Stroke

ARTICLES

Indobufen Versus Warfarin in the Secondary Prevention of Major Vascular Events in Nonrheumatic Atrial Fibrillation

Cristoforo Morocutti, Giuseppe Amabile, Francesco Fattapposta, Alfredo Nicolosi, Sergio Matteoli, Massimo Trappolini, Gabriella Cataldo, Geremia Milanesi, Maurizio Lavezzari, Franco Pamparana, Sergio Coccheri

DOI https://doi.org/10.1161/01.STR.28.5.1015
Stroke. 1997;28:1015-1021
Originally published May 1, 1997

Abstract

Background and Purpose The results of a large prospective randomized trial have shown the efficacy of oral anticoagulation in the secondary prevention of major vascular events in patients with nonrheumatic atrial fibrillation (NRAF); less well established is the role of antiplatelet agents. The present study compared the effects of indobufen, a reversible inhibitor of platelet cyclooxygenase, with those of warfarin in this setting.

Methods A total of 916 patients with NRAF and a recent (≤15 days) cerebral ischemic episode were admitted to this multicenter, randomized study, during which they were treated with either indobufen (100 or 200 mg BID) or warfarin (to obtain an international normalized ratio of 2.0 to 3.5) for 12 months. The two groups (462 on indobufen and 454 on warfarin) were well balanced in terms of their main baseline characteristics. The primary outcome of the study was the combined incidence of nonfatal stroke (including intracerebral bleeding), pulmonary or systemic embolism, nonfatal myocardial infarction, and vascular death.

Results At the end of follow-up, the incidence of primary outcome events was 10.6% in the indobufen group (95% confidence interval, 7.7% to 13.5%) and 9.0% in the warfarin group (95% confidence interval, 6.3% to 11.8%), with no statistically significant difference between treatments. The frequency of noncerebral major bleeding complications was low: only four cases (0.9%) of gastrointestinal bleeding were observed, all of them in the warfarin group.

Conclusions We conclude that, within the limitations of its design, this study may help the medical community in devising appropriate antithrombotic strategies for NRAF patients for whom oral anticoagulants are contraindicated or do not represent a feasible approach to treatment.

antiplatelet therapy atrial fibrillation thromboembolism warfarin

Ischemic stroke is due to cardiogenic embolism in approximately 15% of cases,[1] and NRAF is the most common cardiac disease associated with cerebral embolism.[2] A 10% to 20% incidence of stroke recurrence has been reported during the year after a first ischemic episode in patients with NRAF, with some studies describing a recurrence rate of up to 15% during the

first month.[3 4] The value of antithrombotic therapy in the secondary prevention of thromboembolic events in such patients has been examined by the placebo-controlled EAFT,[5] in which oral anticoagulant treatment (INR, 2.5 to 4.0) reduced the risk of stroke and major vascular events by approximately 70% and 50%, respectively. However, this clear-cut benefit was associated with a greater risk of major hemorrhagic events. In the same study, aspirin (300 mg/d) led to a nonsignificant 20% reduction in the risk of important vascular events,[5] suggesting that antiplatelet prophylaxis may not be as effective as oral anticoagulation. Consequently, the search for a safer and effective alternative to oral anticoagulation is still ongoing.

Indobufen is a reversible inhibitor of platelet cyclooxygenase activity,[6 7 8] which has been shown to be effective as an antithrombotic agent in the prevention of graft occlusion after coronary artery bypass surgery[9 10 11] as well as in the prevention of thromboembolic events in heart disease patients at risk of embolism.[12] The present study was designed to compare the efficacy and safety of indobufen and of warfarin in the prevention of major vascular events in NRAF patients who had experienced a recent cerebral ischemic episode.

Subjects and Methods

Patient Selection

SIFA was a prospective, randomized, open study involving 80 Italian centers. The eligible patients were subjects of either sex older than 30 years with chronic or paroxysmal NRAF, who had had a transient ischemic attack or ischemic stroke in the previous 2 weeks. At least two ECGs documenting stable AF during the 3 weeks before study entry were required for the diagnosis of chronic AF; intermittent AF had to be documented by means of ECGs and/or Holter monitoring recordings showing sinus rhythm between at least two episodes of AF during the preceding 12 months.

The qualifying event for admission to the study was the occurrence of a cerebrovascular ischemic episode no more than 15 days before study entry (with no evidence of hemorrhage on CT), classified as follows: (1) nondisabling stroke, eg, focal neurological deficit for more than 24 hours leading to a disability of grade 3 or less on the modified Rankin scale, or (2) transient ischemic attack, with a nonevolutive course lasting less than 24 hours.

