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## Warfarin-Aspirin Recurrent Stroke Study (WARSS) Trial Is Warfarin Really a Reasonable Therapeutic Alternative to Aspirin for Preventing Recurrent Noncardioembolic Ischemic Stroke?

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Eleven years ago, on June 1, 1991, Dr J.P. Mohr addressed delegates of the International Conference on Stroke, Geneva, about anticoagulants as a therapeutic strategy in stroke. He bemoaned the fact that heparin and warfarin had the “bad luck” to be manufactured initially in the post-World War II period, before drugs were evaluated by controlled clinical trials. As a consequence, clinicians judged their effectiveness on the basis of theory and compared their personal experience with historical controls and with those found in the literature. With the passage of time, the drug patents expired, the views and practices of clinicians became polarized, and any commercial and scientific motive to conduct controlled clinical trials of anticoagulation in secondary stroke prevention, once called for, disappeared. Dr Mohr sadly concluded that “there are no [reliable] data really” for anticoagulation after ischemic stroke. This was probably the platform from which he planned, with colleagues, the Warfarin-Aspirin Recurrent Stroke Study (WARSS).<sup>1</sup>

### What Was the Rationale for Comparing the Effectiveness of Warfarin and Aspirin in Noncardioembolic Ischemic Stroke?

Noncardioembolic ischemic stroke underpins ≈60% of all first-ever and recurrent strokes. The major causes are (1) thrombotic occlusion of large and medium-sized arteries that is due to in situ atherothrombosis or atherothromboembolism and (2) thrombotic occlusion of small perforating intracerebral arteries affected by microatheroma/lipohyalinosis.

The formation of thrombus on the subendothelial tissue of arteries depends on the initial formation of a platelet plug (by means of platelet adhesion, activation, and aggregation) and the generation of a meshwork of fibrin (by means of the coagulation cascade). Antiplatelet drugs are designed to prevent the formation of the “white” platelet plug, and anticoagulants are designed to prevent the formation of the “red” fibrin clot. Theoretically, antiplatelet and anticoagulant

therapy should be effective in preventing recurrent noncardioembolic stroke, provided that they can both be administered safely over a long period of time.

### What Was the Previous Evidence for the Effectiveness of Warfarin and Aspirin in Noncardioembolic Ischemic Stroke?

#### Indirect Comparisons of Effectiveness Compared With Control

A systematic review of 11 randomized controlled trials (RCTs) of aspirin versus control in ≈10 000 patients with previous stroke or transient ischemic attack (TIA) revealed that long-term aspirin therapy reduced the relative risk of recurrent serious vascular events (stroke, myocardial infarction [MI], or death due to a vascular cause) by 13% (95% CI 6% to 19%), corresponding to an absolute risk reduction of ≈1% per year (ie, from 7% to 6% per year).<sup>2,3</sup>

A systematic review of 9 RCTs of anticoagulation versus control in 1214 patients with previous stroke or TIA showed that long-term oral anticoagulation was associated with no significant reduction in the rate of serious vascular events during follow-up (odds ratio [OR] 0.96, 95% CI 0.68 to 1.37). However, oral anticoagulation was associated with a trend toward a reduction in recurrent ischemic/unknown stroke (OR 0.79, 95% CI 0.56 to 1.13) but at the expense of an increase in fatal symptomatic hemorrhagic stroke (OR 2.54, 95% CI 1.19 to 5.45), thus nullifying any overall effect on recurrent stroke of all types (ischemic and hemorrhagic) during follow-up (OR 0.92, 95% CI 0.67 to 1.27).<sup>4</sup>

#### Direct “Head-to-Head” Comparisons

A systematic review of 4 RCTs of oral anticoagulants versus antiplatelet therapy in a total of 1870 patients with previous TIA or minor stroke of presumed arterial origin showed that compared with antiplatelet therapy, long-term oral anticoagulant therapy with a high international normalized ratio (INR,

