

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



**Transient Ischemic Attacks in Patients With Atrial Fibrillation: Implications for
Secondary Prevention: The European Atrial Fibrillation Trial and Stroke
Prevention in Atrial Fibrillation III Trial**

Robert G. Hart, Lesly A. Pearce and Peter J. Koudstaal

Stroke 2004;35;948-951; originally published online Feb 26, 2004;

DOI: 10.1161/01.STR.0000120741.34866.1D

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
Copyright © 2004 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/35/4/948>

Subscriptions: Information about subscribing to Stroke is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:
410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Transient Ischemic Attacks in Patients With Atrial Fibrillation

Implications for Secondary Prevention: The European Atrial Fibrillation Trial and Stroke Prevention in Atrial Fibrillation III Trial

Robert G. Hart, MD; Lesly A. Pearce, MS; Peter J. Koudstaal, MD

Background and Purpose—Transient ischemic attacks (TIAs) are infrequent in patients with atrial fibrillation, and little is known about the long-term prognosis and response to antithrombotic therapy.

Methods—This study was a pooled analysis of participants in 2 randomized trials, the European Atrial Fibrillation Trial and the Stroke Prevention in Atrial Fibrillation III Trial, comparing those with prior TIA to those with prior stroke.

Results—Among 834 atrial fibrillation patients with prior TIA (n=222), prior ischemic stroke (n=551), or both (n=61), the mean age was 71 years, 64% were men, and 56% had hypertension. The frequency of major vascular risk factors was similar for both types of cerebral ischemia. The annualized rate of ischemic stroke during aspirin therapy was 7% per year (95% confidence interval, 4 to 12) for prior TIA and 11% per year (95% confidence interval, 9 to 15) for prior stroke ($P=0.08$ for rate difference) and was reduced by 56% ($P=0.09$) and 63% ($P<0.001$), respectively, by anticoagulation.

Conclusions—Atrial fibrillation patients with TIA have a lower long-term risk of subsequent stroke than those with prior stroke, but their stroke risk during aspirin therapy is still high. For atrial fibrillation patients with either type of cerebral ischemia, recent or remote, secondary prevention with adjusted-dose warfarin instead of aspirin results in substantial absolute reductions in ischemic stroke. (*Stroke*. 2004;35:948-951.)

Key Words: anticoagulants ■ aspirin ■ atrial fibrillation ■ cerebral ischemia, transient ■ stroke

Atrial fibrillation is a strong, independent risk factor for ischemic stroke, but this common cardiac dysrhythmia is only weakly associated with transient ischemic attack (TIA).¹⁻⁴ Most strokes in patients with atrial fibrillation are cardioembolic caused by embolism of left atrial appendage thrombi, but an important minority is caused by coexisting intrinsic cerebrovascular diseases in these typically elderly, often hypertensive patients. The relative infrequency of TIAs in atrial fibrillation patients prompts speculation that the mechanism of ischemia may less often be cardioembolic and is more likely a result of intrinsic cerebrovascular diseases. If so, then the prognosis for recurrent ischemia and the response to antithrombotic therapy might be different for atrial fibrillation patients with TIAs versus those with prior ischemic stroke.

Little is known about the prognostic implications of TIAs in atrial fibrillation patients and the relative efficacy of antithrombotic therapies for long-term secondary prevention. Previously reported analyses from the European Atrial Fibrillation Trial (EAFT) and Stroke Prevention in Atrial Fibrillation (SPAF) III trial combined patients with prior TIA and

those with prior ischemic stroke.⁵⁻⁷ Here, participants in these 2 randomized trials with prior TIA versus prior ischemic stroke at study entry are considered separately to explore the management implications for secondary stroke prevention.

Methods

In both the EAFT and SPAF III trials, TIA was diagnosed if focal neurological symptoms and signs resolved completely in ≤ 24 hours; stroke required symptoms or signs to persist longer. Key differences between the 2 trials relevant to these analyses are summarized in Table 1.

All 1001 EAFT participants had experienced TIA or nondisabling ischemic stroke between 1 day and 3 months before entry and were randomly assigned to receive adjusted-dose oral vitamin K antagonist, aspirin 300 mg/d, or placebo as previously described.⁷ The target international normalized ratio (INR) range was 3 to 4.5. All participants had CT before study entry; there was no specific requirement for carotid imaging before entry into EAFT (or the SPAF trial). Mean follow-up was 2.3 years per patient. Prior TIAs were not recorded in EAFT participants with recent stroke as their qualifying event; hence, those with prior stroke include an uncertain fraction who also had prior TIA. For these analyses, only EAFT participants who were deemed eligible for anticoagulation and randomized to receive either anticoagulation or aspirin (n=454) are

Received August 25, 2003; final revision received December 16, 2003; accepted December 22, 2003.

