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A SELF-TEST ON A CLINICAL CASE

Anticoagulation therapy in an elderly woman with atrial fibrillation

A 78-YEAR-OLD WOMAN with hypertension, diabetes, and a 2-year history of paroxysmal atrial fibrillation comes in for an office visit after hospitalization for an episode of symptomatic atrial fibrillation. She was discharged on a regimen of aspirin, metoprolol, an angiotensin-converting enzyme inhibitor, and an oral hypoglycemic. She has never taken anticoagulants and before this hospitalization had never been on prophylactic aspirin therapy.

Her medical history also includes an ejection fraction of 35% to 40% (normal 50% to 75% of end-diastolic volume at rest), osteoarthritis of the knees, and early Alzheimer disease. She lives in an assisted living facility where she prepares her own breakfast and lunch and eats a communal supper. A nurse's aide administers her daily medications and checks her blood sugar regularly.

The patient performs all activities of daily living (washing, bathing, dressing, toileting, feeding) and most of the instrumental activities of daily living (shopping, light cleaning, laundry, food preparation, telephoning), but she has delegated her personal bookkeeping to her son. She has stopped driving a car but is able to shop and socialize using transportation provided either by her assisted living facility or by the community.

She reports falling last year on an icy sidewalk. She has mild dyspnea on exertion since leaving the hospital, but overall she feels much better. She neither smokes nor drinks. She is pleasant and conversant. On physical examination, she has a steady gait and an irregularly irregular heart rhythm. Jugular venous distention is at the upper limits of normal. No bruits are noted over the carotid arteries. Her lungs are clear except for a few bibasilar crackles. Trace lower-extremity pitting edema is noted, as is a decrease in sensation to vibration and light touch in a bilateral stocking distribution.

Would this elderly woman with atrial fibrillation benefit from long-term anticoagulation?

ATRIAL FIBRILLATION IS COMMON IN THE ELDERLY

Atrial fibrillation is the most common cardiac dysrhythmia, affecting approximately 2.2 million people in the United States. The average age of a patient with atrial fibrillation is 75 years; the prevalence is 1 in 20 among people over age 69,[1] and 1 in 11 in people over age 80.[2]

The underlying pathophysiologic process is thought to be one or more focal rapid-firing sources of electrical activity, which initiate multiple (more than five) wavelets in the atria. Some traveling wavelets cycle back to their origin (reentry) and maintain the atrial fibrillation. Without organized electrical activation, effective contraction of the atria is lost. Ventricular filling is suboptimal, and cardiac output is diminished by 15% to 20%. If the arrhythmia persists, then atrial remodeling, both electrical and mechanical, make the arrhythmia more resistant to cardioversion.

In anticoagulation, one must balance the risk of thromboembolism vs bleeding

WHAT ARE THE RISK FACTORS FOR ATRIAL FIBRILLATION?

1 Which of these factors does not predispose to atrial fibrillation?

- ❑ Valvular heart disease
- ❑ Hypertension
- ❑ Thyrotoxicosis

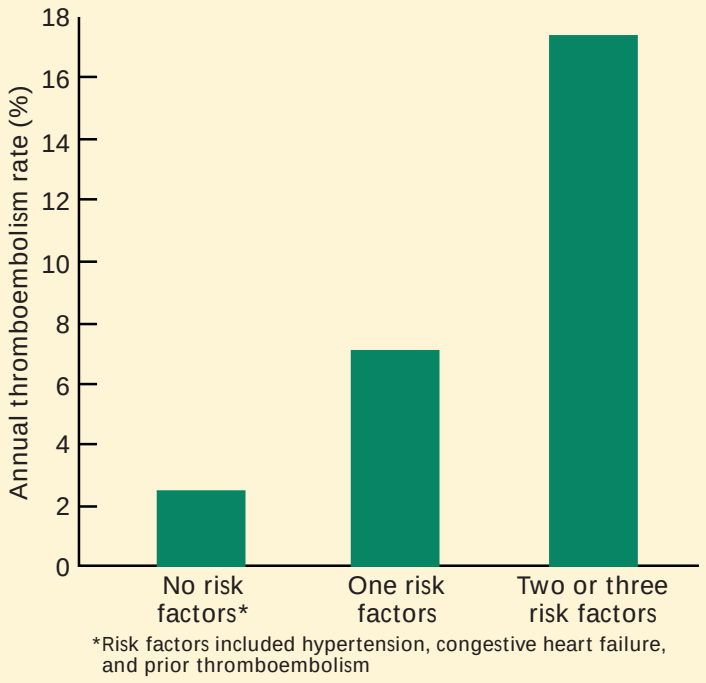

FIGURE 1. Annual rate of thromboembolism by number of risk factors in patients with atrial fibrillation.