Patients were excluded if they had rheumatic AF or if they had undergone cardioversion during the 2 weeks preceding the qualifying event. Other cardiac reasons for exclusion were echocardiographic evidence of intracardiac thrombosis or tumor; left ventricular aneurysm, severe congestive heart failure (New York Heart Association functional class >3), or the presence of prosthetic valves; acute myocardial infarction or unstable angina during the previous month; carotid endarterectomy or coronary or peripheral revascularization procedures performed during the previous 6 months; severe arterial hypertension poorly controlled by drugs; and acquired or congenital valvular disease (except mitral valve prolapse or mitral annulus calcification). The neurological exclusion criteria included CT brain scan evidence of cerebral hemorrhage, documented arteriovenous malformation or tumor, severe involutive cerebral disease, or the presence of a carotid lesion requiring surgical intervention. Other reasons for exclusion included the need for chronic anticoagulant therapy, contraindication to the study drugs, severe renal or hepatic insufficiency, a life expectancy of less than 12 months because of other medical conditions, or the patient's refusal to participate.

Each patient was required to give informed consent after receiving adequate information about the meaning of randomization, the intended treatment, and the estimated risk-benefit ratio. Moreover, to improve compliance since the assigned treatment was to be continued at home, each patient's attending physician was informed of the type of treatment being given, its duration, and the examinations to be performed during follow-up.

The study protocol was approved by the ethics committees of the participating centers.

Treatment

The patients were assigned to one of the treatments by means of a blocked randomization procedure stratified by center, with blocks of four patients (two assigned to each treatment) being used to ensure a good balance between treatments even in small recruiting centers. The treatment (indobufen or warfarin) was assigned centrally by telephone through a randomization

service in Milan. Indobufen was administered orally at the recommended dose of 200 mg BID, which was lowered to 100 mg BID in patients with impaired renal function (creatinine clearance <80 mL/min). Anticoagulant treatment with warfarin was adjusted to ensure INR values within the range of 2.0 to 3.5. Throughout the study period, no drugs were permitted that would affect platelet aggregation or blood coagulation or that might interfere with the action of the study drugs. The planned duration of treatment was 12 months. The physician in charge at each center was free to discontinue treatment whenever the occurrence of a severe adverse event or of a concomitant disease made this necessary.

Assessments

Baseline

At entry, each patient's medical history was taken and he/she underwent a physical examination. The clinical characteristics of the qualifying cerebral event (type, location, duration of symptoms, and vascular territory involved) were recorded, together with the patient's demographic data, vascular risk factors, cardiac history and status, and neurological history. The following diagnostic procedures were also performed: routine blood laboratory tests, baseline 12-lead ECG, M-mode and two-dimensional echocardiography, duplex ultrasonography of the supra-aortic trunks, CT brain scan, and chest roentgenography.

Follow-up

Every 3 months, each patient underwent a clinical examination, ECG, and laboratory tests (INR), and a record was made of the occurrence of any outcome events, the degree of disability, the appearance of any adverse drug reactions, and the patient's compliance with the prescribed drugs. All deaths and their causes were recorded, with death certificates being obtained in the case of deaths occurring outside the hospital. The times and reasons for all patient withdrawals were identified. Study medication was withdrawn when an end point occurred or when the patient experienced a major hemorrhage.

Outcome Events

The study was planned to test the effect of the two treatments in the prevention of any major vascular event regardless of its origin, since we thought that this approach would have more value in everyday clinical practice.

Therefore, the combined incidence of the following vascular events was considered the primary outcome of the study: nonfatal stroke (including intracranial bleeding), nonfatal myocardial infarction, systemic or pulmonary embolism, and vascular death. CT-documented ischemic or hemorrhagic stroke was defined as the sudden onset of a focal neurological deficit lasting for more than 24 hours. The stroke was classified as major if the patient's Rankin classification disability score was greater than 3 four weeks after the acute onset.

A diagnosis of myocardial infarction required at least two of the following criteria: history of chest discomfort, development of a pathological Q wave on ECG tracings, and elevation of specific cardiac enzymes to values of more than twice the upper normal limit.

Systemic embolism was defined as acute ischemia of the limbs or internal organs, associated with clinical or radiological evidence of arterial occlusion, without any severe atherosclerotic vascular disease. In the case of pulmonary embolism, lung perfusion scintigraphy was required. Vascular death included fatal stroke, fatal myocardial infarction, sudden death (occurring within 1 hour of the onset of symptoms), and death due to heart failure, systemic or pulmonary embolism, noncerebral hemorrhagic events, or other vascular causes.

If a patient died within 4 weeks of a major event, this was recorded as fatal. All of the outcome events were independently classified by three members of the Steering Committee who were unaware of the treatment allocation. The final judgment was based on the consensus of at least two members, who reviewed, in a blinded fashion, original medical records. If consensus was not reached, the case was submitted to the Steering Committee.

Hemorrhagic Events

Noncerebral and nonfatal bleeding events were classified as major if they were severe, ie, they made it necessary to hospitalize the patient, administer a blood transfusion, or perform surgery. All other hemorrhagic events were classified as minor.

