

Efficacy of Anticoagulation for Stroke Prevention and Risk Stratification in Atrial Fibrillation: Translating Trials into Clinical Practice

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Abstract

As one of the most powerful independent risk factors for ischemic stroke and the most clinically relevant arrhythmia, atrial fibrillation (AF) poses a serious clinical and public health threat as the global population ages. AF increases the risk of ischemic stroke 4- to 5-fold¹ although this statistic varies with age of the patient. Indeed, the prevalence rises to 1 in 25 people aged ≥ 60 years and 1 in 10 people aged ≥ 80 years.² More than 2.3 million Americans have diagnosed AF, and that number is expected to increase dramatically over the coming decades.² Ischemic stroke causes the most major disability and remains the third leading cause of death in the United States. Therapeutic strategies and optimal risk stratification offer the best hope for decreasing the burden of AF-related thromboembolism.

This article focuses on the randomized trial evidence for the efficacy and safety of oral vitamin K antagonists (eg, warfarin) for stroke prevention in AF. In particular, this article explores how well these findings translate into clinical practice, especially among patients with AF treated outside of clinical trials. Discussion centers on using evidence-based data to guide treatment for patients who are at increased risk for stroke. Such strategies would enhance the net benefit of oral anticoagulation. Concluding points provide information on improving risk stratification for stroke in patients with AF.

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Randomized Trial Evidence for Efficacy of Oral Vitamin K Antagonists

Multiple randomized trials completed during the late 1980s and through the 1990s investigated the efficacy of oral vitamin K antagonists for the prevention of thromboembolism (primarily ischemic stroke) in patients with nonvalvular atrial fibrillation (AF). Six randomized trials involving more than 4600

patients with AF compared oral anticoagulation with a control group.³⁻⁸ The 5 studies of primary prevention in patients with AF and no prior transient ischemic attack, ischemic stroke, or other systemic embolism include:

- Atrial Fibrillation, Aspirin, and Anticoagulation (AFASAK);
- Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF);
- Stroke Prevention in Atrial Fibrillation (SPAF-I);
- Canadian Atrial Fibrillation Anticoagulation (CAFA); and
- Stroke Prevention In Nonrheumatic Atrial Fibrillation (SPINAF).

A single secondary prevention study, the European Atrial Fibrillation Trial (EAFT), studied subjects with AF and a recent transient ischemic attack or minor stroke. Together these 6 studies are outlined in **Table 1**. These studies primarily included patients with persistent, permanent, and to a lesser degree, paroxysmal or intermittent AF. Patients with valvular causes of AF were excluded from these trials. Except for EAFT, which used phenprocoumon or acenocoumarol, these trials used warfarin as the oral anticoagulant. Notably, the control group in the BAATAF trial took aspirin. The primary prevention trials showed a consistent benefit of oral vitamin K antagonist therapy for stroke prevention, with relative risk reductions ranging from 52% to 82%. In EAFT, the benefit of oral anticoagulation in secondary prevention was similar, with a relative risk reduction of 66%. The absolute decrease in stroke was greater because of the higher baseline risk in these patients.

Several primary prevention trials (AFASAK-1, SPAF-II, SPAF-III, AFASAK-2, and Hellemons and colleagues)^{3,9-12} and the secondary prevention trial, EAFT,⁸ also evaluated the potential utility of the antiplatelet agent, aspirin, at various doses (50-325 mg daily) compared with oral vitamin K antagonist therapy (Table 2). Overall, warfarin caused a greater reduction in the risk of ischemic stroke compared with aspirin, especially in patients considered at higher risk for stroke (eg, SPAF-III). Furthermore, the combination of aspirin with low-dose warfarin does not appear to convey any greater benefit than aspirin alone for preventing thromboembolism in AF. Statistically significant results were found in 3 of 7 individual trials. This may be related to a variety of factors, including different inclusion criteria between trials, sample size issues, and/or varying target anticoagulation intensity in warfarin-treated patients.