DATA FROM THE 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.

- ❑ Congestive heart failure
- ❑ Cigarette smoking

An increased propensity for atrial fibrillation is found in disorders that increase the atrial size or decrease the tissue wavelength (the conduction velocity multipled by the refractory period of a propagating wavelet). Thus, the risk factors predisposing patients to atrial fibrillation or leading to progression from paroxysmal to chronic atrial fibrillation include valvular heart disease, rheumatic heart disease, heart failure, pericarditis, pulmonary embolism, chronic obstructive pulmonary disease, atrial myxoma (rare), hypertension, diabetes, alcohol intoxication, thyrotoxicosis, age-related degeneration of sinus node function (eg, sick sinus syndrome), and increased vagal or sympathetic tone (which, in susceptible persons, can cause postprandial or exercise-related paroxysms, respectively).

Cigarette smoking is not directly linked to atrial fibrillation.

CLINICAL SYMPTOMS

2 What is the most common symptom in patients with atrial fibrillation?

- ❑ Dizziness
- ❑ Syncope
- ❑ Chest pain
- ❑ Palpitations
- ❑ Dyspnea

About 52% of patients hospitalized with atrial fibrillation present with dyspnea, which is the most common symptom. In addition, 34% present with chest pain, 26% with palpitations, and 19% with dizziness or syncope. Impaired exercise tolerance is another presenting symptom.[3] Most of these symptoms are attributed to diminished cardiac output. There may be cognitive deficits as well. Some patients with atrial fibrillation report attention deficit, memory problems, and language deficits even without clinical or computed tomographic evidence of cerebral ischemia.

STROKE IS THE MAJOR COMPLICATION

The major complication of atrial fibrillation is stroke. Approximately 70% of strokes associated with atrial fibrillation are thromboembolic.[4] Cerebral emboli appear to result from hemodynamic stasis in the atria, in which thrombi form that can embolize to the brain and other organs.

This theory, however, does not explain why young adults with "lone" atrial fibrillation (ie, without apparent predisposing conditions) have a very low annual stroke risk (< 1%). Also, although most cerebral emboli in atrial fibrillation originate in the heart, they may also come from other sites, including the carotid arteries, cerebral vessels, and the aorta.

A newer theory is that patients with atrial fibrillation actually have a hypercoagulable state. For example, they have high plasma levels of fibrin D-dimer and beta-thromboglobulin and increased plasma vis-

cosity,[5,6] which suggests that they are producing and metabolizing fibrin at a high rate and also have increased platelet activation. These abnormalities were found to be independent of the underlying structural heart disease.[7]

HOW GREAT IS THE STROKE RISK?

3 Which of these statements is false?

- ❑ The risk of ischemic stroke is five times higher in patients with atrial fibrillation than in comparable patients in sinus rhythm
- ❑ The risk of ischemic stroke with atrial fibrillation increases with age
- ❑ Young patients with lone atrial fibrillation have a low risk of ischemic stroke
- ❑ Patients with paroxysmal atrial fibrillation have a significantly lower risk of ischemic stroke than comparable patients with chronic atrial fibrillation
- ❑ Atrial fibrillation contributes relatively less to stroke risk in Hispanics and blacks than it does in whites

The annual risk of ischemic stroke in nonvalvular atrial fibrillation is five times higher than in the general population, ie, approximately 5% per year. In young patients with lone atrial fibrillation the annual stroke risk is low—less than 1%. Risk factors for embolic stroke with atrial fibrillation include increasing age, female gender, diabetes, hypertension, heart failure, valvular disease, and prior thromboembolic events. Risk also increases with the number of risk factors (FIGURES 1 AND 2).[1,8] According to the Northern Manhattan Study, atrial fibrillation contributes relatively less to stroke in Hispanics and blacks.[9] This may reflect a lower mean age of stroke in these populations.

Surprisingly, patients with paroxysmal atrial fibrillation are at the same risk of ischemic stroke as patients with chronic atrial fibrillation.