Statistical Methods

Sample Size

SIFA was a prospective, randomized, open clinical trial planned to test the equivalence of the effects of antiaggregant and anticoagulant treatments. Since the absolute equivalence of two treatments can never be demonstrated, we chose to indicate a prespecified difference below which the two treatments could be defined as equivalent.[13]

On the basis of the results of previous studies, it was assumed that the proportion of successes (ie, the probability of remaining free of one of the events considered a primary end point during the first year of follow-up) would be 0.86 in the warfarin group. The sample size was calculated in such a way as to exclude the possibility that the difference in the success rate between the warfarin and indobufen groups exceeded 0.06. The power (1−β) was set at 90% and the α level at 0.10. In studies of treatment equivalence, α can be safely set at a high level (10% or 20%), since the wrong conclusion of finding a difference when this does not exist would not be a serious mistake because its clinical implications would be to keep patients on the standard treatment. The sample size was calculated for a one-sided test, which is customary when the objective is to ensure that the new agent is not inferior to the standard treatment. On the basis of these assumptions, the required sample size was 880 patients (440 per group).

Analysis

The statistical methods used in the univariate analyses included *t* tests for the differences between mean values, χ^2 tests for the comparison of proportions, and hazard ratios (relative risks) to measure the associations between outcomes and variables.[14] Probability of remaining free of events was estimated by the Kaplan-Meier method,[15] and cumulative event-free survival was compared between treatments with the log-rank test. The multivariate analyses made to control for potential confounders and prognostic factors were performed with the Cox proportional hazard model.[16 17]

The equivalence of the treatments on the basis of the assumptions described above was tested by means of the appropriate χ^2 test.[18 19] All of the statistical evaluations were performed with both intention-to-treat and on-treatment analyses.

The on-treatment analysis included all of the primary end points occurring during the course of drug administration or within 15 days of drug discontinuation.

Results

Baseline Patient Characteristics

A total of 916 patients were admitted to the study: 462 in the indobufen and 454 in the warfarin group. The baseline characteristics of the patients are given in Table 1⇓. Approximately two thirds of the patients were older than 70 years, and there was a slightly higher prevalence of women. The two groups were comparable in terms of the qualifying cerebral ischemic event, type of AF, prevalence of vascular risk factors, presence and degree of heart failure, echocardiographic parameters, and CT scan and supra-aortic trunk ultrasound findings.

Collapse inline View popup

Table 1.

Baseline Characteristics of 916 Patients With NRAF and a Recent Cerebral Ischemic Episode

	Indobufen (n=462)	Warfarin (n=454)

	Indobufen (n=462)	Warfarin (n=454)
Men, %	45.5	48.5
Mean±SD age, y	72.8±8.3	72.2±8.1
Age <70 y, %	31.0	34.1
Stroke, %	50.0	48.7
Chronic AF, %	71.6	72.5
Hypertension, %	55.8	54.6
Diabetes, %	20.3	15.4
Hyperlipidemia, %	19.5	18.9
Current smoking, %	18.4	20.5
Angina pectoris, %	7.6	8.6
Myocardial infarction, %	8.2	7.9
Mean±SD BP, mm Hg		
Systolic	148.4±18.6	149.0±17.7
Diastolic	85.9±9.7	86.1±9.3
NYHA functional class, %		
II	29.9	30.0
III	2.8	3.1
Mean±SD left atrial diameter, mm	43.0±7.9	43.7±8.5
LV fractional shortening ≤30%, %	49.8	51.8
CT brain scan, %		
Appropriate lesion	33.5	34.1
Multiple infarct	8.2	6.8
Carotid stenosis ≥50%, %	10.8	9.5
Mean±SD interval between qualifying event and start of treatment, d	9.9±4.8	9.7±4.7

BP indicates blood pressure; NYHA, New York Heart Association; and LV, left ventricular. *P*>.05 for all comparisons between the two treatment groups.

Follow-up

Nine patients (7 in the warfarin and 2 in the indobufen group) were lost to follow-up immediately after hospital discharge. Adverse reactions led to drug withdrawal in 30 patients (21 in the warfarin and 9 in the indobufen group). An additional 51 patients (31 in the indobufen and 20 in the warfarin group) withdrew for other reasons (refusal to continue, onset of a concomitant disease, or decision of the attending physician). Eight patients were temporarily withdrawn from treatment for 30 days or less. Patient compliance with the anticoagulant treatment was quite satisfactory: of the 2560 INR determinations, 83.5% fell within the prespecified range; 14.1% were below 2.0 and 2.4% above 3.5. In the indobufen group, 75% of the patients received 200 mg BID and 25% received 100 mg BID.

Outcome Events

As shown in Table 2⇓, a total of 90 outcome events were recorded during follow-up, 49 in the patients randomized to indobufen (10.6%; 95% CI, 7.7% to 13.5%) and 41 in those randomized to warfarin (9.0%; 95% CI, 6.3% to 11.8%).