Following the completion of these studies, meta-analyses using pooled patient data from available randomized trials summarized the effects of various antithrombotic therapies for stroke prevention (Table 3).¹³⁻¹⁵ In these pooled analyses, adjusted-dose warfarin therapy had an overall relative risk reduction of 68% for ischemic stroke compared with no antithrombotic treatment. In comparison, aspirin was less effective and of borderline statistical significance. Compared with aspirin, adjusted-dose warfarin therapy was associated with a 52% relative risk reduction for stroke. In addition, these trials revealed the bleeding risks of anticoagulant therapy. Use of oral vitamin K antagonists is associated with a modest risk of major hemorrhage (typically defined as fatal or permanent disability, leading to hospitalization, requiring blood transfusions, or occurring at a critical anatomic site, such as intracranial bleeding) and minor bleeding. This was particularly true if international normalized ratio (INR) levels were >3.0. In these trials, there was no significant major bleeding risk associated with adjusted-dose anticoagulation. The annual rate of major hemorrhage was 1.3% in anticoagulated patients compared with 1.0% in control subjects.¹³ The observed annual rate of intracranial hemorrhage was approximately 0.3% in anticoagulated subjects com-

Table 1. Summary of Randomized Trial Results of Anti-coagulation Compared With Control for Stroke Prevention in Atrial Fibrillation

| Trial | Annual Stroke Rate (%) | | | Relative Risk Reduction |
|-------------------|------------------------|---------|----------|-------------------------|
| | INR Target | Control | Warfarin | |
| AFASAK | 2.8-4.2 | 5.5 | 1.6 | 71* |
| BAATAF | 2.0-3.0 | 3.0 | 0.4 | 86* |
| SPAF-I | 2.0-4.5 | 7.4 | 2.3 | 69* |
| CAFA | 2.0-3.0 | 5.2 | 2.5 | 52 |
| SPINAF | 2.0-3.0 | 4.3 | 0.9 | 79* |
| EAFT [†] | 2.5-4.0 | 12.3 | 3.9 | 66* |

INR indicates international normalized ratio; AFASAK, Atrial Fibrillation, Aspirin, and Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; SPAF-I, Stroke Prevention in Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; SPINAF, Stroke Prevention In Nonrheumatic Atrial Fibrillation; EAFT, European Atrial Fibrillation Trial. * $P < .05$.

[†]Enrolled patients with recent prior transient ischemic attack or minor stroke.

Table 2. Summary of Randomized Trial Results of Anti-coagulation Compared With Aspirin for Stroke Prevention in Atrial Fibrillation

| Trial | Annual Stroke Rate (%) | | | Relative Risk Reduction |
|-------------------------------|------------------------|------------------|----------|-------------------------|
| | INR Target | Aspirin | Warfarin | |
| AFASAK-1 | 2.8-4.2 | 5.2 | 2.7 | 48* |
| SPAF-II: | | | | |
| Age ≤75 years | 2.0-4.5 | 1.9 | 1.3 | 33 |
| Age >75 years | 2.0-4.5 | 4.8 | 3.6 | 27 |
| SPAF-III | 2.0-3.0 | 7.9 [†] | 1.9 | 74* |
| AFASAK-2 | 2.0-3.0 | 2.7 | 3.4 | -21 |
| Hellemons et al ¹² | 2.5-3.5 | 3.1 [†] | 2.5 | 19 |
| EAFT [†] | 2.5-4.0 | N/A | N/A | 40* |

INR indicates international normalized ratio; AFASAK, Atrial Fibrillation, Aspirin, and Anticoagulation; SPAF, Stroke Prevention in Atrial Fibrillation; EAFT, European Atrial Fibrillation Trial.

* $P < .05$.

[†]Included "low-dose" warfarin therapy.

[†]Enrolled patients with recent prior transient ischemic attack or minor stroke.

Table 3. Summary of Meta-analyses of Antithrombotic Therapy for Stroke Prevention in Atrial Fibrillation

| Treatment Comparisons | Relative Risk Reduction (%) (95% Confidence Interval) |
|---|--|
| Adjusted-dose oral anticoagulation versus no antithrombotic therapy | 68 (50-79) |
| Aspirin versus no antithrombotic therapy | 21 (0-38) |
| Adjusted-dose oral anticoagulation versus aspirin | 52 (37-63) |

pared with 0.1% among control subjects. In clinical context, these findings suggest that treating 1000 patients with AF for 1 year would prevent 23 ischemic strokes and cause an excess of 9 major bleeding events. As expected, as the baseline risk of stroke increases, a greater net benefit exists for using oral vitamin K antagonists.

Can Results from Trials Be Implemented into Practice?

