Think Aspirin for Intracranial Arterial Stenosis

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High-dose aspirin is just as effective as warfarin in treating intracranial arterial stenosis, and appears much safer, with significantly lower rates of death, myocardial infarction, and major hemorrhage over 2 years, Marc Chimowitz, M.B., and colleagues have reported.

"The common practice of administering warfarin rather than aspirin for symptomatic intracranial arterial stenosis is not supported by the results of this trial," said Dr. Chimowitz of Emory University, Atlanta.

Enrollment in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial ended early because of the high rate of serious adverse events in the warfarin patients.

In addition to being safer for patients, the researchers said, aspirin therapy did not require constant monitoring of international normalized ratios (INRs) and treatment of warfarin-associated bleeding. Aspirin also is much cheaper, the investigators noted (N. Engl. J. Med. 2005;352:1305-16).

Ralph Sacco, M.D., an investigator in the Northern Manhattan Stroke Study, noted in an interview that the WASID trial's findings add to existing data to dispel beliefs about the benefit of warfarin for certain stroke populations.

The conclusion that warfarin provides no survival benefit over aspirin, but confers added risk, is more expensive, and requires intensive monitoring, should reshape its risk/benefit profile for some patients, said Dr. Sacco, professor of neurology and epidemiology at Columbia University, New York.

Dr. Chimowitz and his associates reported on the trial's final analysis that included 569 patients with symptomatic intracranial arterial stenosis who were

Light Tx May Surpass Melatonin

SAN DIEGO — Melatonin supplements may be popular to shift circadian rhythms, but bright-light therapy is more effective, Milton Erman, M.D., said at a psychopharmacology congress sponsored by the Neuroscience Education Institute.

People with sleep disorders from working night shifts especially may benefit from therapy to shift their circadian rhythms to match the imposed sleep schedule, said Dr. Erman of the University of California, San Diego.

If the patient mainly is bothered by disrupted or insufficient sleep (wakefulness) or by excessive sleepiness while awake, try focusing treatment on one or the other, he suggested. If sleep problems include both wakefulness and sleepiness, it may be best to try to shift the patient's circadian rhythm.

Light therapy is inexpensive and safe for shifting circadian rhythm. Bright light or light plus exercise worked better than exercise alone, melatonin alone, or placebo to treat night-shift workers in a 1999 study.

Light therapy or light plus exercise shifted sleep/wake phases by 7-8 hours, compared with approximately 5 hours for melatonin and 3 hours with placebo. Patients achieved close to 7.5 hours of sleep per sleep phase with light therapy or light plus exercise, compared with approximately 6.5 hours of sleep with melatonin or placebo, Dr. Erman said.

To shift the circadian sleep phase, the timing of therapy is critical, whether using light, exercise, or melatonin. Any of these in the morning will advance the circadian rhythm so the patient goes to sleep earlier. To stay up later than usual, delay sleep by exercising or using light or melatonin in the late afternoon or early evening, he said.

For patients complaining mainly of wakefulness, benzodiazepines or nonbenzodiazepine hypnotics such as zolpidem (Ambien) can improve the quantity and quality of sleep, but studies suggest that improvements in job performance are short term. For sleepiness, modafinil (Provigil) is safer than stimulants and is approved to treat chronic shift-work disorder.

Dr. Erman has been a speaker and consultant for, or received honoraria from, the companies that make zolpidem and modafinil.

—Sherry Boschert

randomized to either warfarin 5 mg daily or aspirin 650 mg twice daily.

The patients' mean age was about 63 years; about 61% were men. All had a history of either stroke or transient ischemic attack caused by 50%-90% stenosis of a major intracranial artery. The mean follow-up was 1.8 years.

The primary outcome—stroke, brain hemorrhage, or death from vascular causes other than stroke—occurred in 22% (62) of the aspirin patients and 21.8% (63) of the warfarin patients. Myocardial infarction or sudden death occurred significantly more often in the warfarin group than in the aspirin group (7.3% vs. 2.9%).

The overall rate of death was significantly higher in the warfarin group than in the aspirin group: 5.9% (17) vs. 4.3% (12). However, chance probably accounted for some of the deaths that were higher in the warfarin group, especially the six cancers.

Major hemorrhages occurred significantly more often in the warfarin group (8.3% vs. 3.2%). Brain hemorrhage occurred in 2 warfarin patients and 1 aspirin patient; gastrointestinal hemorrhage in 10 warfarin patients and 6 aspirin patients; ocular hemorrhage in 4 warfarin patients and 1 aspirin patient; genitourinary hemorrhage in 3 warfarin patients; aortic aneurysm in 1 aspirin patient; and other bleeds in 4 warfarin patients.

In a posthoc analysis, INRs of less than 2.0 were associated with a significantly higher risk of ischemic stroke and major cardiac events, and INRs of 3.0 or greater were associated with a significantly higher risk of hemorrhage, than were INRs in the therapeutic range of 2.0-3.0.

In an accompanying editorial, Walter Koroshetz, M.D., said the observed mortality differences could be due to a failure to keep patients at a therapeutic level of anticoagulation. Warfarin subjects obtained optimal anticoagulation (INR 2.0-3.0) only 63% of the time. The rate of major cardiac events was 10.8 per 100 patient-years with a subtherapeutic INR, but only 0.4 per 100 patient-years with a therapeutic INR.

"Unfortunately, it is extremely difficult, if not impossible, to achieve a consistent therapeutic INR with warfarin in a population study or in routine practice," said Dr. Koroshetz of Massachusetts General Hospital, Boston.

"Two large studies have been negative for warfarin in noncardioembolic stroke," Dr. Sacco noted. "And one of these was also stopped early due to adverse events and no signal that warfarin's benefit was greater than aspirin." ■