significantly higher (35·5% with ximelagatran *vs* 52·1% with warfarin) than in those who did not take aspirin (23·7% with ximelagatran *vs* 26·3% with warfarin).

Adverse events

Adverse events arose in 1452 (85%) patients randomised to warfarin and 1472 (87%) assigned to ximelagatran (p=0·228; table 3). Concentration in serum of alanine aminotransferase rose above three times the upper limit of normal in 14 (1%) patients in the warfarin group and 107 (6%) in the ximelagatran group (p<0·0001). Rises in ximelagatran-treated patients typically took place between 2 and 6 months after initiation of treatment and returned

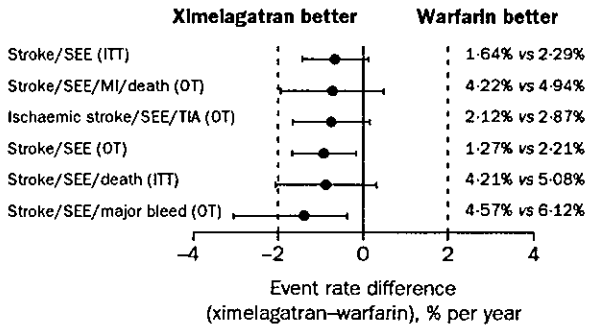


Figure 3: **Event rate comparisons for various composite endpoints and sensitivity analyses.**

ITT=intention-to-treat analysis. MI=myocardial infarction. OT=on-treatment analysis. SEE=systemic embolic event. TIA=transient ischaemic attack. Comparisons are presented first for the primary objective, followed by the two secondary objectives, two prespecified sensitivity analyses for the primary endpoint, and an explanatory post-hoc analysis.

	Ximelagatran (n=1704)	Warfarin (n=1703)
Adverse event		
Respiratory infection	312 (18%)	306 (18%)
Epistaxis*	117 (7%)	197 (12%)
Accident, injury, or both	147 (9%)	164 (10%)
Back pain	139 (8%)	144 (8%)
Dizziness	130 (8%)	152 (9%)
Dyspnoea	114 (7%)	149 (9%)
Purpura	120 (7%)	130 (8%)
Pain	113 (7%)	123 (7%)
Headache	113 (7%)	110 (6%)
Diarrhoea	112 (7%)	106 (6%)
Coughing	105 (6%)	100 (6%)
Chest pain	99 (6%)	104 (6%)
Oedema	94 (6%)	109 (6%)
Bronchitis	95 (6%)	102 (6%)

Adverse events shown occurred in 5% or more of the study population. *Also included in table 2 as minor bleeding.

Table 3: **Adverse events (%)* among patients in each treatment group**

towards baseline without clinical sequelae either spontaneously (n=59) or after cessation of treatment (n=48). Elevations reached greater than five times the upper limit of normal in 57 patients assigned to ximelagatran (3·4%). Four patients developed jaundice for which a possible alternative cause was identified. One had fatal gastric carcinoma with hepatic metastases. Another with hepatitis B and choledocholithiasis recovered following stone removal and resumed ximelagatran without further incident. A third with diabetes mellitus and cholelithiasis developed hyperbilirubinaemia during concurrent treatment with flucloxacillin; liver function returned to normal after both drugs were stopped and ximelagatran was then resumed uneventfully to the end of the study. The fourth developed a focal neurological deficit 5 days after beginning treatment with ximelagatran, but CT of the brain did not show acute infarction. Hyperbilirubinaemia developed 22 days after warfarin was substituted for ximelagatran and abdominal ultrasound imaging showed gallstones. Although the patient recovered, ximelagatran was not resumed. Of the 121 patients who had an increase in alanine aminotransferase concentrations three times above the upper limit of normal, 52 discontinued study drug prematurely, 48 in the ximelagatran group and four in the warfarin group. 59 patients in the ximelagatran group continued treatment with raised serum concentrations of alanine aminotransferase. 55 of these returned to normal, three returned to less than twice the upper limit of normal, and one in whom the amount of alanine aminotransferase was greater than twice the upper limit of normal before the study remained at this value. Of the 48 patients in the ximelagatran group with increased amounts of alanine aminotransferase who stopped treatment, 42 returned to normal, four returned to less than twice the upper limit of normal, and two died of unrelated diseases.