Evidence from existing randomized trials suggests that oral vitamin K antagonists may have advantages compared with aspirin or placebo for stroke prevention. However, some residual concerns still exist among many clinicians. For instance, can these results be duplicated in clinical practice where sicker patients with AF are managed with less intensive anticoagulation monitoring? Several observational studies have been performed to evaluate the effectiveness and safety of antithrombotic therapy for prevention of thromboembolism in AF outside of randomized trials. Unfortunately, many of these studies have been limited by including patients from selected clinical settings (eg, long-term care institutions), modest sample sizes, and few thromboembolic and bleeding events to generate accurate and precise event rates (Table 4).¹⁶⁻²³ In 2 studies of high-risk patients with AF who suffered an ischemic stroke, warfarin was found to be significantly more effective than either aspirin or no antithrombotic therapy for secondary prevention.^{16,17} Among a sample of patients hospitalized with AF, prescription

of warfarin therapy at discharge was associated with lower risks of stroke and transient ischemic attack compared with aspirin or no antithrombotic therapy.^{19,20} Furthermore, the reported risk of ischemic stroke was 1.3%²³ to 2.0 per 100 person-years¹⁸ in 2 studies involving selected patients treated with warfarin.

Recently, 2 larger studies of the effectiveness of warfarin therapy have been reported. In Denmark, a sample of 5124 people with diagnosed AF had a stroke rate of 3 per 100 person-years. Warfarin therapy was associated with lower risk of stroke in men (adjusted relative risk 0.6, 0.4-1.0) but not in women.²⁴ The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study,²⁵ a contemporary population-based cohort of 13 559 ambulatory adults with diagnosed nonvalvular AF in northern California, collected longitudinal information on warfarin use along with associated clinical outcomes. In this study, the rate of thromboembolism was significantly reduced in subjects taking warfarin (1.33 vs 2.53 per 100 person-years, respectively), with an adjusted 49% (95% confidence interval, 39%-57%) decreased risk.²⁶

In addition, the ATRIA study has shown that anticoagulation to a therapeutic INR level of 2.0 to 3.0 can reduce both the incidence of ischemic stroke as well as reduce the severity and short-term risk of death in patients with AF.²⁷

Some physicians are concerned about the risk of major hemorrhage when anticoagulation is used outside of clinical trials in older patients with AF. Reassuringly, intracranial hemorrhage and its associated high mortality and morbidity rates occurred at relatively low rates on anticoagulation (range, 0%-0.8%) in most observational studies. These rates are similar to those reported in randomized trials, although the absolute number of events were low (Table 4).^{16-18,21} In the ATRIA study, anticoagulation with warfarin was independently associated with a small but increased risk of intracranial hemorrhagic events (adjusted relative risk 1.57, 1.09-2.26).²⁶ The absolute risk of intracranial hemorrhage with warfarin treatment was relatively close to the rate in the control patients who were not receiving warfarin (0.51 vs 0.33 per 100 person-years, respec-

tively). Notably, approximately 80% of patients in the ATRIA study cohort were managed by specialized pharmacists or nurses in anticoagulation clinics, so these results may not be applicable to other care settings.

Stroke Risk Stratification in Atrial Fibrillation

Both randomized trial evidence and findings from large observational studies show that oral vitamin K antagonist therapy effectively reduces the risk of ischemic stroke in patients with nonvalvular AF and is substantially more effective than treatment with aspirin. Oral vitamin K antagonist therapy leads to a higher risk of major bleeding and is associated with greater lifestyle inconveniences (eg, dietary restrictions and frequent INR testing) compared with aspirin. Therefore, anticoagulation therapy needs to be limited to patients who are at higher intrinsic risk of stroke or are at an acceptable risk of hemorrhage. Because of the relatively low rates of bleeding observed in trials and clinical populations with well-managed anticoagulation services, and the lack of definitive data on predictors of major bleeding with anticoagulation, physicians have focused on improving risk stratification for ischemic stroke.^{28,29}

The most rigorous data on risk factors for stroke in patients with AF have come primarily from subjects enrolled in trials of antithrombotic therapy who were randomized not to receive oral vitamin K antagonists.^{8,30-32} Risk stratification schemes have been derived from pooled analyses from the Atrial Fibrillation Investigators (AFI),³³ 2 analyses from the SPAF investigators,^{31,34} and the recently published Framingham score³⁵ (Table 5). Additional derived schemes include the Congestive Heart Failure, Hypertension, Age, Diabetes, and Stroke (CHADS₂) score³⁶ and the American College of Chest Physicians (ACCP) Consensus Guidelines on Antithrombotic Therapy.³⁷