From the University of Texas Health Science Center, San Antonio (R.G.H.); Minot, ND (L.A.P.); and Erasmus Medical Center, Rotterdam, the Netherlands (P.J.K.).

Correspondence to Robert G. Hart, MD, Department of Medicine (Neurology), University of Texas Health Science Center, 7703 Floyd Curl Dr, MSC 7883, San Antonio, TX 78229-3900. E-mail hartr@uthscsa.edu

© 2004 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000120741.34866.1D

TABLE 1. Key Features of the EAFT vs SPAF III Trial*

Trial Feature	EAFT ⁷	SPAF III Trial ^{5,6}
Time period	1988–1993	1993–1996
Participants, n		
Total	1001	1044
Prior stroke	772†	214
Prior TIA	215	115
Prior stroke and TIA	14†	51
Neither (other high-risk participants)	0	664
Median interval since most recent cerebral ischemic event, mo	0.5	27
Anticoagulation intensity		
INR target	3.0–4.5	2.0–3.0
Mean achieved	~3.0	2.4
Aspirin dosage, mg/d	300	325‡
Mean duration of follow-up	2.3 yrs	1.1 yrs

*Selected features relevant to these analyses. For these analyses, only EAFT participants who were eligible for anticoagulation and randomized to receive anticoagulation or aspirin are considered (n=454).

†Prior TIAs were not recorded in EAFT participants with recent stroke as their qualifying event; and hence, prior stroke includes an unknown fraction who also had prior TIA.

‡SPAF III participants assigned to aspirin also received low, ineffective doses of warfarin (see Methods); for these analyses, these patients are pooled with EAFT patients assigned to aspirin.

considered. Hypertension was defined as a history of hypertension or current drug treatment for hypertension.

Details of the design and main results of the SPAF III trial have also been reported previously.^{5,6} Of the 1044 high-risk participants, 380 (36%) had prior TIA or prior ischemic stroke; eligibility required that >1 month had elapsed since the most recent cerebral ischemic event and that stroke be nondisabling (patients had to be independent in basic activities of daily living and able to ambulate in some fashion).⁶ Participants were randomly assigned to receive either

adjusted-dose warfarin (target INR, 2 to 3) versus aspirin 325 mg/d plus low, fixed-dose warfarin (mean achieved INR, 1.3). The trial was terminated after a mean follow-up of 1.1 years because of the pronounced benefits of adjusted-dose warfarin.⁵ The low, fixed dose of warfarin offered minimal additional protection over aspirin alone,⁵ and for these analyses, SPAF III patients assigned to this combination were pooled with those from EAFT receiving aspirin. Hypertension was defined as an observed blood pressure of $\geq 140/90$ mm Hg on at least 2 occasions or current drug treatment for hypertension.

Distributions of patient characteristics were compared between groups by use of Student's *t* test or the χ^2 test (Fisher's exact test if any expected cell was <5). Relative risk of stroke was estimated through the use of Cox proportional-hazards regression, and relative risk reduction was computed by subtracting this relative risk estimate from unity, with statistical significance determined by the likelihood ratio test. The differential effect of warfarin versus aspirin according to the type of cerebral ischemic event or trial was assessed by testing the statistical significance of an interaction term in the model after adjustment for main effects. Annualized ischemic stroke rates were computed by dividing the number of observed first strokes during the trial by the number of patient-years of observation, with comparison of rates and the 95% confidence intervals (CIs) computed with Poisson regression models. All statistical tests were 2 sided, and statistical significance was accepted at $P=0.05$.

Results

Among 834 participants with prior cerebral ischemia in the EAFT (n=454) and SPAF III trial (n=380), the mean age was 71 years; most (64%) were male, and about half (56%) had hypertension. A major difference between participants in the 2 trials was the interval between the last cerebral ischemic event and trial entry: a median of 0.5 months in the EAFT compared with 27 months in the SPAF III trial (Table 1). In both trials, the frequencies of the major vascular risk factors were similar for patients with TIA versus those with prior ischemic stroke, excepting a higher frequencies of diabetes ($P=0.02$) in those with prior stroke (Table 2).

