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See Dr. Susman's editorial "Diving for PURLs" PAGE 878

Stroke prevention: Age alone does not rule out warfarin

Practice changer

Warfarin is as safe as aspirin and more effective for stroke prevention in elders with atrial fibrillation.

Strength of recommendation (SOR)

A: Well-designed randomized controlled trial of elderly patients in the primary care setting, consistent with findings from prior RCTs

Mant et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study [BAFTA]): a randomised controlled trial. *Lancet* 2007; 370:493-503.¹

ILLUSTRATIVE CASE

An 85-year-old woman with hypertension and chronic atrial fibrillation has transferred her care to you. She takes an aspirin a day for cardiovascular prevention. You know that warfarin is better than aspirin for preventing stroke but worry about the increased risk of bleeding with warfarin.

Should you recommend that she stay on aspirin or switch to warfarin?

BACKGROUND

BAFTA: A realistic study

We have been reluctant to use warfarin in elders with atrial fibrillation for good reason: risk of hemorrhage. Since there are few trials looking at use of warfarin among elders in primary care settings,

we are uncertain about the balance of benefits and harms.

The BAFTA study¹ is the first trial to compare outcomes of warfarin vs aspirin in elders specifically, in the less-than-ideal conditions of real life.

Guidelines mirror uncertainties

This uncertainty is reflected even in guidelines for anticoagulation in elderly patients with atrial fibrillation.

- The 2004 American College of Chest Physicians Seventh Conference on Antithrombotic and Thrombolytic Therapy recommends treating all patients with atrial fibrillation and high risk of stroke with warfarin. Their definition of high-risk includes any patient with 1 or more of the following risk factors: age >75 years, prior ischemic stroke, transient ischemic attack or systemic embolism, congestive heart failure, impaired left ventricular systolic function, hypertension, or diabetes mellitus.²

- In contrast, the 2006 guidelines for the management of patients with atrial fibrillation from the American College of Cardiology, American Heart Association, and European Society of Cardiology, are more conservative. They recommend that patients with more than 1 risk factor take warfarin, and patients with only 1 risk factor (for example, a patient older than 75 years of age with no other risk factors) take either warfarin or aspirin.³

FAST TRACK

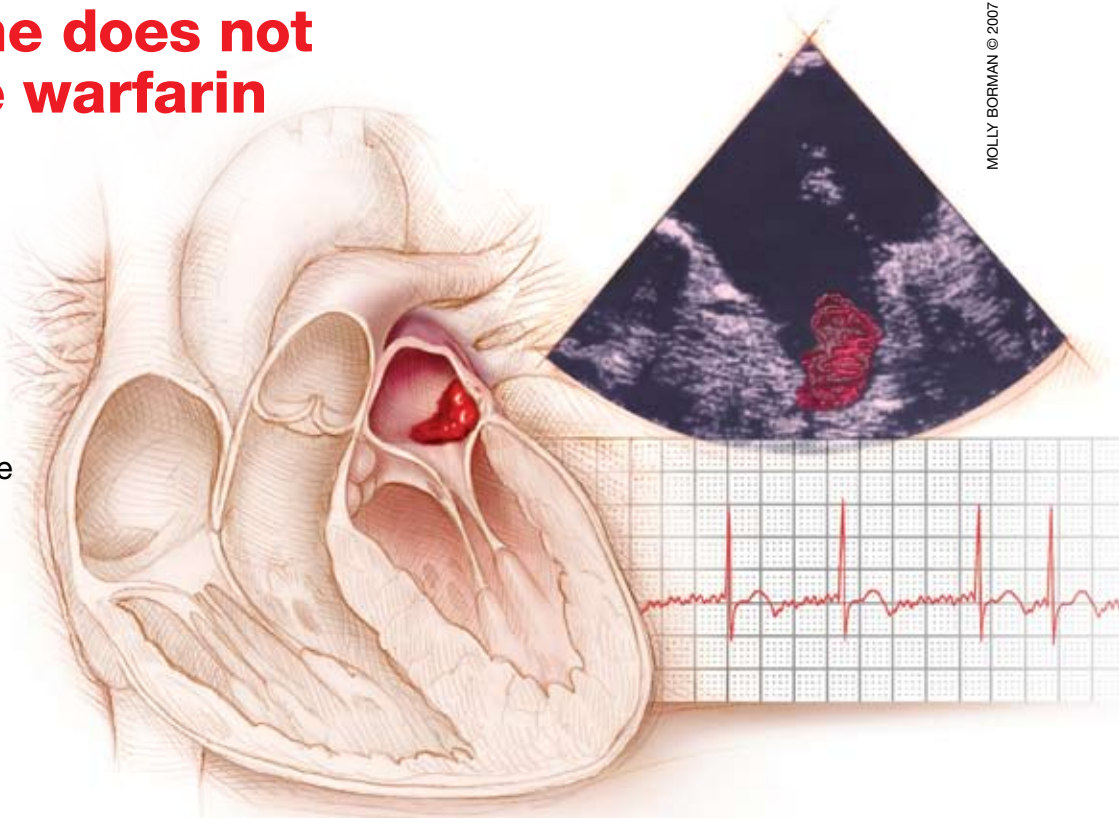
Seriously consider warfarin therapy for most of your elderly patients with atrial fibrillation

PURLs methodology

The criteria and findings leading to the selection of this study as a Priority Update from the Research Literature can be accessed at www.jfponline.com/purls.

