Anticoagulation for stroke prevention: Yes, no, maybe

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Most of the interest in antithrombotics for stroke prevention has been for the prevention of later recurrence, over a period of, say, 2 years or more. Part of the reason for this has been the assumption that sufficient time would be needed for the event rate to show itself, since events in the first few hours or days, during hospitalization, might be difficult to study with any degree of success.

STROKE PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION

The results of *primary* prevention trials in the setting of atrial fibrillation make it widely assumed that not only those seeking prevention of a first stroke (primary prevention) but also those with atrial fibrillation who have already suffered a stroke require dose-adjusted oral anticoagulation (to a target international normalized ratio [INR] of 2.5 ± 0.5). Although warfarin has proved itself superior to a range of other therapies, including placebo, rates of recurrent stroke, even on warfarin, are higher than those of first stroke.[1,2] The INR effects in *secondary* prevention trials show a similar-shaped curve to that for primary prevention trials, flattening between INRs of 1.5 to 2.0 and remaining relatively stable for higher values to 3.0.

Issues of safety have not been as well established. Acceptably low hemorrhage rates have been reported with INRs of 2.0 to 3.0 in patients with atrial fibrillation in some studies of prevention of first and recurrent stroke.[3] Yet major hemorrhagic complications at an INR of 2.8 (treatment range of 2.2 to 3.5) forced discontinuation of a trial for prevention of recurrent stroke in patients with atrial fibrillation, although the lower-intensity range of 1.5 to 2.1 proved safe.[4] These more recent experiences leave unsettled the actual safety of anticoagulants in the prevention of recurrent, as opposed to primary, ischemic stroke.

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PREVENTION OF NONCARDIOGENIC STROKE: THE WARSS FINDINGS

As recently as 1989, a report from the World Health Organization expressed dissatisfaction with the lack of a proven medical therapy to prevent recurrent ischemic stroke.[5] In the decade that followed, considerable effort was directed toward this problem, along several lines. Initially, concerns for safety with warfarin prompted work that was largely limited to antithrombotic agents of the platelet antiaggregant type.

Warfarin vs aspirin for noncardiogenic stroke

The Warfarin-Aspirin Recurrent Stroke Study (WARSS)[6] took as its point of departure the question of whether the 30% risk reduction for primary stroke in the setting of atrial fibrillation could be approximated for noncardioembolic recurrent ischemic stroke. No precedent existed for such a finding except the supportive evidence that at least some instances of noncardioembolic stroke appeared, on clinical grounds, to suggest an embolic mechanism, even though none could be found, a category embraced by the general term "cryptogenic stroke."[2] A target of 30% risk reduction at least allowed for the calculation of sample size using the roughly 8% per year recurrence rate achieved in most trials with aspirin. WARSS was therefore never conceived as an equivalence trial. The patients in WARSS underwent a degree of laboratory workup reflecting current standards of care.

The overall rates of stroke and death (372 of 2,206 patients, 16.9%) at 2 years (recorded as 761 days, or 1 month beyond 2 years) in WARSS approximated those of the original hypotheses used to calculate sample size, and sufficed for prespecified analyses. By intent-to-treat analysis comparing the two treatment arms, there was no difference for the primary outcome of death or recurrent ischemic stroke (relative risk [RR] = 1.13 for warfarin; 95% CI, 0.92 to 1.38; P = .25). Among patients treated with warfarin, 47 died and 149 suffered recurrent ischemic stroke, for a total of 196 primary events among 1,103 warfarin recipients (17.7%). Among patients treated with aspirin, 53 died and 123 suffered recurrent ischemic stroke, for a total of 176 primary events among 1,103 aspirin recipients (15.9%).

Because more than 30 patients (< 1.5% of the total) ended their study participation for a variety of uncontrollable reasons (moving to another state, etc), a special computation was made to undertake an efficacy analysis for the remaining 2,164 patients. The findings of the trial were not changed.