The efficacy of adjusted-dose warfarin versus aspirin was not significantly different for ischemic stroke or TIA for

TABLE 2. Comparison of Atrial Fibrillation Patients With Prior TIAs vs Prior Ischemic Stroke

	EAFT			SPAF III Trial		
	Prior TIA (n=107)	Prior Stroke* (n=337)	Prior TIA and Stroke (n=10)	Prior TIA (n=115)	Prior Stroke (n=214)	Prior TIA and Stroke (n=51)
Time (median) since most recent event, mo	0.5	0.5	0.5	22‡	36	48
Age (mean), y	70	71	71	72	72	73
Male, %	63	59	40	65	69	75
Hypertension, %	42	46	60	59‡	74	73
Diabetes mellitus, %	9	13	10	12†	24	12
Current tobacco smoking, %	21	21	10	10	10	4
Blood pressure (mean) at entry, mm Hg	147/85	146/85	146/80	137/77	141/79	142/80
Coronary artery disease, %	14	17	20	30	39	35
Intermittent atrial fibrillation, %	28	22	50	13	15	12
Peripheral vascular disease, %	8	4	0	10	14	20

Only EAFT participants who were deemed eligible for anticoagulation and randomized to anticoagulation or aspirin are considered.

*Prior TIA was not recorded in EAFT participants with recent stroke as their qualifying event; hence, prior stroke includes an uncertain fraction who also had prior TIAs.

† $P<0.05$, ‡ $P<0.01$ comparing those with prior TIA only vs those with prior stroke within each trial (ie, columns 2 with 3 for the EAFT and columns 5 with 6 for the SPAF III trial).

TABLE 3. Prognosis of Patients With Prior TIA Versus Prior Stroke*

	Patients Receiving Aspirin/Warfarin, n	Annualized Ischemic Stroke Rate on Aspirin, %/y (95% CI)	Annualized Ischemic Stroke Rate During Anticoagulation, %/y (95% CI)	RRR, Warfarin vs Aspirin, %
EAFI				
Prior ischemic stroke	175/162	11 (8–14)	4%/yr (2–7)	63*†
Prior TIA	50/57	6 (3–12)	4%/yr (1–9)	37
SPAF III trial				
Prior ischemic stroke	116/98	13 (8–21)	5%/yr (2–12)	61†
Prior TIA	57/58	9 (4–19)	2%/yr (0.2–12)	80
Combined analysis				
Prior ischemic stroke	291/260	11 (9–15)	4%/yr (3–6)	63†
Prior TIA	107/115	7 (4–12)	3%/yr (1–7)	56

RRR indicates relative risk reduction.

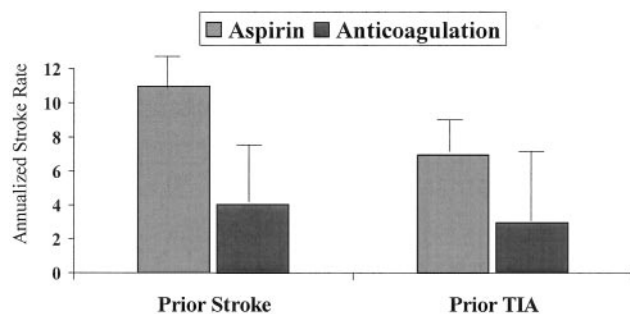
*Mean observation of 2.3 years in the EAFI, 1.1 years in the SPAF III trial, and 1.7 years in the combined analysis; patients known to have had both prior ischemic stroke and prior TIA are excluded. Probability values for differential effect (statistical interaction) of warfarin vs aspirin by trial are 0.9 for prior ischemic stroke and 0.3 for prior TIA.

† $P < 0.05$.

either trial individually ($P > 0.4$ for each interaction term) or for ischemic stroke ($P = 0.9$ for interaction term) or TIA ($P = 0.3$ for interaction term) across trials (Table 3), and the data were pooled. The annualized rate of ischemic stroke during aspirin therapy was 7% per year (95% CI, 4 to 12) for TIA patients versus 11% per year (95% CI, 9 to 15) for those with prior stroke ($P = 0.08$ for rate difference). The relative risk reduction in ischemic stroke by warfarin versus aspirin was 56% ($P = 0.09$) for those with prior TIA versus 63% ($P < 0.001$) for those with prior stroke (the Figure). The absolute rate reduction in stroke by anticoagulation over aspirin averaged 4% per year for TIA patients and 7% per year for those with prior stroke.