The net clinical benefit (post-hoc analysis) of treatment with ximelagatran compared with warfarin was assessed by calculating the combined rates of deaths, primary events, and major bleeding during the time on treatment; 143 such events arose with warfarin (6·1% per year) and 104 occurred with ximelagatran (4·6% per year; relative risk reduction 25% [95% CI 4 to 42]; p=0·019).

Discussion

In this study, we have established efficacy of the oral direct thrombin inhibitor ximelagatran in a fixed dose compared with well-controlled warfarin for prevention of stroke and systemic embolism in high-risk patients with atrial fibrillation. Furthermore, although anticoagulation intensity was not monitored or regulated in patients assigned to ximelagatran, these patients had less bleeding than those assigned to warfarin and carefully adjusted according to contemporary treatment standards. These findings set ximelagatran apart as a new oral anticoagulant drug since vitamin K antagonists were introduced more than half a century ago, representing a distinct innovation in long-term anticoagulant treatment.

Thrombin has a central role in thrombogenesis, cleaving fibrinogen to form fibrin and activating platelets and several coagulation factors. Although other anticoagulant drugs—such as warfarin and heparin—ultimately result in inhibition of thrombin, most do so by indirect mechanisms. Oral ximelagatran is bioconverted to melagatran, a direct inhibitor of soluble and fibrin-bound thrombin. The anticoagulant efficacy of ximelagatran compares favourably with warfarin and dalteparin for prevention and treatment of venous thromboembolism.[28] Ximelagatran has not been associated with clinically relevant pharmacokinetic food interactions and has low potential for drug interactions based on the cytochrome P450 enzyme system,[14,15,18] potentially simplifying long-term clinical use.

This study was designed to ensure that recruited patients would be representative of those generally seen in clinical practice, and eligibility for anticoagulation was based on prevailing practice guidelines.[4,5] Clinical characteristics pertinent to thromboembolism and bleeding risks were well balanced between treatment groups. Even so, the rate of all strokes and systemic embolism in patients assigned to warfarin was lower than the rate in placebo-controlled trials of cohorts at comparable risk.[2] One reason for this lower rate might be that the intensity of warfarin anticoagulation was assiduously maintained, with INR values falling within the target range for 66% of the entire duration of exposure, a rate much better than generally achieved in previous trials or in routine clinical practice.[2] Patients were taking a median of seven concomitant prescribed drugs, including antihypertensive drugs, angiotensin-converting-enzyme inhibitors, angiotensin-II antagonists, and lipid-lowering agents; hence, well-controlled blood pressure and lipid values could also have contributed to the low event rate.

In these high-risk patients with atrial fibrillation, ximelagatran administered in a fixed dose of 36 mg twice daily proved at least as effective as well-controlled warfarin for prevention of stroke and systemic embolism (primary events) when judged on the basis of intention to treat. The effectiveness against thromboembolism was associated with substantially reduced overall risk of bleeding compared with warfarin. Efficacy of ximelagatran was consistent across predefined subgroups of patients, irrespective of independent established stroke risk factors. Since patients with calculated creatinine clearance less than 30 mL/min were not eligible to participate, additional studies will be needed to assess safety and efficacy of ximelagatran treatment in patients with impaired renal function.

Among the other observations was development of raised serum concentrations of transaminases in some patients exposed to ximelagatran—alanine aminotransferase exceeded three times the upper limit of normal in 6·3% of patients. The mechanism of this reaction remains undetermined despite extensive investigation, but similar abnormalities in other trials[13,29] indicate a need to monitor liver function for several months after initiation of treatment with ximelagatran. Although the net clinical benefit of treatment with anticoagulant drugs can be assessed in several ways, survival free of both primary

events and major bleeding was longer with ximelagatran than with warfarin in our post-hoc analysis.

An important limitation of the study design was the possibility of bias resulting from open-label treatment, but the number of patients withdrawing from the study for reasons other than death before the end of study was small (138; 4·1%), and the rate of early permanent discontinuation of study drug was lower than reported in studies of warfarin for this indication.[30] The primary endpoint was objectively confirmed in every case and clinically robust, and the system for masked local and central validation of all suspected outcome events provided a consistent assessment, enhancing the credibility of the efficacy findings.