Observations from WARSS

Taken as a condensed summary, the overall findings from WARSS failed to confirm 30% superiority of warfarin over aspirin. They also failed to show a statistically significant difference betweeen the two treatment arms. WARSS was not powered to be an equivalence trial, and the results should be understood to have failed to confirm statistically significant differential therapeutic effects for the two treatments. A difference might exist, but the study's findings do not allow a statement of difference or of equivalence. That said, data seeking differences for any clinically identifiable subtypes of ischemic stroke are even more limited. The results leave unclear whether warfarin can be justified for any but obvious cardioembolic strokes, or whether each of the treatments appears justifiable for any of the stroke subtypes.

Two other general findings are worth comment as well. First, several clinicians expressed concern that the time required for warfarin to take effect might bias the trial toward early recurrent events in the warfarin arm, nullifying any beneficial effects later. To address this concern, a prespecified null hypothesis was explored for the slope of events for the first 30 days; there was no statistically significant difference between the two treatment groups for this period. A second concern related to safety and hemorrhage, as discussed in the following section.

■ INR RANGE, COMPLICATIONS, AND PREVENTION OF RECURRENT STROKE: WARSS AND BEYOND

Safety in WARSS at the 1.4 to 2.8 INR range was to prove adequate. To the surprise of many of the investigators, major hemorrhage rates proved comparable between the aspirin and warfarin groups. Major hemorrhage occurred in 68 patients, 38 of whom were randomized to warfarin (3.44% incidence) and 30 to aspirin (2.71% incidence). The difference was not statistically significant (RR for warfarin = 1.28; 95% CI, 0.80 to 2.07; P = .304), and rates of major adverse events were below the prespecified threshold for ending the trial early. "Major hemorrhage" was defined as any intracranial or intraspinal hemorrhage, hemorrhage into the eye, or any hemorrhage in any other site leading to transfusion. Rates of *minor* hemorrhage in WARSS were significantly higher for warfarin than for aspirin, a finding replicated in other trials.

At issue in any trial comparing warfarin with aspirin is the choice of the target INR. For WARSS, the range selected approximated that in the atrial fibrillation trials, where efficacy and safety had been demonstrated at ranges from 1.5 to 3.0. The range of 1.4 to 2.8 was also selected in part on the basis of results from studies of levels of the prothrombin split product F1+2, indicating that suppression of thrombosis could be achieved by values of 1.4 and higher.[7] The clinicians participating in the trial were prepared to accept this range as safe and presumably suitable for a test of efficacy. No clinical trial data had demonstrated safety of INRs above 2.5 at the time the trial was begun.

Hemorrhage risk in SPIRIT/ESPRIT

Complications with warfarin have been well documented in trials in populations with no prior stroke,[4,8,9] as well as in the stroke population, which is mainly elderly and at higher risk for hemorrhage.[6,10] Few studies have addressed the risk of serious hemorrhage in a setting of prior ischemic stroke. One such effort was the Stroke Prevention in Reversible Ischemia Trial (SPIRIT).[11] This study, which began after WARSS had started enrolling patients and shared protocol details with WARSS, was an *open-label* comparison of warfarin with lower-dose aspirin following transient ischemic attack or stroke. Outcomes were reviewed by a panel blinded to therapy. No monitoring of INRs, institutional audits, or central laboratory performance of INRs

were part of the research plan.

This study, undertaken with a planned INR range of 3.0 to 4.5 (actual reported mean INR of 3.5), was brought to an end after the first interim analysis. The complications of therapy were due almost entirely to hemorrhage, and these events occurred mainly in the warfarin group.[9] Among the 1,316 patients reported to have been enrolled at the first interim analysis, 81 of 651 patients in the anticoagulation group had had events, compared with 36 of 665 patients in the aspirin group (hazard ratio = 2.3; 95% CI, 1.6 to 3.5). The bleeding incidence, calculated from this small sample, was estimated to have been increased by a factor of 1.43 (95% CI, 0.96 to 2.13) for each 0.5-unit increase in the achieved INR. No reports from SPIRIT have appeared documenting the stability of the INRs in the treated patients over time or documenting the percentages of patients above the upper or below the lower ranges of the planned INRs. For this reason, it cannot yet be inferred whether the rates of serious hemorrhage were related to large fluctuations, to time well above the targeted range, or to any other variable apart from the reported mean. The study has undergone revision and has restarted under a new name, ESPRIT.[12]

Apart from this open-label study, other efforts in nonstroke settings with higher INR ranges than those used in WARSS have also had mixed results where warfarin was assessed in comparison with[13] or in combination with[14] aspirin. In these latter trials, the cohort mainly has consisted of patients with cardiac disease, not stroke.