Age alone does not preclude warfarin

The key finding from the BAFTA study is that advanced age alone is not a contraindication to the use of warfarin for stroke prevention in elderly patients with atrial fibrillation



CLINICAL CONTEXT

Reasonable concerns

Fewer than half of the 10% to 12% of people older than 75 with atrial fibrillation are taking warfarin for stroke prevention. In one study, only 35% of patients 85 years and older with no known contraindication to anticoagulation received warfarin.⁴ Possible reasons for this low rate include:

- cost of monitoring warfarin
- concerns about compliance
- increased risk of hemorrhage
- prior studies focused on younger patients, in closely monitored settings.

These factors lead us to speculate that many physicians believe that the risks of warfarin in elderly patients in primary care settings outweigh any potential benefit.

We think this study demonstrates that we should seriously discuss and consider warfarin therapy for most of our elderly patients with atrial fibrillation.

STUDY SUMMARY

Primary care setting, elders only

This prospective randomized open-label trial was designed to test the effectiveness and safety of warfarin vs aspirin in the elderly, in a realistic primary care setting. The study compared the frequency of stroke, intracranial hemorrhage, and other significant arterial embolism in patients taking either warfarin or aspirin.

Inclusion criteria. Patients were at least 75 years old (average 81.5 years) with an ECG within the previous 2 years showing atrial fibrillation or atrial flutter. Seventy percent of the patients had been previously diagnosed with atrial fibrillation and 30% were identified because they had an irregular pulse on exam.

Exclusion criteria included rheumatic heart disease, major nontraumatic hemorrhage in the past 5 years, intracranial

Warfarin was superior to aspirin in all subgroups, including patients over the age of 85

TABLE

**BAFTA study: Warfarin was as safe as aspirin
and more effective in preventing stroke in the elderly**

PRIMARY EVENTS	WARFARIN (488 patients)		ASPIRIN (485 patients)		WARFARIN VS ASPIRIN
	Total events	Risk per year	Total events	Risk per year	
Stroke	21	1.6%	44	3.4%	RR=0.46 (95% CI, 0.26–0.79) P=.003
Stroke, other intracranial hemorrhage, or systemic embolism	24	1.8%	48	3.8%	RR=0.48 (95% CI, 0.28–0.80) P=.003

RR, relative risk; CI, confidence interval.

Source: Mant J, Hobbs FD, Fletcher K et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; 370:493–503.

FAST TRACK

BAFTA is the first randomized controlled trial of warfarin vs aspirin for atrial fibrillation that included only patients 75 years and older, in a primary care setting

hemorrhage, endoscopically proven peptic ulcer disease in the past year, esophageal varices, allergy to either study drug, terminal illness, surgery in past 3 months, blood pressure greater than 180/110 mm Hg, or if the primary physician judged that a patient should either be on warfarin or not, based on risk factors.

Patient characteristics. The patients were recruited from 260 general practices in England and Wales. At baseline, 39% to 40% of the patients were already taking warfarin, 12% to 13% had had a prior stroke, 53% to 55% had hypertension, 13% to 14% had diabetes, 19% to 20% had heart failure, and 10% to 12% had a history of myocardial infarction. Patients were followed for an average of 2.7 years.

Aspirin and warfarin regimens. Patients were assigned to either aspirin at a dose of 75 mg/day or warfarin with a target international normalized ratio (INR) of 2.5 and an acceptable range of 2 to 3. Because the study aimed to reflect a realistic primary care setting, the frequency and method of INR testing was left to the discretion of participating physicians.

Patients who had been taking aspirin or warfarin prior to the study discontinued that medicine if they were assigned to the other treatment. Sixty-seven percent of the patients assigned to warfarin continued this treatment throughout

the study, and 78% of those who either stopped taking warfarin or never started it were put on either aspirin or clopidogrel. Seventy-six percent of the patients assigned to aspirin took the medicine for the entire study period, while 70% of those who stopped taking aspirin or never started it were either switched to or stayed on warfarin.

INR values. Patients on warfarin had INR values between 2.0 and 3.0 for 67% of the time, below range for 19%, of the time, and above range for 14% of the time. Twenty-two percent of practices had all components of INR monitoring done at the hospital (phlebotomy, INR analysis, and warfarin dosing), 19% of the practices completed all 3 components on site, and the remaining practices had various combinations of onsite and hospital monitoring.