As shown in Table 5, the identified clinical predictors of stroke are largely overlapping across the various risk stratification schemes, with commonly identified factors including older age, prior systemic thromboembolism, and a history of hypertension. Other factors identified less consistently by

these schemes were female sex, diagnosed heart failure (significant left ventricular systolic function), diabetes mellitus, and systolic blood pressure level. In the AFI and SPAF trials, patients who had 1 or more of the proposed risk factors suffered higher annual rates of stroke, depending on the number and type of risk factor (eg, AFI, 4.3%-8.1%; SPAF, 2.6%-7.1%).^{31,32} A recent study from the Framingham Heart Study, which enrolled 705 patients with new-onset AF, used a scoring system that assigned points according to age, gender, systolic blood pressure, diabetes status, and prior stroke or transient ischemic attack. Using a threshold annual predicted rate of stroke of ≤ 1.5 per 100 person-years, the proportion of patients who were considered at "low risk" and less likely to benefit from anticoagulation was 14.3%.³⁵

The CHADS₂ risk index combined variables from the AFI and SPAF-I-II schemes to create a point system using administrative claims data in which 2 points were given for a previous diagnosis of stroke or transient ischemic attack, and 1 point each for age ≥ 75 years, a history of hypertension, diabetes, or congestive heart failure (scoring range, 0-6).³⁶ Among 1733 hospitalized Medicare beneficiaries aged 65 to 95 years with nonvalvular AF not discharged on warfarin, a greater CHADS₂ score was associated with a progressively higher risk of stroke. Few patients had a very high score of ≥ 5 , and $< 7\%$ of patients had a score of zero (ie, low risk).

Guidelines from the ACCP also have been developed based on existing studies, and the most recently published version stratifies patients into high-, moderate-, and low-risk groups for stroke.³⁷ High-risk patients either have ≥ 1 high risk factor (ie, prior transient ischemic attack, systemic embolus, or stroke; history of hypertension; poor left ventricular systolic function; age > 75 years; rheumatic mitral valve disease; prosthetic heart valve) or > 1 moderate risk factor (ie, age 65-75 years, diabetes mellitus, coronary artery disease with preserved left ventricular systolic function). Moderate-risk patients have only 1 moderate risk factor, and low-risk patients have no risk factors. An upcoming substantive revision to these guidelines is expected in mid-2004.

Table 4. Comparison of Observational Studies of the Effectiveness and Safety of Antithrombotic Therapy for AF

| Study | Setting | Population | Ischemic Stroke | | | | | |
|------------------|-------------------------|---|-----------------|-------------------------------|-----|---------------------------|----|--------------------------------|
| | | | N | Warfarin Risk (%) (95% CI) | N | Aspirin Risk (%) (95% CI) | N | No Risk (%) (95% CI) |
| Evans, 2001 | Hospital | 386 acute stroke patients with AF (214 warfarin, 172 aspirin) | 19 | 4.2 (2.3-6.2)*† | 33 | 9.2 (6.1-12.4)* | — | N/A |
| Evans, 2000 | Hospital | 288 ischemic stroke patients with AF eligible for and given warfarin | 16 | 3.8 (2.0-5.6)*† (on warfarin) | — | N/A | 16 | 8.5 (4.3-12.7)† (off warfarin) |
| Gage, 2000 | Hospital | 597 with chronic nonvalvular AF (203 warfarin, 125 aspirin, 269 none) | 9 | 5.5 (2.6-10.2)§ | 8 | 8.3 (3.7-15.8) | 16 | 7.8 (4.5-12.4) |
| Kalra, 2000 | Hospital | 167 with chronic nonvalvular AF with "high stroke risk" and eligible for warfarin | 6 | 2.0 (0.7-4.4) | — | N/A | — | N/A |
| Caro, 1999 | Hospital | 221 with chronic nonvalvular AF (87 warfarin, 31 aspirin, 65 "blended," 38 none) | 4 | 1.8 (0-4.5) | 4 | 5.2 (1.4-12.8) | 7 | 5.9 (2.4-11.7) |
| Aronow, 1999 | Long-term care facility | 312 with chronic AF (125 warfarin, 187 aspirin) | 40 | 32 (23.9-40.9) | 122 | 65.2 (57.9-72.0) | — | N/A |
| Goldenberg, 1999 | Nursing homes | 87 with chronic nonvalvular AF given warfarin | 4 | 4.6 (1.3-11.4)¶ | — | N/A | — | N/A |
| Gottlieb, 1994 | Managed care plan | 156 with nontransient AF given warfarin | 5 | 1.3 (0.36-3.3)† | — | N/A | — | N/A |

AF indicates atrial fibrillation; CI, confidence interval; NA, not applicable or not available.