■ ISCHEMIC STROKE SUBTYPES AND DIFFERENTIAL EFFECTS OF THERAPY IN WARSS

Prior studies may have wisely shied away from attempts at characterizing the mechanism of ischemic stroke. Such efforts have a long history and a well-known degree of disagreement as to nomenclature and successful application of algorithms, having been described,[15] refined,[16] debated and contrasted with others,[17] expanded,[18] and, for at least some definitions, validated as clinically recognizable.[19]

Accepting a minor degree of uncertainty in the exact application of diagnostic algorithms, the WARSS project classified recurrent ischemic strokes into three broad groups: lacunar, large-artery, and cryptogenic. Given the debates that continue on the mechanism of infarction each of these is thought to represent, it was notable that the number and percentage of events were found to be similar in each of the three major infarct subtypes:

- For lacunar stroke, primary events occurred in 107 of 612 patients (17.5%) on warfarin and in 95 of 625 patients (15.2%) on aspirin.
- For cryptogenic stroke, primary events occurred in 42 of 281 patients (14.9%) on warfarin and in 48 of 295 patients (16.3%) on aspirin.
- For large-artery stroke, primary events occurred in 27 of 144 patients (18.7%) on warfarin and in 18 of 115 patients (15.6%) on aspirin.

Were no further efforts made to analyze the basis for the diagnosis in such cases, there would be ample basis for concluding that prior trials loosely diagnosing "stroke" or "ischemic stroke" should suffice to settle the essential homogeneity of the therapeutic effects between an anticoagulant and a platelet antiaggregant. However, in the analysis plan constructed by the investigators and reviewed with the National Institutes of Health–supported performance, safety, and monitoring board, a number of detailed subset analyses had been planned and were undertaken. The results were presented at the Joint International Stroke Meeting in San Antonio, Tex. (Feb. 8, 2002), in a special symposium devoted to WARSS. The general results from parallel studies conducted within the WARSS cohort were presented, showing no effect on recurrent stroke and no differential response to warfarin or aspirin for any of the following groups:

- Patients showing an antiphospholipid profile considered sufficient for a diagnosis of the antiphospholipid syndrome
- Patients whose circulating values of the prothrombin split product F1.2 (formerly known as F1+2) were measured
- Patients with or without a cardiac patent foramen ovale.

Within the cryptogenic stroke group, which was the only subtype group showing the faintest hint of a warfarin effect (although not statistically significant), exploratory analyses found a 30% risk reduction (P = .02) for nonhypertensive patients whose infarcts affected the cerebral convexity or the convexity plus a deep ipsilateral infarct, or whose infarct was "large and deep" (beyond the size bounds usually considered examples of lacunar infarction). For many clinicians, the cryptogenic subtype is suspected to contain many occult examples of embolism, even if no obvious source is found. This 30% risk reduction could mean that such cases represent a

link to the effects found at similar levels of risk reduction with warfarin. The data supporting this possibility come from a randomized, double-blind trial with prespecified subset analyses, and while these data may not satisfy the most vocal critics, they could provide a link with a warfarin effect in atrial fibrillation to occult embolism without atrial fibrillation. Further studies would be useful, but support for yet another warfarin trial may be limited.

Similar subset analyses provided no comfort for those whose practice has been to consider warfarin the stronger of the two agents for large-artery disease and lacunes. In these settings, warfarin use was associated with, if anything, a slightly higher rate of primary events. The lacune group (n = 1,237) was of sufficient size that the lack of difference between the two treatment arms, even a clear numerical difference favoring aspirin, is likely to blunt further similar direct comparisons. The large-artery stroke subgroup contained smaller numbers (n = 259) but also showed no treatment differences by intent-to-treat analysis. Subset analyses showed a far higher recurrence rate for the warfarin arm in primary brainstem infarction. One can only speculate how these data influence the ongoing trial comparing warfarin with aspirin,[20] which seeks a 50% risk reduction favoring warfarin.