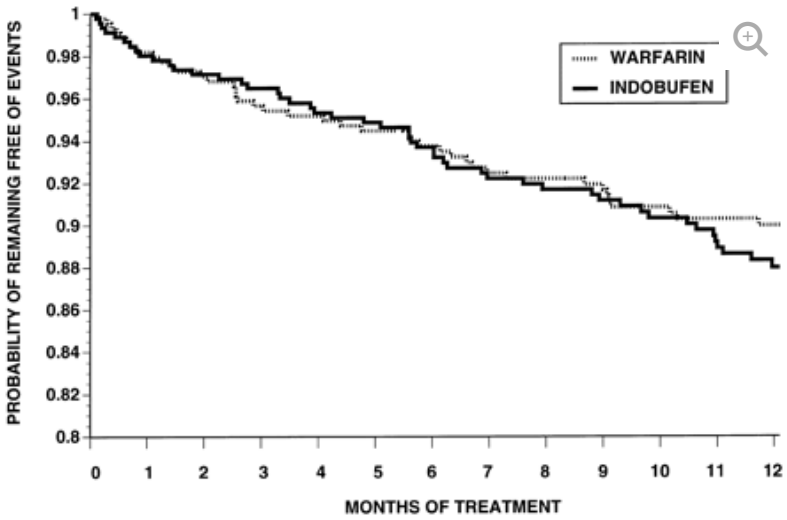
View inline **View popup**

Table 2.

Primary Outcome Events Recorded During Follow-up Analyzed According to Intention-to-Treat Principle

Intention-to-treat analysis showed that the proportion of patients developing a primary outcome event was not significantly different between the two treatment groups: the observed difference was 0.016 (95% CI, −0.016 to 0.048), well below the 0.06 prespecified as the greatest tolerable difference. This is further confirmed by the results of the χ^2 test used to test the equivalence between the two treatments (χ^2=5.02; *P*<.025). The on-treatment analysis also failed to reveal any statistically significant differences between the two treatment groups, since the 79 on-treatment primary events were 44 in the indobufen-treated patients (9.7%; 95% CI, 6.9% to 12.5%) and 35 in the warfarin-treated patients (7.9%; 95% CI, 5.3% to 10.5%). The higher number of primary events in the intention-to-treat analysis was due to 8 cases of stroke (4 in each group) and 3 cases of vascular death (1 on indobufen and 2 on warfarin).

The Figure⇓ shows the Kaplan-Meier event-free survival curves for the two treatment groups (intention-to-treat). The probability of remaining free of primary events at 12 months was 90.0% for the warfarin group and 88.0% for the indobufen group (log-rank test: χ^2=0.52; *P*=.47).



Download figure
Open in new tab
Download powerpoint

Figure 1.

Comparative survival curves for primary outcome events: vascular death, nonfatal stroke (including intracerebral bleeding), nonfatal myocardial infarction, and nonfatal systemic or pulmonary embolism.

When the survival analysis was restricted to the patients on treatment, the 12-month cumulative event-free survival rate was 91.3% in the warfarin group and 89.2% in the indobufen group (*P*=.47).

A total of 41 fatal and nonfatal strokes occurred during follow-up, 23 in the indobufen group (5%) and 18 in the warfarin group (4%) (*P*>.05); the type and severity of the events are reported in Table 3⇓. The nonsignificant difference between the two treatments was due to an excess of minor ischemic strokes in the indobufen group, which was partially balanced by a slight excess of cerebral bleeding in the warfarin group. The INR values measured when the event occurred were below 2.0 in 2 of the 10 patients experiencing an ischemic stroke and were within the expected range in the 4 patients with hemorrhagic stroke. The number of major or fatal strokes was 17 in the patients randomized to indobufen and 15 in those randomized to warfarin.

View inline **View popup**

Table 3.

Cerebral Outcome Events in the Two Treatment Arms

A total of 7 nonvascular deaths were observed during the study: 4 in the indobufen group and 3 in the warfarin group.

To study the effect of prognostic factors, all of the variables in Table 1⇑ were inserted in a series of univariate Cox regression analyses, and those that proved to be associated with an increased risk for stroke or recurrent vascular events (at a statistical significance level of *P*<.10) were included, together with treatment, in two multivariate models (one for stroke and one for combined primary events). The results are given in Table 4⇓. Prior myocardial infarction and stroke as a qualifying event were retained as independent risk factors for both recurrent stroke and combined vascular events, whereas female sex was a predictor for recurrent stroke only. This multivariate analysis confirmed the absence of any statistically significant difference between treatments even after we controlled for the influence of prognostic factors.

View inline View popup

Table 4.

