Catch the WAVE

A new trial cautions against combined antiplatelet therapy and anticoagulation in treating PAD.

BY RAVI K. VEERASWAMY, MD, AND ROSS MILNER, MD

The results of the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial were recently reported in the *New England Journal of Medicine*.[1] The WAVE trial examined the effects of warfarin plus an antiplatelet agent versus an antiplatelet agent alone in managing patients with peripheral arterial disease (PAD). More than 2,100 patients from seven countries were randomized, and the mean follow-up was 35 months. There were two coprimary endpoints: a combined rate of stroke, cardiovascular death, and myocardial infarction (MI); and stroke, cardiovascular death, MI, or severe ischemia of the peripheral or coronary arteries leading to urgent intervention.

TARGET INTERNATIONAL NORMALIZED RATIO

The target international normalized ratio (INR) was 2 to 3. Patients at an increased risk from bleeding complications, including those with a recent stroke, history of chronic nonsteroidal use, or history of GI bleeding, were excluded. Those randomized to dual therapy were maintained at the target INR for 2 to 3 weeks and were only included in the study if they did not have any bleeding complications during that run-in phase.

INR was monitored regularly and was in the specified range approximately 62% of the time. Approximately 30% of the measurements were subtherapeutic, and only 7% of INR values were greater than 3. Patient demographics were similar in both groups, as were physiologic variables, such as blood pressure and ankle-brachial indices. Use of ACE inhibitors, statin agents, and beta-blockers were also statistically similar.

ADVERSE EVENTS

The most significant adverse event was bleeding, which was separated into life-threatening, moderate, and mild bleeding. Life-threatening bleeding was defined as being fatal, intracranial, requiring surgical intervention, or requiring transfusion of at least 4 units of blood products. Moderate bleeding was defined as intraocular or requiring ≤3 units of blood products, and all other bleeding was considered minor.

There was no statistical difference in reaching either endpoint between the two treatment groups. However, the risk of bleeding complications was significantly greater in the group that received both warfarin and antiplatelet therapy. Life-threatening bleeding (4% vs 1.2%), moderate bleeding (2.9% vs 1%), and minor bleeding (38.6% vs 10.6%) were all more likely to occur in the dual-therapy group as compared to the antiplatelet arm alone.

DISCUSSION

The conclusion of the WAVE trial was that using warfarin and an antiplatelet agent did not offer any advantage over antiplatelet therapy alone in terms of preventing stroke, death, or ischemic complications in the cardiac or peripheral vascular beds, but it did lead to an increased risk of bleeding and its attendant complications.

The WAVE trial is an important study for all vascular specialists. It has previously been shown that anticoagulation is beneficial in preventing ischemic cardiac events, and thus it was logical to study whether warfarin plus an antiplatelet agent would be protective as compared to platelet therapy alone.[2-4] Although it was assumed that the risk of bleeding would be higher, it was postulated that the reduction in vascular events might offset the increased bleeding risk. Obviously, this was not the case.

It is also a relevant study because many patients are given antiplatelet agents for their atherosclerotic disease and anticoagulation for other reasons, such as cardiac arrhythmia or prosthetic valves. The results of this trial indicate that the risks and benefits of dual therapy should be carefully considered given the high risk of bleeding demonstrated with this regimen.

The strengths of the trial are in its randomization and in the careful follow-up of the subjects. For example, documentation that the INR was below 3 more than 90% of the time helps allay fears that excessive anticoagulation skewed the results. The division of bleeding into life-threatening, major, intracranial, and minor was also helpful. The attempt to remove patients at higher risk for bleeding by instituting the several-week-long run-in time period was also appropriate. In fact, 23 people were excluded from the trial for bleeding during this phase. This, in combination with excluding those with a propensity for bleeding complications, likely minimized the difference in adverse event occurrence. This leads to the conclusion that in the general population with perhaps less stringent screening and less vigilance on INR monitoring, widespread use of combination

therapy would lead to an even higher rate of bleeding complications than noted in this study.

The study included centers from several different countries, and an attempt was made to demonstrate that the majority of the results were valid across countries. Subgroup analysis indicates that there was little variability from one nation to another. One exception was that the rate of bleeding complications was higher in China than in other countries, despite similar INR levels. This leads to obvious concerns about the lack of control over factors including diet, inherent drug metabolism, and other medications that may affect the rate of bleeding. It should also be noted that although close attention was given to monitoring anticoagulation, it was much harder to control antiplatelet therapy. For example, excessive dosing of clopidogrel or even aspirin may have exacerbated the bleeding complications. It is also striking that almost one third (29.5%) of the patients in the dual-therapy pool permanently discontinued oral anticoagulation. It is unclear what the median length of dual therapy was or how long the average patient continued both medications.

Despite these concerns, however, the uniformity of the data is compelling across various countries with different antiplatelet regimens and with similar rates of bleeding, and there were no data showing an improvement in the studied endpoints. It is likely that this report will significantly alter clinical practice and skew practitioners away from dual therapy with anticoagulation and antiplatelet therapy in patients with PAD. ■

Ravi K. Veeraswamy, MD, is Assistant Professor of Vascular Surgery at Emory University School of Medicine in Atlanta, Georgia. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Veeraswamy may be reached at (404) 778-4465; ravi.veeraswamy@emoryhealthcare.org.

Ross Milner, MD, is Assistant Professor of Surgery in the Division of Vascular Surgery in the Emory University School of Medicine, Atlanta, Georgia. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Milner may be reached at (404) 727-8407; ross.milner@emoryhealthcare.org.

1. Arnand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med. 2007;357:217-227.
2. Hurlen M, Abdelnoor, M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med. 2002;347:969-974.
3. Johnson WC, Williford WO. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. Vasc Surg. 2002;35:413-421.
4. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348:1329-1339.