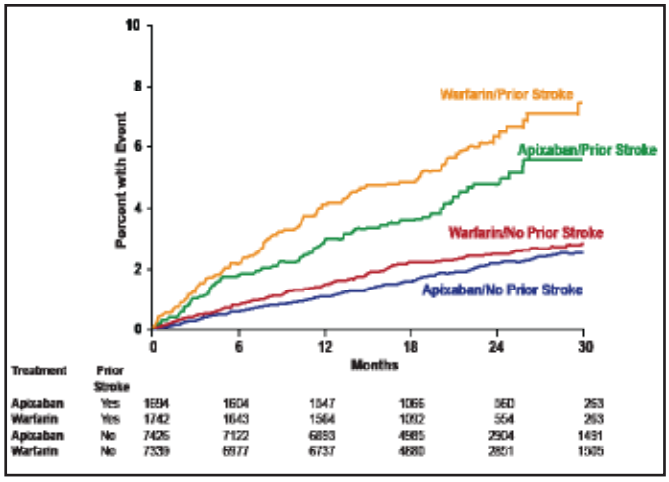
Figure 1. Stroke Substudy Primary Outcome.



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Overall, the trial demonstrated that in patients with AF and prior stroke or TIA, apixaban is superior to warfarin in preventing stroke or SE; causes less bleeding, especially intracranial bleeding; and results in lower mortality. These outcomes are consistent with those of the main ARISTOTLE trial.

No Compelling Evidence to Use Warfarin or Aspirin in HF Patients

Written by Rita Buckley

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction Trial [WARCEF; NCT00041938] found no compelling evidence to use warfarin for all patients. Shunichi Homma, MD, Columbia University College of Physicians and Surgeons, New York, New York, USA, reported outcomes from the study.

WARCEF was a randomized, double-blind, multicenter, international clinical trial. The primary outcome was to determine if warfarin or aspirin was superior for preventing the combined endpoint of death, ischemic stroke, or intracerebral hemorrhage (ICH) in patients with left ventricular ejection fraction (LVEF) ≤35% in sinus rhythm. The mean follow-up was 3.5 years, ranging from 1 to 6 years.

The main secondary aim was to determine if warfarin or aspirin was superior for preventing death, ischemic stroke, or ICH plus myocardial infarction or heart failure (HF) hospitalization in patients with LVEF ≤35% in sinus rhythm.

A total of 2305 patients were randomized to receive either warfarin (target INR 2 to 3.5; n=1142) or 325 mg/day of aspirin (n=1163). Key inclusion criteria included normal sinus rhythm, LVEF ≤35%, no defined cardioembolic source, and being on an optimal HF regimen.

Baseline characteristics were similar between the two groups, as was baseline time in the therapeutic range (63%; 2 to 3.5). The mean INR was 2.5±0.95. The number of patient-years in the aspirin group was 4033; in the warfarin group, the number of patient years was 4045. The primary analysis was treatment-by-time interaction.

The combined primary outcome was not significantly different between groups, occurring at a rate of 7.47% per year among warfarin patients versus 7.93% per year in those who were assigned to aspirin (HR, 0.93; 0.79 to 1.10; p=0.40; Figure 1). There was, however, a suggestive benefit of warfarin for the primary outcome at 4 years and beyond (HR, 0.894; 0.800 to 0.998; p=0.046; Figure 2).

Figure 1. Primary Outcome.

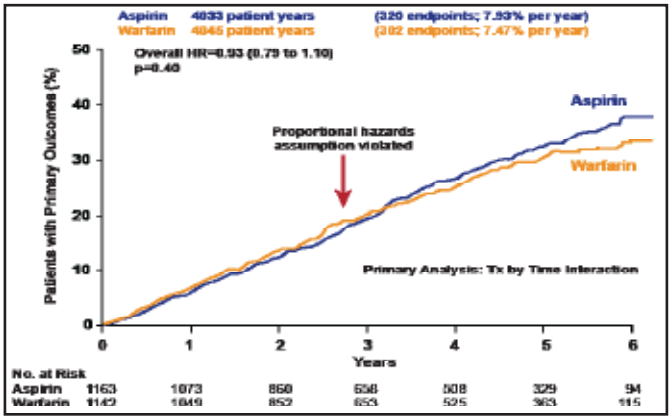

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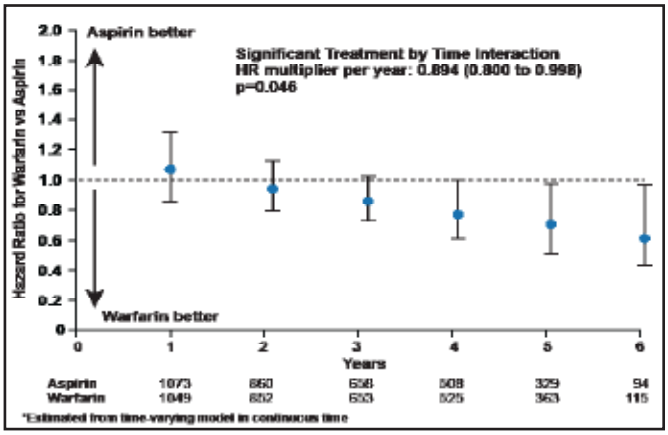
Figure 2. Warfarin vs Aspirin Hazard Ratios by Year of Follow-Up (Prespecified Time-Varying Analysis).



