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Q/ Do A-fib patients continue to benefit from vitamin K antagonists with advancing age?

EVIDENCE-BASED ANSWER

A/ YES, patients with atrial fibrillation who are between the ages of 50 and 90 years continue to benefit from vitamin K antagonist therapy (warfarin) (strength of recommendation [SOR]: A,

meta-analysis of randomized controlled trials [RCTs] and large cohorts). Regardless of age, warfarin produces a reduction in risk of thrombotic events that is 2- to 4-fold greater than the risk of hemorrhagic events.

Evidence summary

A meta-analysis of 12 randomized trials of stroke prevention in patients with atrial fibrillation (8932 patients, 63% male, mean age 72 years, 19.6% \geq 80 years) examined outcomes of ischemic stroke, serious bleeding (systemic or intracranial hemorrhages requiring hospitalization, transfusion, or surgery) and cardiovascular events (ischemic stroke, myocardial infarction, systemic emboli, and vascular death).¹ Patients were randomized to oral anticoagulants (3430 patients), antiplatelet therapy (3531 patients), or no therapy (1971 patients).

Warfarin target international normalized ratios (INRs) ranged from 1.5 to 4.2. Previous stroke or transient ischemic attack varied across studies but averaged 22% (patient baseline characteristics were evenly distributed among all arms of all 12 studies, suggesting appropriate randomizations). Fifteen percent of patients had diabetes, 50% had hypertension, and 20% had congestive heart failure. They were followed for a mean of 2 years.

Overall, patients experienced 623 ischemic strokes, 289 serious bleeds, and 1210 cardiovascular events. After adjusting for treatment and covariates, age was independently associated with higher risk for each outcome. For every decade increase in age,

the hazard ratio (HR) for ischemic stroke was 1.45 (95% confidence interval [CI], 1.26-1.66); serious hemorrhage, 1.61 (95% CI, 1.47-1.77); and cardiovascular events, 1.43 (95% CI, 1.33-1.53).

Benefits of warfarin outweigh increased risk of hemorrhage

Treatment with vitamin K antagonists, compared with placebo, reduced ischemic strokes (HR = 0.36; 95% CI, 0.29-0.45) and cardiovascular events (HR = 0.59; 95% CI, 0.52-0.66) but increased the risk of serious hemorrhage (HR = 1.56; 95% CI, 1.03-2.37) in patients from 50 to 90 years of age. The benefits of decreased ischemic strokes and cardiovascular events consistently surpassed the increased risk of hemorrhage, however.

Across all age groups, the absolute risk reductions (ARRs) for ischemic stroke and cardiovascular events were 2% to 3% and 3% to 8%, respectively, whereas the absolute risk increase for serious hemorrhage was 0.5% to 1%. For those ages 70 to 75, for example, warfarin decreased the rate of ischemic stroke by 3% per year (number needed to treat [NNT] = 34; rates estimated from graphs) and the rate of cardiovascular events by 7% (NNT = 14) but increased the risk of serious hemorrhage by approximately 0.5% per year (number need to harm = 200).

Warfarin prevents major strokes more effectively than aspirin

A randomized open-label trial with blind assessment of endpoints, included in the meta-analysis, followed 973 patients older than 75 years (mean 81.5 years) with atrial fibrillation for 2 to 7 years.² Researchers evaluated warfarin compared with aspirin for the outcomes of major stroke, arterial embolism, and intracranial hemorrhage. Major strokes comprised fatal or disabling strokes. Researchers excluded patients with minor strokes, rheumatic heart disease, a major nontraumatic hemorrhage within the previous 5 years, intracranial hemorrhage, peptic ulcer disease, esophageal varices, or a terminal illness.

Compared with aspirin, warfarin significantly reduced all primary events (ARR = 1.8% vs 3.8%; relative risk reduction [RRR] = 0.48; 95% CI, 0.28-0.80; NNT = 50). Warfarin decreased major strokes more than aspirin (21 vs 44 strokes; ARR = 1.8%; relative risk [RR] = 0.46; 95% CI, 0.26-0.79; NNT = 56) but didn't alter the risk of hemorrhagic strokes (6 vs 5 absolute events, respectively; RRR = 1.15, 95% CI, 0.29-4.77) or other intracranial hemorrhages (2 vs 1 event, respectively; RR = 1.92; 95% CI, 0.10-113.3). Wide confidence intervals and the small number of hemorrhagic events suggest that the study wasn't powered to detect a significant difference in hemorrhagic events.

Large study finds net benefit for warfarin treatment

A retrospective cohort including all 182,678 Swedish Hospital Discharge Register patients with atrial fibrillation (260,000 patient-years) evaluated the net benefit of anticoagulation treatment decisions over an average of 1.5 years.³ The Swedish National Prescribed Drugs Registry, which includes all Swedish pharmacies, identified all patients who were prescribed warfarin during the study years of July 2005 through December 2008. The patients were divided into 2 groups, warfarin or no warfarin, and assigned risk scores using CHA2DS2-VASc and HAS-BLED.^{4,5}

Researchers defined net benefit as the number of ischemic strokes avoided in patients taking warfarin, minus the number of excess intracranial bleeds. They assigned a

weight of 1.5 to intracranial bleeds vs 1 for ischemic strokes to compensate for the generally more severe outcomes of intracranial bleeding.

Warfarin produced a net benefit at every CHA2DS2-VASc score greater than 0 (aggregate result of 3.9 fewer events per 100 patient-years; 95% CI, 3.8-4.1; NNT = 26). Kaplan-Meier composite plots of all-cause mortality, ischemic stroke, and intracranial bleeds showed a net benefit favoring warfarin use for all combinations of CHA2DS2-VASc greater than 0 (patients older than 65 years never have a CHA2DS2-VASc score of 0 because they're assigned 1 point at ages 65 to 74 years and 2 points at 75 years and older) and HAS-BLED scores (all curves $P < .00001$).

Hazard ratios (HRs) of every combination of scores favored warfarin use (HRs ranged from 0.26-0.72; 95% CIs, less than 1 for all HRs; aggregate benefit at all risk scores: HR = 0.51; 95% CI, 0.50-0.52,). The risk of intracranial bleed, or any bleed, on warfarin at all risk strata was less than the corresponding risk of ischemic stroke (or thromboembolic event) without warfarin except among the lowest risk patients (CHA2DS2-VASc = 0). The difference between thromboses and hemorrhages increased as the CHA2DS2-VASc score increased. Of note, a smaller percentage of the highest risk patients were on warfarin.

Editor's takeaway

We have solid evidence that, although the risks of systemic and intracranial bleeding from warfarin therapy in older patients with atrial fibrillation increase steadily with advancing age, so do the benefits in reduced ischemic stroke, myocardial infarction, thrombotic emboli, and overall cardiovascular death. Most important, the benefits continue to outweigh the risks by a factor of 2 to 4, even in the oldest age groups. **JFP**

References

1. van Walraven C, Hart R, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation. *Stroke*. 2009;40:1410-1416.
2. Mant J, Hobbs FD. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study):

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Patients with A-fib continue to benefit from vitamin K antagonist therapy (warfarin) at ages ranging from 50 through 90 years.

- a randomised controlled trial. *Lancet*. 2007;370:493-503.
3. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation*. 2012;125:2298-2307.
 4. Friberg L, Rosenqvist M, Lip G. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500-1510.
 5. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The Euro Heart Survey. *Chest*. 2010;138:1093-1100.