Results of Multivariate Cox Regression Analysis Including Treatment and Risk Factors for Combined Primary Events and Stroke Alone

Adverse Reactions

Fifty-four adverse reactions were recorded during follow-up: 21 in the patients treated with indobufen (mainly stomach pain, nausea, and vomiting) and 33 in those treated with warfarin (mainly bleeding complications). These adverse reactions led to treatment withdrawal in 9 patients on indobufen and 21 on warfarin. Twenty-six noncerebral bleeding episodes occurred during the study: 3 in the indobufen group (0.6%) and 23 (5.1%) in the warfarin group, including all 4 cases of major gastrointestinal bleeding (Table 5⇓). This difference was statistically significant ($P<.01$). When the bleeding complications occurred, the INR values were out of the desired range in only 3 cases (two >3.5, one <2.0).

View inline View popup

Table 5.

Noncerebral Bleeding Episodes Recorded in the Two Treatment Arms

Discussion

Patients with NRAF and a recent cerebrovascular ischemic episode are at high risk of subsequent major vascular events.[20] [21] The value of anticoagulation in reducing the risk of vascular recurrences in these patients has been established by a large secondary prevention study (EAFT),[5] in which aspirin was found to be a significantly less effective therapeutic option. However, because of the problems connected with oral anticoagulation, the search for a more convenient and safer effective therapy is still ongoing.

The recently published SPAF III trial,[22] which evaluated the combination of low-intensity fixed-dose warfarin plus aspirin 325 mg/d, failed to find a more convenient alternative to conventional anticoagulant treatment in NRAF patients at high risk of stroke. However, for low-risk NRAF patients aged up to 75 years, aspirin represents a valid alternative to lifetime anticoagulation, as shown in the SPAF I[23] and II[24] studies.

In the present study the frequency of the primary events observed in the patients treated with warfarin (9%), as well as the incidence of recurrent stroke (4%), was similar to results of the EAFT study group in the patients receiving anticoagulation treatment and not statistically different from results in the indobufen group (10.6% and 5%, respectively). It should be acknowledged, however, that the relatively small number of patients in our study does not allow us to exclude small though clinically meaningful differences in efficacy between indobufen and warfarin. The slightly higher rate (17.8% excess) of outcome events in the indobufen-treated patients was mainly due to nondisabling ischemic strokes. The absence of any statistical difference between treatments also remained after adjustment for the influence of prognostic factors, which according to the multivariate analysis were female sex, stroke at admission, and a history of myocardial infarction.

The results observed with indobufen are consistent with the data obtained in a previously reported placebo-controlled trial[12] involving heart disease patients at increased embolic risk, in which indobufen markedly reduced the risk of all embolic events by approximately two thirds. The favorable results obtained with indobufen in this setting may be due to its profound inhibition of the cyclooxygenase activity of both constitutive and inducible prostaglandin endoperoxide synthases,[25] [26] which are likely

to be involved in sustaining enhanced thromboxane A_2 biosynthesis during acute cerebral ischemia.[27] Moreover, it should be noted that approximately 20% of ischemic strokes in NRAF are considered to have an atherothrombotic mechanism,[28] against which antiplatelet treatment has proved to be effective.[29]

In terms of safety, there was a statistically significant between-treatment difference in the incidence of noncerebral hemorrhagic events: 5.1% of the patients treated with warfarin (including four who required hospitalization) versus only 0.6% of those treated with indobufen. However, the incidence of severe hemorrhagic events in our warfarin treatment group was lower than that reported in other randomized studies,[30] probably because the close monitoring during follow-up favored patients remaining within the optimal range.[31]

Our study design does not allow us to indicate whether an early start of antithrombotic prophylaxis after a cerebral event (≤15 days) may provide more effective protection against a recurrence of embolic events. However, because it is known that the risk of recurrent brain ischemia[32] is higher during the first few weeks, the fact that early treatment was not associated with any increase in hemorrhagic risk in our study suggests that it is wise to start secondary prevention as early as possible. Moreover, as a result of the relatively short follow-up, this study does not provide information on the long-term benefit-risk balance of the two treatments investigated. A further limitation of the study is related to its open nature, which does not allow us to rule out the potential for nonblinded observer's bias affecting outcomes, although these were mostly fatal or disabling and were independently classified by three members of the Steering Committee who were unaware of treatment allocation. However, within these limitations we believe that the results of this study may be of value in better defining the place of antiplatelet agents in patients with NRAF, given the limited amount of trial data available.

Therefore, we conclude that SIFA may help the medical community in devising appropriate antithrombotic strategies for NRAF patients for whom oral anticoagulants are contraindicated or do not represent a feasible approach to treatment.

Selected Abbreviations and Acronyms

AF	=	atrial fibrillation
CI	=	confidence interval
EAFT	=	European Atrial Fibrillation Trial
ECG	=	electrocardiogram, electrocardiographic
INR	=	international normalized ratio
NRAF	=	nonrheumatic atrial fibrillation
SIFA	=	Studio Italiano Fibrillazione Atriale
SPAF	=	Stroke Prevention in Atrial Fibrillation

Appendix A1

SIFA Group

Steering Committee. C. Morocutti, MD (Chairman), G. Amabile, MD, F. Fattapposta, MD, Cattedra di Clinica Neurologica e Istituto Malattie Nervose e Mentali, Università La Sapienza, Roma; G. Bono, MD, Clinica Neurologica, Università, Pavia; G. Cataldo, MD, Dipartimento Cardiologico De Gasperis, Ospedale Cà Granda-Niguarda, Milano; S. Coccheri, MD, G. Palareti, MD, Cattedra e Divisione di Angiologia, Università di Bologna; S. Matteoli, MD, II Clinica Medica, Policlinico Umberto I, Roma; G. Milanesi, MD, Divisione di Cardiologia, Ospedale Crema; P. Rizzon, MD, Cattedra di Cardiologia, Università di Bari.