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3.0 to 4.5) was associated with a significantly higher rate of recurrent serious vascular events in the 1316 patients randomized (OR 2.38, 95% CI 1.63 to 3.48).<sup>5</sup> This was mainly because of a higher rate of major bleeding complications (OR 5.42, 95% CI 3.21 to 9.13) and recurrent stroke of any type (OR 2.06, 95% CI 1.22 to 3.45).<sup>5</sup> However, there was no difference in the rate of recurrent ischemic stroke (OR 1.02, 95% CI 0.48 to 2.16).<sup>5</sup>

Among the 493 patients randomized to long-term oral anticoagulant therapy with a medium INR (2.1 to 3.6) or antiplatelet therapy, there was no difference in the rate of recurrent ischemic stroke (OR 0.96, 95% CI 0.36 to 2.54), recurrent stroke of any type (OR 0.81, 95% CI 0.35 to 1.87), recurrent stroke or vascular death (relative risk 1.07, 95% CI 0.54 to 2.12), or the rate of major bleeding complications (OR 1.21, 95% CI 0.56 to 2.59).<sup>5</sup>

### What Was the Unresolved Burning Question?

Given that antiplatelet therapy was the antithrombotic treatment of first choice for the prevention of recurrent serious vascular events in patients with previous noncardioembolic TIA or ischemic stroke,<sup>3</sup> the unresolved burning question asked by the WARSS investigators was whether low- or medium-intensity oral anticoagulation was more effective than (ie, superior to) antiplatelet therapy (the gold standard). It was not whether anticoagulation was equivalent to antiplatelet therapy, presumably because anticoagulation would not be accepted into clinical practice (even if proven equivalent to antiplatelet therapy) because of greater bleeding risks and the inconvenience and cost associated with repeated blood INR tests.

Four randomized trials have now set out to address this question: the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT),<sup>6</sup> the Warfarin-Aspirin Symptomatic Intracranial Disease Study (WASID),<sup>7,8</sup> and the Aortic Arch Related Cerebral Hazard (ARCH) trial (principal investigators G.A. Donnan and P. Amarenco), which are still ongoing, and WARSS, which is now reported.<sup>1</sup>

### What Are the Strengths of WARSS?

The strengths of WARSS, for which the investigators are to be congratulated, are that it is by far the largest-ever randomized trial of oral anticoagulant therapy (low-medium INR) versus antiplatelet therapy, increasing the evidence base by  $\approx$ 450% (ie, from 493 patients to 2699 patients). Moreover, the patients, attending clinicians, and outcome evaluators were all blinded to knowledge of the treatment allocation (ie, it was a double-blind study), which is a remarkable effort for a study in which the effect of 1 intervention (warfarin) needs to be monitored by frequent blood (INR) tests. Furthermore, the daily INR values were maintained within the target range (1.4 to 2.8) in 71% of the patients; follow-up at 2 years was complete for 98.5% of the patients; and the etiologic subtype of the index ischemic stroke was identified, allowing for an analysis of the consistency of the overall treatment effects in etiologic subtypes of stroke.

### What Are the Weaknesses of WARSS?

The main weaknesses of WARSS, in my opinion, relate to the choice of the INR range (1.4 to 2.8) for patients allocated warfarin, the choice of the primary outcome event, and the estimated likely treatment effect to reject the null hypothesis.

The lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation is an INR of  $\approx$ 1.8.<sup>9</sup> Patients with an INR of 1.7 have twice (95% CI 1.6 to 2.4) the odds of stroke as those with an INR of 2.0, and patients with an INR of 1.5 have a 3.3 (2.4 to 4.6) times the odds of stroke as those with an INR of 2.0.<sup>9</sup> If the same applies to patients with TIA/ischemic stroke due to arterial disease (which appears to be the case<sup>10</sup>), then an acceptable target INR as low as 1.4 is likely to be ineffective. Any possible favorable or unfavorable treatment effects of warfarin are likely to be underestimated in WARSS because the median daily INR for patients taking warfarin was only 1.9 and because 16.3% of the daily INR values were  $<$ 1.4.