*Target international normalized ratio of 2.0 to 3.0.

†Annual event rate.

‡Excluding intracranial hemorrhage.

§Includes ischemic stroke or transient ischemic attack.

||Per 100 patient-years.

¶Ischemic and hemorrhagic stroke.

Finally, several transthoracic echocardiographic studies have identified moderate-to-severe left ventricular dysfunction by itself was a significant incremental risk factor. Left atrial diameter has not been found to add independent prognostic infor-

mation after accounting for other known risk factors.³⁰ Transesophageal echocardiographic (TEE) studies have demonstrated that the presence of thrombus or a dense and spontaneous echo-contrast in the left atrium or a complex plaque in the aortic

| Intracranial Hemorrhage | | | | | | Major Hemorrhage | | | | | |
|-------------------------|------------------------------|---|---------------------------|---|----------------------|------------------|-----------------------------|---|---------------------------|---|------------------------------|
| N | Warfarin Risk (%) (95% CI) | N | Aspirin Risk (%) (95% CI) | N | No Risk (%) (95% CI) | N | Warfarin Risk (%) (95% CI) | N | Aspirin Risk (%) (95% CI) | N | No Risk (%) (95% CI) |
| 3 | 0.7 (0-1.4) [†] | 1 | 0.3 (0-0.8) [†] | — | N/A | 11 | 2.5 (1.0-3.9) ^{††} | 2 | 0.6 (0-1.3) ^{††} | — | N/A |
| 3 | 0.5 (0.2-0.8) [†] | — | N/A | — | N/A | 15 | 2.5 (1.2-3.8) [†] | — | N/A | — | N/A |
| — | N/A | — | N/A | — | N/A | — | N/A | — | N/A | — | N/A |
| 1 | 0.3 (0.03-2.7) | — | N/A | — | N/A | 4 | 1.4 (0.2-4.6) | — | N/A | — | N/A |
| 0 | 0 | 0 | 0 | 0 | 0 | 4 | 1.8 (0.2-3.4) | 0 | 0 | 1 | 0.1 (0.03-5.4) |
| 1 | 0.8 (0.02-4.4) | 0 | 0 | — | N/A | 4 | 3.2 (0.9-8.0) | — | N/A | — | N/A |
| — | N/A | — | N/A | — | N/A | 11 | 12.6 (6.5-21.5) | — | N/A | — | N/A |
| 0 | 0 | — | N/A | — | N/A | 2 | 0.65 (0.08-2.3) | — | N/A | — | N/A |

arch as high risk factors for stroke. However, there is no clear evidence that TEE findings contribute significant independent prognostic information for the majority of patients with chronic atrial AF. These findings do not appear to merit the

added financial expense and periprocedural risks of the procedure.

Conclusion

The clinical and public health impact of AF will continue to expand with the growing

Table 5. Independent Predictors of Stroke for Atrial Fibrillation

| Characteristic | Atrial Fibrillation Investigators | SPAF-I-II or I-III | Framingham Study |
|---|-----------------------------------|--------------------|------------------|
| Older age | + | + | + |
| Female sex | | + | + |
| Prior ischemic stroke or transient ischemic attack | + | + | + |
| Heart failure or moderate-to-severe left ventricular systolic dysfunction | | + | |
| History of hypertension | + | + | |
| Systolic blood pressure | | | + |
| Diabetes mellitus | + | | + |

SPAF indicates Stroke Prevention in Atrial Fibrillation.

elderly population worldwide. The consistent evidence from many randomized trials and large “real-world” studies demonstrate the advantage of oral vitamin K antagonist (warfarin) therapy for stroke prevention. With careful anticoagulation monitoring, this therapy has generally acceptable levels of bleeding. Complete consensus does not yet exist on the optimal risk stratification scheme to identify which individual patients are at a high enough risk for stroke to justify the use of oral anticoagulants. Present evidence suggests that the presence of 1 or more risk factors for stroke warrants an evaluation for eligibility to receive anticoagulation therapy. Despite the available data, warfarin appears to be underused. Novel methods are needed to improve evidence-based use of this therapy to prevent thromboembolism in patients with AF.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22:983-988.
 2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national impli-

cations for rhythm management and stroke prevention: the Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study. *JAMA*. 2001;285:2370-2375.

3. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. 1989;1:175-179.
 4. Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1990;323:1505-1511.
 5. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation*. 1991;84:527-539.
 6. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *J Am Coll Cardiol*. 1991;18:349-355.
 7. Ezekowitz MD, Bridgers SL, James KE, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*. 1992;327:1406-1412 [erratum in: *N Engl J Med*. 1993;328:148].
 8. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. *Lancet*. 1993;342:1255-1262.
 9. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II study. *Lancet*. 1994;343:687-691.
 10. 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.
 11. Gullov AL, Koefoed BG, Petersen P, et al. Fixed mini-dose warfarin and aspirin alone and in combination versus adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med*. 1998;158:1513-1521.
 12. Hellemons B, Langenberg M, Lodder J, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin. *BMJ*. 1999;319:958-964.
 13. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449-1457.
 14. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomized trials. The Atrial Fibrillation Investigators. *Arch Intern Med*. 1997;157:1237-1240.
 15. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288:2441-2448.
 16. Evans A, Perez I, Yu G, Kalra L. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? *Stroke*. 2001;32:2828-2832.
 17. Evans A, Perez I, Yu G, Kalra L. Secondary stroke prevention in atrial fibrillation: lessons from clinical practice. *Stroke*. 2000;31:2106-2111.
 18. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N. Prospective cohort study to determine if trial efficacy of

anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ*. 2000;320:1236-1239.

19. Gage BF, Boechler M, Doggette AL, et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. *Stroke*. 2000;31:822-827.

20. Caro JJ, Flegel KM, Orejuela ME, Kelley HE, Speckman JL, Migliaccio-Walle K. Anticoagulant prophylaxis against stroke in atrial fibrillation: effectiveness in actual practice. *CMAJ*. 1999;161:493-497 [erratum in: *CMAJ*. 2000;162:973].

21. Aronow WS, Ahn C, Kronzon I, Gutstein H. Incidence of new thromboembolic stroke in persons 62 years and older with chronic atrial fibrillation treated with warfarin versus aspirin. *J Am Geriatr Soc*. 1999;47:366-368.

22. Goldenberg GM, Silverstone FA, Rangu S, Leventer SL. Outcomes of long-term anticoagulation in frail elderly patients with atrial fibrillation. *Clin Drug Invest*. 1999;17:483-488.

23. Gottlieb LK, Salem-Schatz S. Anticoagulation in atrial fibrillation. Does efficacy in clinical trials translate into effectiveness in practice? *Arch Intern Med*. 1994;154:1945-1953.

24. Frost L, Johnsen SP, Pedersen L, Toft E, Husted S, Sorensen HT. Atrial fibrillation or flutter and stroke: a Danish population-based study of the effectiveness of oral anticoagulation in clinical practice. *J Intern Med*. 2002;252:64-69.

25. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med*. 1999;131:927-934.

26. Go AS, Hylek EM, Phillips KA, et al. Effectiveness and safety of warfarin to prevent thromboembolism among 13,559 patients with atrial fibrillation: how well do results of randomized trials apply to clinical practice? The ATRIA study. *Circulation*. 2002;106(suppl):II-515.

27. Hylek EM, Go AS, Chang Y, et al. Effect of intensity

of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019-1026.

28. Hart RG, Bailey RD. An assessment of guidelines for prevention of ischemic stroke. *Neurology*. 2002;59:977-982.

29. Thomson R, McElroy H, Sudlow M. Guidelines on anticoagulant treatment in atrial fibrillation in Great Britain: variation in content and implications for treatment. *BMJ*. 1998;316:509-513.

30. Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation. *Arch Intern Med*. 1998;158:1316-1320.

31. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. *Stroke*. 1999;30:1223-1229.

32. Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation. I: clinical features of patients at risk. *Ann Intern Med*. 1992;116:1-5.

33. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154:1449-1457.

34. Stroke Prevention in Atrial Fibrillation I. Risk factors for thromboembolism during aspirin therapy in patients with atrial fibrillation: The Stroke Prevention in Atrial Fibrillation Study. *J Stroke Cerebrovasc Dis*. 1995;5:147-157.

35. Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA*. 2003;290:1049-1056.

36. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864-2870.

37. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. *Chest*. 2001;119:194S-206S.