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The warfarin group (n=268) had a death rate of 6.63% per year. The death rate in the aspirin group (n=263) was 6.52% per year (HR, 1.01; 95% CI, 0.85 to 1.21; p=0.91).

However, the difference in ischemic stroke was significant, with the per-year death rate in the warfarin group (n=23) of 0.72% compared with 1.36% in the aspirin group (n=55; p=0.005).

The main secondary outcome occurred at a rate of 12.7% per year in warfarin-treated patients versus 12.15% per year in the aspirin-treated group (p=0.33). Major hemorrhage per year, however, occurred in 1.78% of patients in the warfarin group versus 0.87% in patients who were taking aspirin (p<0.001). Significant differences were observed in gastrointestinal hemorrhage (p=0.01) and "all other bleeds" (p=0.01). Importantly, no difference in intracerebral or intracranial bleeding was found; combined, the annual rates were 0.27% in the warfarin group compared with 0.22% in the aspirin group (p=0.82).

The authors concluded that there was no overall difference for the primary outcome, although there was a suggestive benefit with warfarin at 4 years and beyond. Warfarin reduced ischemic stroke risk throughout follow-up, but patients who were on the drug had more major hemorrhages than those in the aspirin group (1.78% vs 0.87%). Intracerebral and intracranial outcomes were similar. No significant difference was observed for the main secondary outcome.

Given no overall benefit of warfarin and increased risk of bleeding, the study found no compelling evidence to use warfarin for all patients. Based on effectiveness in preventing stroke and the possible benefit of warfarin after 4 years, analyses are underway to better identify patients that will benefit from warfarin or aspirin.

AXIS 2 Clinical Outcomes No Different Than Placebo

Written by Rita Buckley

AX200 was a novel and promising drug candidate with a comprehensive preclinical and clinical package that fulfilled Stroke Therapy Academic Industry Roundtable (STAIR) and European Stroke Organization recommendations; yet, no difference was observed in clinical outcome or imaging compared with placebo in acute ischemic stroke patients, according to results from the AX200 for the Treatment of Ischemic Stroke Phase 3 trial [AXIS-2; NCT00927836]. E. Bernd Ringelstein, MD, Westfälische Wilhelms Universität Münster, Münster, Germany, reported outcomes from the study.

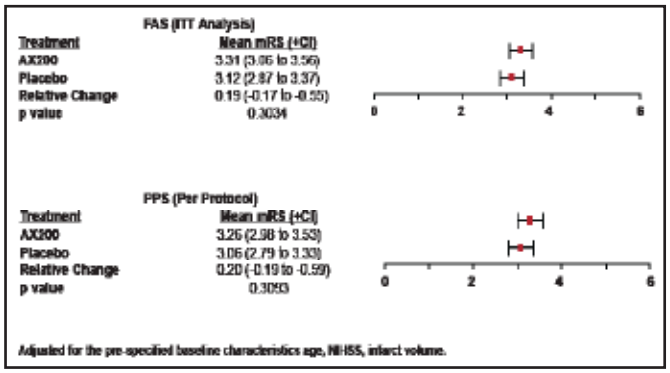
AXIS 2 was a randomized, double-blind, placebo-controlled, two-arm, multinational, multicenter trial that included 328 patients with acute ischemic stroke in the middle cerebral artery territory. The objective was to demonstrate the efficacy of AX200 (rhG-CSF; filgrastim) versus placebo. The most relevant inclusion criteria were that patients had to be <9 hours from symptom onset, have a National Institute of Health Stroke Scale (NIHSS) of 6 to 22, have a diffusion-weighted imaging lesion >15 cm^3, and be aged ≤85 years. Recombinant tissue plasminogen activator (rtPA) was allowed if patients were still eligible after lysis (ie, had an NIHSS of at least 6).

Patients were randomized to receive 135 µg/kg of AX200 over 72 hours intravenously or placebo, with one-third given over 30 minutes as a priming dose. The primary endpoint was modified Rankin scale (mRS) score at Day 90. The secondary endpoint was NIHSS at Day 90. Additional analyses were performed on infarct growth, adverse events, mortality, cytokines, and hematology.

The study was conducted at 51 sites in 7 countries. Intention-to-treat (ITT; n=323) and per-protocol analyses (n=272) were performed. Patients had a mean age of 63±10 years, and there were no significant differences in demographics. Hematology tests showed an expected increase in white blood cells and monocytes and a small decrease in platelets. No significant differences were observed in serious adverse events.

There were no significant differences between AX200 and placebo patients in the primary efficacy endpoint (mRS at Day 90) in either the ITT or per-protocol groups, and there was broad overlap in confidence intervals (Figure 1). The same outcome was seen in the secondary endpoint (NIHSS at Day 90; Figure 2). No significant differences between the AX200 and control groups were observed in the subgroup analysis for rtPA pretreatment, either.

Figure 1. mRS Day 90 AXIS200 Efficacy Endpoint.



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