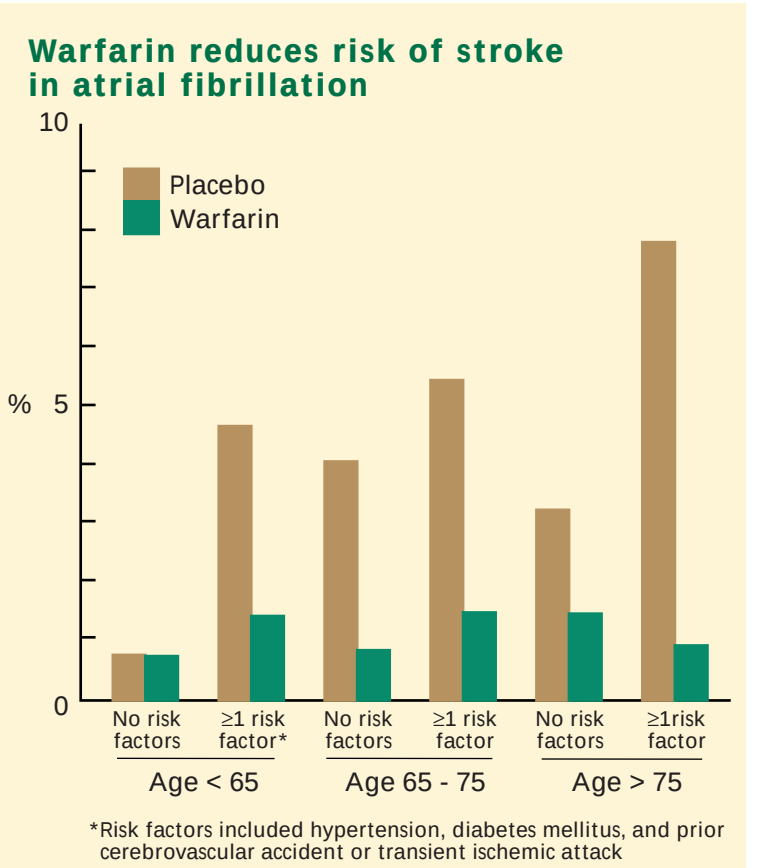

FIGURE 2. Annual rate of stroke by age and risk factors.

DATA FROM THE 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.

INITIAL TREATMENT OF ATRIAL FIBRILLATION

The initial treatment of atrial fibrillation should target precipitating or reversible causes such as thyrotoxicosis or alcohol intoxication. Long-term management includes three strategies[10]:

- Rate control using a beta-blocker, calcium-channel antagonist, digoxin, or radiofrequency ablation of the atrioventricular node followed by implantation of a ventricular permanent pacemaker
- Prevention of thromboembolism with long-term antithrombotic agents such as warfarin and aspirin
- Restoration of normal sinus rhythm by electrical or chemical cardioversion, the maze

procedure, internal atrial defibrillation, or radiofrequency ablation of a single focus.

Patients with atrial fibrillation of more than a 2-day duration who undergo cardioversion are at increased risk of cardioembolic stroke during the 30 days after the procedure. The underlying mechanism for stroke during cardioversion is thought to be dislodgement of preexisting stasis-induced thrombi.

The conventional cardioversion strategy involves 3 weeks of anticoagulation prior to cardioversion and 4 weeks of anticoagulation after cardioversion, targeting an international normalized ratio (INR) of 2 to 3. An alternative strategy is to perform transesophageal echocardiography first, then proceed to early cardioversion if no atrial thrombus is detected. This strategy decreases the risk of bleeding complications. It is also anticipated, in an ongoing trial, to decrease the risk of embolism from 2.9% to 1.2%.[11]

Anticoagulation for 4 weeks after cardioversion is recommended because stasis from atrial stunning may persist for several weeks, regardless of the cardioversion strategy used.

Paroxysmal and chronic atrial fibrillation carry the same stroke risk

RISKS, BENEFITS OF LONG-TERM ANTICOAGULATION

4 Which statement about long-term antithrombotic treatment is false?

- ❑ Adjusted-dose warfarin with an INR of 2 to 3 reduces the risk of stroke in patients with atrial fibrillation by 69%
- ❑ Adjusted-dose warfarin (INR 2–3) is superior to aspirin in preventing ischemic stroke in patients with atrial fibrillation
- ❑ Aspirin reduces stroke risk up to 44% in patients with atrial fibrillation
- ❑ Fixed doses of warfarin (INR 1.2–1.5) plus aspirin 325 mg/day reduce the risk of ischemic and hemorrhagic stroke compared with adjusted-dose warfarin (INR 2–3)

Pooled results of anticoagulation studies in atrial fibrillation demonstrate that warfarin reduces the absolute risk of stroke, from 4.5% per year without warfarin to 1.4% per year with warfarin—a 69% reduction.[1] It also reduces the mortality rate by 33%.[12] The reductions in absolute and relative risk are higher with advanced age (FIGURE 2). On the other hand, the risk of hemorrhagic complications increased, from 0.3% without warfarin to 1.8% with warfarin.