Statistical Coordinating Centers. A. Nicolosi, MD, PhD, Istituto di Tecnologie Biomediche Avanzate, Consiglio Nazionale delle Ricerche, Milano, and GH Sergievsky Center School of Public Health, Columbia University, New York, NY; F. Heiman, MS, E. Oggioni, Data Management and Statistical Analysis, Pharmacia & Upjohn, Milano.

Data Monitoring Committee. B. Magnani, MD, Istituto Malattie Apparato Cardiovascolare, Università di Bologna; R. Paoletti, MD, Istituto di Scienze Farmacologiche, Università di Milano.

Clinical Coordinating Centers. G. Guazzaloca, MD, Cattedra e Divisione di Angiologia, Università di Bologna; M. Trappolini, MD, Unità Coronarica, Policlinico Umberto I°, Roma; S. Iliceto, MD, Cattedra di Cardiologia Università di Bari; M. Lavezzari, MS, F. Pamparana, MD, Direzione Medica, Pharmacia & Upjohn, Milano; L. Provinciali, MD, Clinica Neurologica, Università di Ancona.

Investigators. D. Consoli, G. Grillo, C. Colistra, P. David, Ospedale Civile, Vibo Valentia; G. Filocamo, F. Stirparo, Presidio Ospedaliero, Locri; G. Pulitanò, Policlinico, Reggio Calabria; L. Vigna, M. Sprovieri, Ospedale Civile, Cosenza; M. Brogi, A. Capezzuto, Ospedale Generale Provinciale, Viterbo; C. Cordova, G. Pettirossi, S. Basili, M. Pergolini, Policlinico Umberto I, Rome; F. Ferri, S. Sessa, Ospedale S. Pietro, Rome; A. Papa, E. Cerafogli, Ospedale Generale Provinciale, Rieti; F. Proietti, M. Azzarito, Aurelia Hospital, Rome; G. Rosati, A. Pirisi, M. Zuddas, G. Casu, M. Spanu, F. Bandiera, Università, Sassari; A. Spissu, M. Melis, A. Molari, M.L. Putzu, Ospedale S. Michele, Cagliari; L. Battistin, L. De Zanche, Università, Padua; G. Maccarrone, Ospedale Civile, Castelfranco Veneto; G. Cazzato, R.M. Antonello, F. Iaiza, T. Mesiano, Ospedale Cattinara, Trieste; A. Cesari, N. Simione, Ospedale Civile, Cittadella; F. Chiodo Grandi, L. Antonutti, G. Nider, N. Koscicca, Ospedale Maggiore, Trieste; G. Ferrari, P. Bovi, Ospedale Civile Borgo Trento, Verona; F. Ferro Milone, P. Dudine, Ospedale Civile, Vicenza; V. Pengo, Casa di Cura Villa Maria, Padua; P. Pinelli, M. Cavallo, Ospedale Villa Salus, Mestre; C. Ravenna, G. Pistollato, Ospedale Civile, Mestre; G.C. Berni, A.A. Brancato, Ospedale Florence Careggi; C. Cappelletti, L. Maggi, A. Leopardi, S. Spolveri, Ospedale S. Giovanni di Dio, Florence; L. De Magistris, L. Giglioli, Ospedale, Florence Careggi; C. Giraldi, M. Mazzoni, Ospedale Campo di Marte, Lucca; P. Goretti, Ospedale S. Lorenzo, Colle Val D'Elsa; A. Lagi, A.M. Buccheri, Ospedale S. Maria Nuova, Florence; L. Mazzanti, M. Zocchi, Ospedale Misericordia, Grosseto; A. Muratorio, L. Landucci Pellegrini, Ospedale S. Chiara, Pisa; E. Pieragnoli, F. Manetti, G. Landini, Ospedale S. Maria Annunziata, Antella, Florence; D. Vanni, P. Zolo, Ospedale Civile, Arezzo; A. Colombo, A. Cheldi, G. Cattò, Ospedale Civile, Desio, Milan; G. Finardi, E. Marchesi, G. Perani, V. Ravetta, Policlinico S. Matteo, Pavia; M. Riva, R. Marazzi, C. De Vita, A. Alberti, Ospedale Cà Granda-Niguarda, Milan; S. Ambrosoli, S. Aimi, Ospedale Civile, Fidenza; M. Carreras, Arcispedale S. Anna, Ferrara; D. De Grandis, L. Caniatti, Arcispedale S. Anna, Ferrara; G. Di Biase, A. Balboni, R. Cantore, Policlinico S. Orsola, Bologna; L. Marani, A. Navazio, G. Pinelli, Ospedale Generale, Montecchio, Reggio Emilia; G. Mattioli, A.V. Mattioli, E. Tarabini, Università, Modena; P. Pasini, G. Gobbi, Ospedale