The primary outcomes included disabling stroke (ischemic or hemorrhagic) or clinically significant arterial embolism. There were 24 primary events (1.8% per year) in patients assigned to warfarin compared with 48 primary events (3.8% per year) in those assigned to aspirin, with a relative risk of 0.48 (95% confidence interval [CI], 0.28–0.80 (TABLE)). The number needed to treat for 1 year to prevent 1 primary event was 50, when warfarin was compared to aspirin. Warfarin was superior to aspirin in

all subgroup analyses, including patients over 85 years old.

Secondary outcomes. There were no significant differences between the warfarin and aspirin groups in the secondary outcomes: hospital admission or death as a result of a non-stroke vascular event (6.1% risk per year with warfarin vs 6.3% risk per year with aspirin), all-cause mortality (8.0% vs 8.4%), and major extracranial hemorrhage (1.4% vs 1.6%). Patients assigned to warfarin, including the subgroup of patients older than 85, did not have an increased risk of a major hemorrhage when compared with those assigned to aspirin (1.9% risk per year with warfarin vs 2.0% risk per year with aspirin; relative risk=0.96; 95% CI, 0.53–1.75).¹

WHAT'S NEW?

■ Age alone does not preclude warfarin

The key finding from the BAFTA study is that advanced age alone is not a contraindication to the use of warfarin for stroke prevention in elderly patients with atrial fibrillation.

This is the first randomized controlled trial of warfarin for atrial fibrillation that included only patients ages 75 and older, conducted in a primary care setting.⁵

Limitations of earlier studies. The most recent meta-analysis of antithrombotic therapy for stroke prevention in patients with atrial fibrillation included 29 trials with 28,044 patients. This analysis concluded that although both warfarin and aspirin are effective in reducing the risk of stroke in patients with atrial fibrillation (warfarin by 60% and aspirin by 20%), warfarin was more effective than aspirin (relative risk reduction of 39%), with very small ($\leq 0.3\%$ per year) absolute increases in major extracranial hemorrhage.

The average age of patients in those trials, however, was 71. The authors identified the lack of data on older patients (who are at higher risk

for serious bleeding events) as a limitation of the meta-analysis. Many of these trials took place in settings with closer monitoring of INR and warfarin dosing than is customary in a primary care setting.⁵

CAVEATS

■ Consider the evidence on benefits and risks

Major bleeding from warfarin is a concern, especially in the elderly. A recent cohort study⁶ (summarized as a POEM in this journal⁷) reported high rates of major bleeding (13.1 per hundred person-years or 13.1%) in patients ≥ 80 years of age during their first year of warfarin therapy. Despite the high risk of bleeding events in this cohort study, there was considerable benefit from warfarin therapy.

None of the patients who remained on warfarin had a thrombotic stroke (personal communication with Dr Hylek by the author). The expected rate of thrombotic stroke is in the range of 5% to 6% per year in this high-risk group.

Furthermore, most of the bleeding events were gastrointestinal and did not lead to catastrophic outcomes.

■ Do not add warfarin to aspirin in patients >75 years

Dr Hylek also noted that 40% of the patients in their cohort study were taking both warfarin and aspirin, and, although her study did not have sufficient power to detect a difference, prior studies noted increased risk of bleeding with this combination compared to warfarin alone.^{8,9} For this reason we think the combination of warfarin and aspirin should be avoided in patients over 75.

■ Target INR <3

Our caveat is the same as the POEM author's conclusion:⁷ Patients over 80 should be carefully monitored to keep the INR below 3.0 or for signs of bleeding, especially in the first 90 days of therapy when bleeding is more likely to occur.

CONTINUED

FAST TRACK

Keep the patient's INR under 3.0 and watch for signs of bleeding, especially in the first 90 days of warfarin therapy

A final point that the BAFTA authors make, which is worth repeating here, is that the prior studies showing an increased risk of bleeding complications had INR target rates of 4 to 5, whereas the target in this study was 2 to 3. Two previous studies that also compared aspirin to warfarin with an INR goal of 2 to 3 similarly showed no difference in major bleeding between the 2 groups.^{10,11}

CHALLENGES TO IMPLEMENTATION

■ Meticulous monitoring, patient education

- **Managing warfarin therapy** requires meticulous care to avoid complications and optimize treatment effect.
- **Patients may be reluctant** to take warfarin because they may fear bleeding.
- **Patients who do agree to take warfarin need education** about possible medication interactions, the need for regular INR monitoring, dosage changes, and dietary issues (eg, maintaining a consistent intake of foods containing vitamin K).

■ Contraindications

Contraindications to the use of warfarin include hypersensitivity to warfarin, severe hepatic disease, alcoholism, recent trauma or surgery, history of falling or significant risk of falls, and active gastrointestinal, respiratory, or genitourinary bleeding.

■ INR testing systems

Several randomized trials support the use of monitoring systems such as a pharmacist managed anticoagulation service or decision support software, both of which can improve the percentage of patients with therapeutic INR values.^{12,13}

Using point-of-care INR tests in the office provides immediate results which allow for more timely adjustments of warfarin dose.¹⁴ ■

PURLs methodology

This study was selected and evaluated using the Family Physician Inquiries Network's Priority Updates from the Research Literature Surveillance System (PURLs) methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

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