The primary outcome event (recurrent ischemic stroke or death) was biased toward efficacy rather than efficacy and safety and should have included all the possible important benefits and hazards of warfarin and aspirin. These are nonfatal intracranial hemorrhage at the very least (so that the primary outcome would be recurrent stroke or death), nonfatal extracranial major hemorrhage as well, and also, ideally, nonfatal MI (ie, with the primary outcome event being nonfatal stroke, nonfatal MI, nonfatal extracranial major hemorrhage, or death). The rationale for including nonfatal MI would be to determine whether the proven additional benefits of antiplatelet therapy in preventing MI among stroke patients could be matched, or exceeded, by warfarin.

The WARSS study was powered to detect a 30% relative reduction in the primary outcome event rate for 1 therapy from 16% at 2 years (to 11.2% at 2 years) with 80% power and a 5% two-sided probability of a type I error. From the available evidence before the trial was terminated,<sup>2-5</sup> this was an overoptimistic estimate of the likely treatment effect. Consequently, the trial was underpowered statistically to reliably detect or exclude more modest, but clinically realistic and important, treatment effects.

### How Should the Results of WARSS Be Interpreted?

The results of WARSS can be interpreted in several different ways, as discussed below.

#### Warfarin Is Equally Effective as Aspirin

The WARSS investigators interpreted their failure to reject the null hypothesis (eg, no significant difference in effectiveness between warfarin and aspirin) as indicating that "both warfarin and aspirin [can be regarded] as reasonable therapeutic alternatives."<sup>1</sup> However, failure to reject the null hypothesis is not proof of the null hypothesis or of equivalence. It may simply be the result of inadequate sample size to reliably detect, with 95% confidence, up to a 38% excess hazard of the primary outcome event for warfarin compared with aspirin or up to an 8% excess hazard of the primary outcome event for aspirin compared with warfarin.

WARSS was neither designed nor powered to study equivalence. Equivalence trials set out to prove that treatments are not different. The null hypothesis to be tested (and disproved if the trial shows equivalence) is actually that the treatments are different.<sup>11</sup> When an equivalence trial is designed, a power calculation and sample size determination are performed to assess the probability that a lack of difference would be obtained by chance. Although proof of exact equality is not possible, this issue is resolved in practice by defining an arbitrary practical equivalence margin, called the noninferiority margin.<sup>11</sup> To detect this difference, on average, equivalence trials, compared with conventional superiority trials (eg, WARSS), usually require a 10% larger sample size. The null hypothesis is rejected if the upper limit of the CI for the difference between the treatments is smaller than this predefined margin.<sup>11</sup>

### Warfarin Is a Potentially Hazardous Placebo

Another interpretation of the results of WARSS is that the effect of warfarin was equivalent to that of a placebo. This is based on an indirect comparison of the 13% (95% CI –8% to 38%) excess relative hazard (11.25% excess relative risk) of recurrent ischemic stroke or death among the WARSS patients randomized to warfarin, as opposed to aspirin,<sup>1</sup> with the 13% (95% CI 6% to 19%) excess relative risk of serious vascular events among the 10 000 TIA/ischemic stroke patients randomized to placebo, as opposed to aspirin, in the 11 RCTs reviewed by Algra and van Gijn.<sup>2</sup> However, this indirect comparison is potentially flawed because it compares slightly different estimates (relative risks versus relative hazards) of slightly different outcome events against the same control (aspirin), not each other. Such indirect comparisons are not reliable, in the same way that it is unreliable to compare the United States and Canadian ice hockey teams by their respective performances against the Russian team; it is more reliable to have them oppose each other directly.

### Warfarin Is Not More Effective Than Aspirin

The WARSS investigators aimed to determine whether warfarin would prove to be superior to aspirin in the prevention of recurrent ischemic stroke in patients with a prior noncardioembolic ischemic stroke. They failed, and therefore failed to reject the null hypothesis.