Discussion

Atrial fibrillation patients with prior TIA participating in the EAFI and SPAF III trial had lower rates of subsequent stroke during aspirin therapy than those with ischemic stroke, but the observed stroke rate was still substantial (7% per year) and halved by the use of warfarin. The absolute rate reduction in stroke by anticoagulation was



Stroke rates on aspirin and anticoagulation in atrial fibrillation patients with prior stroke vs prior TIA. Relative risk reduction by warfarin over aspirin was 63% ($P < 0.001$) for those with prior stroke and 56% ($P = 0.09$) for those with prior TIA.

particularly large for atrial fibrillation patients with prior ischemic stroke. These observations were consistent for atrial fibrillation patients with recent cerebral ischemia enrolled in the EAFI and for those with remote TIA and stroke participating in the SPAF III trial.

The limitations of these analyses merit attention. Atrial fibrillation patients with disabling strokes were excluded from both trials. The CIs were wide for the estimates of response to anticoagulation in participant subgroups because of the limited number of observed strokes. The lack of statistically significant interactions does not definitively exclude clinically relevant differences because of potential β error (eg, the observed reduction in stroke by warfarin over aspirin of 37% in the EAFI and 80% in the SPAF III trial among those with TIA). Finally, 8% of SPAF III trial participants and an uncertain fraction of the EAFI participants underwent carotid endarterectomy before trial entry, which could have influenced the observed event rates during aspirin therapy.

There is evidence that atrial fibrillation patients with noncardioembolic stroke may not benefit from treatment with warfarin over aspirin therapy.^{8,9} The response of atrial fibrillation patients with TIA to anticoagulation supports indirectly a cardioembolic mechanism. At present, we remain unconvinced that subgroups of atrial fibrillation patients with prior cerebral ischemia who do not benefit importantly from anticoagulation therapy can be reliably identified.¹⁰

These analyses of participants from 2 large randomized clinical trials revealed no evidence that atrial fibrillation patients with prior TIA should be managed differently from those with prior ischemic stroke regarding long-term secondary prevention. Atrial fibrillation patients with prior TIA, recent or remote, have a high risk of stroke if given aspirin and have substantial reduction in ischemic stroke when treated with adjusted-dose warfarin.

Acknowledgments

This work was supported in part by a grant (RO1 NS24224) from the National Institute of Neurological Disorders and Stroke, National Institutes of Health (Bethesda, Md). Dr Marie-Germaine Bousser (Paris, France) posed the question that stimulated these analyses.

References

1. Mead GE, Lewis SC, Wardlaw JM, Dennis MS. Comparison of risk factors in patients with transient and prolonged eye and brain ischemic syndromes. *Stroke*. 2002;33:2383–2390.
2. Harrison MJG, Marshall J. Atrial fibrillation, TIAs, and completed strokes. *Stroke*. 1984;15:441–442.
3. Weimar C, Kraywinkel K, Rodl J, Hippe A, Harms L, Koth A, Diener HC. Etiology, duration, and prognosis of transient ischemic attacks: an analysis from the German Stroke Data Bank. *Arch Neurol*. 2002;59:1584–1588.
4. Anderson DC, Kappelle LJ, Eliasziw M, Babikian VL, Pearce LA, Barnett HJM. Occurrence of hemispheric and retinal ischemic events during follow-up of patients with atrial fibrillation versus carotid stenosis. *Stroke*. 2002;33:1963–1968.
5. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: the Stroke Prevention in Atrial Fibrillation III randomized clinical trial. *Lancet*. 1996;348:633–638.
6. Stroke Prevention in Atrial Fibrillation Investigators. The Stroke Prevention in Atrial Fibrillation III Study: rationale, design and patient features. *J Stroke Cerebrovasc Dis*. 1997;6:341–353.
7. European Atrial Fibrillation Trial Study Group. European Atrial Fibrillation Trial: secondary prevention of vascular events in patients with nonrheumatic atrial fibrillation and recent transient ischemic attack or minor ischemic stroke. *Lancet*. 1993;342:1255–1262.
8. Evans A, Perez I, Yu G, Kalra L. Should stroke subtypes influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation. *Stroke*. 2001;32:2828–2832.
9. Hart RG, Pearce LA, Miller VT, Anderson DC, Rothrock JF, Albers GC, Nasco E. Cardioembolic vs. noncardioembolic stroke in atrial fibrillation: frequency and effect of antithrombotic agents. *Cerebrovasc Dis*. 2000;10:39–43.
10. 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 transient ischemic attack or minor ischemic stroke and with nonrheumatic atrial fibrillation. *Stroke*. 1995;16:801–806.