Civile, Riccione; V. Pedone, Ospedale Pierantoni, Forlì; O. Ponari, A. Catamo, A. Mombelloni, Ospedali Riuniti, Parma; G. Renzi, A. Grossi, Ospedale Infermi, Rimini; G. Re, C. Lanzarini, Policlinico S. Orsola, Bologna; S. Signorelli, Ospedale Civile, Correggio; F. Solimè, M. Baratti, Ospedale S. Maria Nuova, Reggio Emilia; C. Aramini, C. Strocchi, Ospedale per gli Infermi, Faenza; C. Ciappina, F. Lo Presti, G.F. Scimone, Ospedale Regina Margherita, Messina; A. Galassi, F. Ventura, R. Coco, F. Liberti, Ospedale Cannizzaro, Catania; A.A.M. Grasso, S. Licciardi, Policlinico, Catania; G. Modica, I. Monte, F. Nicoletti, F. Patti, Università, Catania; D. Scuderi, M.R. Di Pasquale, F.G. Picciolo, R. Girasella, Ospedale Piemonte, Messina; C. Bargnani, E. Donati, Presidio Ospedaliero, Rovato; C.A. De Fanti, P. Tiraboschi, Spedali Riuniti, Bergamo; V. Avenia, Ospedale S. Elia, Caltanissetta; A. Pardo, M. Russotto, I. Nardi, M. Sapienza, Ospedale Villa Sofia, Palermo; S. Remirez, Ospedale Provinciale, Trapani; E. Bologna, D. Monno, P.M. Rossini, G. Martino, Ospedale Fatebenefratelli, Rome; P. Giacomini, C. Moroni, Università La Sapienza, Rome; G. Neri, P. Collicelli, Ospedale S. Giovanni Battista, Rome; L. Coli, G. Arcelli, Ospedale Civile, Città di Castello; O. Bacchi, A.M. Panzetta, S. Pocciati, A. Pagliacci, M. Timio, Ospedale Generale, Foligno; G. Benemio, Ospedale Civile, Città della Pieve; N. Miele, Ospedale Generale, Spoleto; R. Paris, Ospedale Civile, Gubbio; C. Valori, Ospedale S. Maria, Terni; M. Paciello, G. Coniglio, W. Serino, Ospedale Generale, Potenza; R. Badino, M. Trucco, Ospedale S. Corona, Pietra Ligure; A. Cognazzo, A. Gagliano, D. Seliak, P. Costa, Ospedale Civile, Savigliano; N. Dagnino, R. Vecchia, M.G. Pini, L. Pizzorno, Presidio Ospedaliero, Sestri Ponente; G. Sacco, S. Cammarata, C. Vecchio, M. Falcidieno, Ospedale Galliera, Genoa;

F. Angeleri, L. Provinciali, Ospedale Torrette, Ancona; M. Cuzzupoli, Ospedale Civile, Fano; D. Gambi, S. Viola, E. De Leonardis, M.G. Tenaglia, Università, Chieti; C. Sconocchini, R. Palermo, Ospedale Civile, Jesi; G. Marcheggiani, M. Lambo, Ospedale Civile, Tolentino; E. Paciaroni, S. Raffaeli, Ospedale INRCA, Ancona; M. Prencipe, R. Totaro, Università, L'Aquila; L. Venturoni, P. Campanaro, L. Ramoni, Ospedale Civile, Giulianova; F. Rossi, F. Pompeo, Istituto Sanatrix, Pozzilli.

Acknowledgments

SIFA was made possible by grants from Farmitalia Carlo Erba, Milano, Italy.

Footnotes

A complete list of participants in this study appears at the end of this article.

Received December 6, 1996.

Revision received February 21, 1997.

Accepted February 27, 1997.

References

. Wolf PA, Dawber TR, Thomas E Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham Study. *Neurology*. 1978;**28**:973-977.

. Cerebral Embolism Task Force. Cardiogenic brain embolism. *Arch Neurol*. 1986;**43**:71-84.

. Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: a randomized trial. *Stroke*. 1983;**14**:668-676.

. Cerebral Embolism Task Force. Cardiogenic brain embolism, second report. *Arch Neurol*. 1989;**46**:727-743.

. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;**342**:1255-1262.

. Mannucci L, Maderna W, Colli S, Lavezzari M, Sirtori CR, Tremoli E. Indobufen is a potent inhibitor of whole blood aggregation in patients with a high atherosclerotic risk. *Thromb Res*. 1987;**48**:417-426.