Adjusted-dose warfarin is superior to aspirin in preventing thromboembolic events in atrial fibrillation, but aspirin may be the best alternative when warfarin is contraindicated and is most beneficial in patients with underlying hypertension. The Stroke Prevention in Atrial Fibrillation (SPAF II) study[13] demonstrated that aspirin decreases ischemic stroke risk by 23% for women and 44% for men.

However, the combination of aspirin and fixed doses of warfarin may not be beneficial. The SPAF II study revealed an unexpected higher risk of ischemic stroke and hemorrhagic complications in patients with atrial fibrillation who were treated with aspirin 325 mg/day in addition to a fixed low dose of warfarin (INR 1.2–1.5) compared with standard adjusted-dose warfarin (INR 2–3) alone (7.9% vs 1.9%).

Even though the mean age of adults with atrial fibrillation is 75 years, only 20% of patients in the large clinical trials were over age 75.[1] This makes it difficult to advise our elderly patients about long-term anticoagulation. Also, the risk of bleeding may be higher in actual practice than in clinical trials, because patients in clinical trials may have higher motivation and closer follow-up.

EVALUATING RISK OF BLEEDING

5 Which is not a risk factor for intracranial hemorrhage in patients receiving anticoagulation therapy for atrial fibrillation?

- ❑ Advanced age
- ❑ Severe noncompliance
- ❑ History of falling
- ❑ Leukoaraiosis (demyelinating ischemic white-matter changes)
- ❑ History of peptic ulcer disease

In selecting candidates for anticoagulation, every patient has to be carefully evaluated for his or her individual thromboembolic

risks and the risk for experiencing an intracranial hemorrhage or major bleeding episode.

The risks of anticoagulation increase with age[14]: the annual incidence of intracranial hemorrhage is 1.8% in patients older than 75 years vs 0.3% for younger patients. Risk also increases with the intensity of anticoagulation, by a factor of 1.43 with each 0.5-mg increase in INR above the goal INR of 2 to 3.[15]

Other factors that increase the risk of intracranial hemorrhage include noncompliance and a history of falling, recent intracranial hemorrhage, and active bleeding. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT)[15] demonstrated that leukoaraiosis (as revealed by computed tomography of the head) strongly predicts warfarin-associated brain hemorrhage.

Risk factors for ischemic stroke in patients with atrial fibrillation include mitral stenosis, prosthetic heart valve, prior stroke, congestive heart failure or moderate to severe left ventricular dysfunction, hypertension, diabetes, and female gender with age older than 75. Guidelines for anticoagulation based on current data are presented in TABLE 1.[16]

Peptic ulcer disease is not a risk factor for intracranial hemorrhage.

INDIVIDUALIZING THE REGIMEN

6 Based on current guidelines and published data, which of the following is the best option for the patient in this case, a 78-year-old woman with early Alzheimer disease, atrial fibrillation, and multiple stroke risk factors?

- ❑ No antithrombotic treatment
- ❑ Aspirin 325 mg/day
- ❑ Fixed low-dose warfarin (INR 1.2–1.5)
- ❑ Fixed low-dose warfarin plus aspirin 325 mg/day
- ❑ Adjusted-dose warfarin (INR 2–3)
- ❑ Individualized treatment

Treatment must be individualized. Reduction in stroke risk for intermediate-risk and high-risk adults up to age 75 is well supported by large clinical studies. Fewer data are available for the oldest patients. Thus, the decision to anticoagulate must be individualized for the oldest patients and reassessed periodically.

Apparently, antithrombotic therapy was not offered to this patient before her hospitalization, even though she carried a diagnosis of paroxysmal atrial fibrillation and thus had a high risk of stroke, given her age and comorbidities. A stroke could force her from the assisted living facility—where she leads a relatively high-functioning life—and into a nursing home.

In her assisted living facility, medications and laboratory test results can be monitored well, even given the history of early dementia. Thus, therapeutic anticoagulation is feasible.

In terms of risk of falling, her gait is steady, and her one fall was on an icy walkway. Because she is younger than 80 years and has no other bleeding risks, she is at low risk for intracranial hemorrhage. According to the guidelines in TABLE 1, this patient would benefit most from anticoagulation with adjusted-dose warfarin with an INR range of 2 to 3. If she were over age 80, the target INR would be adjusted down to 2.0 to 2.5. If she developed a gait disorder or became noncompliant with medications as her dementia progressed, the risks of anticoagulation might outweigh the benefits, and aspirin prophylaxis might become the most expedient choice.

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