

Do Current Guidelines Result in Overuse of Warfarin Anticoagulation in Patients With Atrial Fibrillation?

Recommendations for identifying patients with nonvalvular atrial fibrillation who are at low, moderate, or high risk for thromboembolism have recently converged, advocating almost identical risk-stratification criteria (1–3). The widely promulgated CHADS₂ scheme uses a system that assigns 1 point each for congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for previous stroke or transient ischemic attack (4). Anticoagulation is generally not recommended for patients with atrial fibrillation who are at low risk for thromboembolism (CHADS₂ score of 0; about 20% of patients with atrial fibrillation, who face an average stroke risk of 1% per year), but it is favored for patients at high risk (CHADS₂ score \geq 2; about 45% of patients with atrial fibrillation, whose stroke risk averages 4% to 5% per year) who can tolerate warfarin (1–3). For those at moderate risk (CHADS₂ score of 1; about 35% of patients with atrial fibrillation, with an average stroke risk of 2% per year), either warfarin or aspirin is recommended (1), with warfarin being preferred in a prominent guideline (3). In this issue, Singer and colleagues (5) question the net clinical benefit of adjusted-dose warfarin for at least half of patients with atrial fibrillation, including the one third deemed to have moderate stroke risk (CHADS₂ score of 1), who frequently receive warfarin now.

Singer and colleagues assessed the net clinical benefit of anticoagulation in 13 559 patients with atrial fibrillation who were observed for a median of 6 years in the Kaiser Permanente of Northern California system. For more than 1 decade, this HMO-derived cohort (the ATRIA [AnTicoagulation and Risk Factors In Atrial Fibrillation] population) is among the largest described with this disorder and has been the source of many insights into stroke and anti-thrombotic therapy in patients with atrial fibrillation (6). The time in therapeutic range for patients receiving warfarin was high, averaging 65%—enough to achieve substantial protection against ischemic stroke (7). Although Singer and colleagues adjusted for factors known to predict stroke risk, treatment was not randomly assigned.

Net clinical benefit as defined in the study balanced reduction in ischemic stroke and systemic embolism against the increase in intracranial hemorrhage with anticoagulant therapy (the latter weighted by a factor of 1.5 because of the severity of the health consequences of intracranial bleeding), quantified as annual “ischemic stroke equivalents.” Because 90% of deaths attributed to warfarin involved intracranial hemorrhage (8), Singer and colleagues did not consider major extracranial bleeding or nonstroke mortality in the calculation of net clinical benefit. This neurologically focused view of net clinical benefit overlooks concerns about major extracranial bleeding that might in-

fluence patient preferences and clinical decision making. Net clinical benefit is a complicated issue that is difficult to quantify meaningfully and varies depending on the range of outcomes included and the importance that patients attach to specific health consequences. If Singer and colleagues considered major extracranial hemorrhage, the net clinical benefit of anticoagulation may have been less than the analysis suggests.

During more than 10 000 patient-years of observation, the stroke rate among ATRIA patients with atrial fibrillation who had 1 moderate risk factor for thromboembolism (CHADS₂ score of 1) was only 1.2% per year without anticoagulation (5), which, to our knowledge, is the lowest in the literature to date (1). Warfarin therapy reduced the risk for thromboembolism by 0.6% per year (number needed to treat for 1 year to prevent 1 ischemic stroke equivalent, 170), and this small benefit is even lower when the risk for intracranial hemorrhage is subtracted to calculate net clinical benefit. The low stroke rate might be explained by the use of an administrative database to detect outcomes, but Singer and colleagues argue that decreasing stroke rates in clinical trials reflect a secular trend, perhaps related to better control of hypertension (9) or other risk factors (10). Systolic blood pressures in recent large randomized trials involving patients with atrial fibrillation were, on average, nearly 10 mm Hg lower than those in trials conducted 2 decades ago. Stroke rates in patients with atrial fibrillation may well be a shifting target.

These new observations underscore the importance of risk stratification to identify patients who are likely to benefit most from long-term anticoagulation. Using the CHADS₂ scheme (4), which is 1 of several available risk models (1–3, 11), Singer and colleagues found that ATRIA participants with scores of 0 or 1, about half of patients with atrial fibrillation, gained no net benefit from warfarin. Net benefit was clear when CHADS₂ scores were 2 or greater (5). The patient groups with the largest net benefit were patients with a history of ischemic stroke (2.5% per year; number needed to treat for 1 year to prevent 1 ischemic stroke equivalent, 40) and patients older than 85 years (2.3% per year; number needed to treat to prevent 1 ischemic stroke equivalent, 43). Of note, novel oral anticoagulants for patients with atrial fibrillation are on the horizon, and the net clinical benefit at different levels of intrinsic stroke risk will need to be assessed for these agents.

These results challenge us to reconsider the benefit of warfarin for a substantial proportion of patients with atrial fibrillation. The ATRIA findings require confirmation in other large cohorts of patients with atrial fibrillation. If confirmed, recommendations should be modified to ensure that patients with atrial fibrillation for whom anticoagula-

tion is advocated are likely to accrue net clinical benefit when the small risk for catastrophic cerebral hemorrhage is considered.

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