. Cattaneo M, Bevilacqua C, Lecchi A, Mannucci PM. In vitro and ex vivo effects of indobufen on human platelet aggregation, the release reaction and thromboxane B_2 production. *Haemostasis*. 1990;**17**:293-300.

. Crow MJ, Salter MCP, Donaldson DR, Rajah SM. Inhibition of platelet function with indobufen: correlation with plasma drug level. *Thromb Res*. 1985;**38**:303-306.

. The SINBA Group. Indobufen versus aspirin plus dipyridamole after coronary artery bypass surgery. *Coronary Artery Dis*. 1991;**2**:907-912.

. Cataldo G, Braga M, Pirotta N, Lavezzari M, Rivelli F, Marubini E, on behalf of SINBA. Factors influencing 1-year patency of coronary artery saphenous vein graft. *Circulation*. 1993;88(pt 2):93-98.

. Rajah SM, Nair U, Rees M, Saunders N, Walker D, Williams G, Critchley A, Beton D, Campbell C, Lawson RA, Rahman A, Nair KK, Dyet J, Kushwaha S, Reed A, Powell JD, Drake J. Effects of antiplatelet therapy with indobufen or aspirin-dipyridamole on graft patency one year after coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 1994;**107**:1146-1153.

. Fornaro G, Rossi P, Mantica PG, Caccia ME, Aralda D, Lavezzari M, Pamparana F, Milanesi G. Indobufen in the prevention of thromboembolic complications in patients with heart disease: a randomized, placebo-controlled, double-blind study. *Circulation*. 1993;**87**:162-164.

. Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials.* 2nd ed. Littleton, Mass: PGS Publishing Co; 1985.

. Fleiss JL. *Statistical Methods for Rates and Proportions.* 2nd ed. New York, NY: John Wiley & Sons; 1981.

. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;**53**:457-481.

. Cox DR. Regression models and life tables. *J R Stat Soc B*. 1972;**34**:187-220.

. Cox DR, Oakes D. *Analysis of Survival Data.* London, England: Chapman & Hall; 1984.

. Dunnett CW, Gent M. Significance testing to establish equivalence between treatments, with special reference to data in the form of 2×2 tables. *Biometrics*. 1977;**33**:593-602.

. Blackwelder WC. 'Proving the null hypothesis' in clinical trials. *Control Trials*. 1982;**3**:345-353.

. Min Lai S, Alter M, Friday G, Sobel E. A multifactorial analysis of risk factors for recurrence of ischemic stroke. *Stroke*. 1994;**25**:958-962.

. Van Latum JC, Koudstaal PJ, Venables GS, Van Gijn J, Kappelle LJ, Algra A, for the European Atrial Fibrillation Trial (EAFT) Study Group. Predictors of major vascular events in patients with a transient ischemic attack or minor ischemic stroke and with nonrheumatic atrial fibrillation. *Stroke*. 1995;**16**:801-806.

. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*. 1996;**348**:633-638.

. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. *Circulation*. 1991;**84**:527-539.

. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;**343**:687-691.

. Patrignani P, Ponara MR, Greco A, Fusco O, Natoli C, Iabolelli S, Cipollone F, Ganci A, Creminon C, Maclong J, Patrono C. Biochemical and pharmacological characterization of the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases. *J Pharmacol Exp Ther*. 1994;**271**:1705-1712.

. Patrono C, Patrignani P, Rocca B, Landolfi R. Characterization of biochemical and functional effects of antiplatelet drugs as a key to their clinical development. *Thromb Haemost*. 1995;**74**:396-400.

. Koudstaal PJ, Ciabattoni G, van Gijn J, Nieuwenhims HK, de Groot PG, Sixma JJ, Patrono C. Increased thromboxane biosynthesis in patients with acute cerebral ischemia. *Stroke*. 1993;**24**:219-223.

. Miller VT, Rothrock JF, Pearce LA, Feinberg WM, Hart RG, Anderson DC, on behalf of the Stroke Prevention in Atrial Fibrillation Investigators. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. *Neurology*. 1993;**43**:32-36.

. Barnett HJM, Eliasziw M, Meldrum HE. Drugs and surgery in the prevention of ischemic stroke. *N Engl J Med*. 1995;**332**:238-248.

. Cheng TO. Atrial fibrillation, stroke and antithrombotic treatment. *Am Heart J*. 1994;**127**:961-968.

. The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med*. 1995;**333**:5-10.

. Hart RG, Coull BM, Hart D. Early recurrent embolism associated with non-valvular atrial fibrillation: a retrospective study. *Stroke*. 1983;**14**:448-693.

Stroke

About Stroke

Instructions for Authors

Stroke CME

Guidelines and Statements

Meeting Abstracts

Permissions

Journal Policies

Editorial Office Address:
200 5th Avenue
Suite 1020
Waltham, MA 02451
email: stroke@strokeahajournal.org