I believe that the correct interpretation of the results of WARSS is that warfarin was not proven to be superior to aspirin. It is correct to say, with 95% confidence, that warfarin may be up to 8% more effective than aspirin, and it may be up to 38% less effective. More trials are needed to refine these estimates.

## What Are the Implications of WARSS for Clinical Practice?

The results of WARSS can be generalized only to the type of patients randomized in WARSS (ie, patients with recent noncardioembolic ischemic stroke who do not have high-grade symptomatic carotid stenosis or a contraindication to warfarin therapy) who are followed up and managed in a similar manner.

For these patients, warfarin should probably be used only in the context of an RCT or perhaps if the patient is allergic to, is intolerant of, or has failed effective antiplatelet therapies (eg, aspirin, clopidogrel, or dipyridamole therapy) in isolation and combination, until the results of ongoing clinical trials (eg, ESPRIT, WASID, and ARCH) are known.

## What Are the Implications of WARSS for Research?

### WARSS Trial

It is possible that the WARSS trial failed to detect a favorable overall treatment effect of warfarin compared with aspirin (up to 8% less hazard of the primary outcome event) because of a lack of statistical power. In addition, such a favorable treatment effect may even be >8% if warfarin is used at a higher INR of  $\approx$ 2.0 to 3.0 (ESPRIT, WASID, and ARCH trials) and is used in patients with specific etiologic subtypes of ischemic stroke, such as those with aortic arch atherothromboembolism (ARCH trial), intracranial large-artery atherosclerosis (WASID trial), and the antiphospholipid antibody syndrome (Antiphospholipid Antibody Stroke Study).<sup>12</sup> Finally, evaluating effectiveness by means of a more composite primary outcome event, which includes nonfatal intracranial and extracranial hemorrhage and MI, will not only yield more statistical power but may also provide a better perspective of the overall relative efficacy and safety of warfarin and antiplatelet therapies.

### Ongoing Clinical Trials

#### ESPRIT Trial

The ESPRIT trial is a randomized single-blind trial that aims (in 1 arm of the trial) to compare the efficacy and safety of warfarin (INR 2.0 to 3.0) versus aspirin (in any dose between 30 and 325 mg daily) in patients after cerebral ischemia due to presumed arterial causes (see online discussion at <http://home.wxs.nl/~esprit>).<sup>6</sup> Treatment allocation is random and open, but assessment of outcome is blind to the treatment allocation. The primary outcome is the composite event: “death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication.”<sup>6</sup> As of March 4, 2002,  $\approx$ 800 of a planned 3000 patients have been randomized to warfarin versus aspirin (Ale Algra, MD, written communication, March 2002).

#### WASID Trial

The WASID trial is a randomized double-blind clinical trial that aims (1) to examine whether warfarin (INR 2.0 to 3.0) or aspirin (1300 mg/d) is more effective for preventing stroke (ischemic or hemorrhagic) and vascular death in patients with symptomatic stenosis (50% to 99%) of a major intracranial artery and (2) to identify patients whose rate of ischemic stroke in the territory of the stenotic intracranial artery is sufficiently high to justify a subsequent trial comparing intracranial angioplasty/stenting with the best medical therapy in these patients.<sup>7,8</sup> The WASID trial began enrolling patients in February 1999, with a goal of enrolling 806 patients at 60 sites in the United States and Canada over 3 years.

**ARCH Trial**

The ARCH trial is an open RCT to test the null hypothesis that warfarin (INR 2.0 to 3.0) or clopidogrel (75 mg/d) plus aspirin (75 to 325 mg/d) in patients with a prior ischemic stroke or peripheral embolism associated with proximal aortic plaque with complex ( $\geq 4$ -mm-thick and/or mobile) features is equally effective in preventing subsequent stroke or vascular events. All outcome events will be reviewed by an Endpoint Committee which is blinded to treatment allocation. A total of 1500 patients will be recruited and followed for 5 years.

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