We have shown that ximelagatran, administered in a fixed dose without coagulation monitoring, protects high-risk patients with atrial fibrillation against thromboembolism at least as effectively as well-controlled warfarin, and is associated with less bleeding. The continuing SPORTIF V trial will provide additional estimates of efficacy and safety in a similar population.

Contributors

The authors of this paper are the members of the SPORTIF Executive Steering Committee, all of whom contributed to and approved the text. Those members who were employed by the sponsor during the course of the trial are indicated. All other members served as consultants and received payments from the sponsor to attend meetings related to the trial, and for travel expenses, speaking engagements or research.

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Conflict of interest statement

G W Albers, H C Diener, J L Halperin, S B Olsson, P Petersen, and A Vahanian have served as consultants and received payments from AstraZeneca to attend meetings related to the trial, and for travel expenses, speaking engagements or research. L Frison, M Grind, J Horrow, M Nevinson, and S Partridge are employees of AstraZeneca.

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≪肥満を背景としうる関連疾患とその治療≫
肥満と脳虚血

内山真一郎*

はじめに●

肥満は心血管疾患の潜在因子になっていると考えられ，とくに脳血管障害の発症リスクとして最近注目されている．肥満は加齢とともに増加し，高血圧，糖尿病，高脂血症に関連するので，これらのリスクファクターを介して脳卒中のリスクを高めていると考えられるが，最近，肥満はアディポサイトカインを介して直接的に動脈硬化や血栓形成を促進することも明らかにされた．また，最近行われた大規模な疫学研究によれば，高体重やbody mass index(BMI)で示される一般的な肥満よりも内臓脂肪型肥満(abdominal obesity)のほうが脳卒中のリスクと密接に関連していることも示唆されている．

本稿では，脳卒中と肥満に関してこれまでに報告されているエビデンスと最近提唱されたガイドラインを紹介し，脳卒中に肥満が関与するメカニズムを考えてみたい．

肥満と虚血性脳卒中の疫学●

Health Professional Follow-Up Study[1]によれば，心血管疾患や脳卒中の既往がない40～75歳の男性の医療従事者28,643人を5年間追跡調査し，年齢で補正した脳卒中の相対リスク(RR)をクインタイル(5分位)間で比較したところ，最低5分位と比較した最高5分位のRRはBMIでは1.29(95%信頼区間(CI)；0.73～2.27)であったが，ウエスト・ヒップ比では2.33(95%CI；1.25～4.37)であった(Table 1)．これらの結果は，男性ではBMIよりも内臓脂肪型肥満が脳卒中の予知因子になることを示唆している．

一方，女性ではBMIが増加するほど虚血性脳卒中のリスクが増加するという成績が報告されている．Nurses' Health Study[2]によれば，冠動脈疾患・脳卒中・癌に罹患したことのない33～53歳の女性看護師116,759人を16年間追跡調査したところ，年齢，喫煙，閉経後ホルモン薬の使用，閉経の状態で補正した多変量解析では，BMIが27 kg/m²以上の女性は虚血性脳卒中のリスクが有意に増加し，RRは21 kg/m²未満の女性と比べて27～28.9 kg/m²のBMIで1.42(95%CI；0.91～2.22)，29～31.9 kg/m²のBMIで1.62(95%CI；1.04～2.52)，32 kg/m²以上のBMIで1.82(95%CI；1.17～2.84)であった(Table 3)．また，BMIで補正した多変量解析では，調査開始までの18年間で増加した体重は虚血性脳卒中のリスクに相関しており，体重減少か5 kg未満の体重増加と比較したRRは，11～19.9 kgの増加で1.69(95%CI；1.26～2.29)，20 kg以上の増加で2.52(95%CI；1.80～3.52)であった．これらの成績は，女性では肥満と体重増加のいずれもが虚血性脳卒中の重要なリスクファクターであることを示唆している．

日本人の成績としては，久山町研究においてBMIは脳梗塞全体では明らかなリスクファクターとはなっていなかったが，性別・病型別サブ解析では女性のラクナ梗塞の発症には独立したリスクファクターとなっていたことが報告されている[3]．また，55～68歳の非喫煙日系米国人男性1,163人においてBMIと血栓塞栓性脳卒中の関

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