Pursued below the first level of analysis, the WARSS findings suggest that future trials should not be content to merely count "strokes" but would profit from as detailed a data-collection mechanism as is now slowly emerging in more recent clinical trial designs, addressing issues of diagnosis subtype and estimates of severity.[21] The field has gone beyond head counts to now demand information that bears on therapy directed at the cause of the clinical event. We should follow the lead of infectious disease specialists, who look to the nature of the organism and its sensitivities to various antimicrobials as the point of departure in treating a fever of infectious origin. Until stroke specialists insist on the same, we will still be using the vascular equivalent of broad-spectrum antibiotics.

■ COMBINED WARFARIN AND ASPIRIN THERAPY

Painful experience argues against the simple assumption that a decision between these two drug classes can be avoided by their simple combination for the prevention of recurrent ischemic stroke. No trial has directly assessed this point, but "stroke" as an outcome in several trials suggests that clinicians will be disappointed if they infer that the two agents can be managed safely if the INR is kept below 3.0.

A range of studies have pursued the possibility that a combination of aspirin and warfarin may achieve the best of both with a minimum of complications. Unfortunately, none of the efforts as yet appears to either show such benefits or achieve them without worrisome hemorrhagic complications. Two sets of studies exist, the first after myocardial infarction (MI) and the other in the setting of atrial fibrillation.

Post-MI studies. The original Coumadin Aspirin Reinfarction Study[22] showed no superiority of fixed-dose warfarin (1 or 3 mg) plus 80 mg of aspirin over 160 mg of aspirin alone. The recently completed Warfarin-Aspirin Reinfarction Study (WARIS-II)[23] achieved benefits with warfarin (INR of 2.0 to 2.5) plus aspirin (75 mg) vs aspirin (160 mg) alone, as well as with warfarin (INR of 2.8 to 4.2) vs aspirin (160 mg). However, the hope that hemorrhagic complications could be avoided with the combination if the INR were adjusted to the range of 2.0 to 2.5 was not realized: hemorrhagic complication rates were comparable to those for warfarin with high INR ranges. The CHAMP study[24] fits between these two extremes, having compared warfarin (INR of 1.5 to 2.5) plus 81 mg of aspirin with 162 mg of aspirin alone (there is no expected difference between 160 mg and 162 mg if none has been found for wider differences in dose). As in other studies, no benefits accrued for the prevention of recurrent MI, and the combination group had a far higher rate of major bleeding (1.28 vs 0.72 events per 100 person-years; $P < .001$).

Atrial fibrillation study. A recent French study in the setting of atrial fibrillation has come to similarly disappointing conclusions.[25] This 49-institution, placebo-controlled, double-blind trial randomized patients with atrial fibrillation aged 65 years or older who had had a prior "thromboembolic event" to either the oral anticoagulant fluindione plus placebo or fluindione plus aspirin. The targeted INR was 2.0 to 2.6. The primary end point was a composite of stroke (ischemic or hemorrhagic), MI, systemic arterial emboli, or vascular death. The 157 patients were followed for a mere 0.84 years, on average. The imbalance was great, with 10 nonfatal hemorrhagic complications in the combination group (13.1%) vs 1 in the anticoagulation-only group (1.2%) ($P = .003$).

The findings to date suffice to argue against safe-

ty, even given unsettled possible benefits from higher-dose combination therapies. The findings also argue that those inclined to use any combination therapy are, at best, unlikely to see enough patients in their practice to test any benefits and, at worst, unlikely to be aware of the risks from hemorrhagic complications amply documented in these studies. Assuming the findings are broadly representative for vascular disease in general, they may also dampen enthusiasm for combined warfarin and aspirin therapy in other vascular beds, cerebrovascular beds in particular.

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