Aortic Arch Atheroma
A Plaque of a Different Color or More of the Same?

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See related article, p 1248.

Despite the common occurrence of aortic arch atherosclerosis in patients with stroke, evidence-based treatment for this disease has remained fundamentally uncharted territory. After Winter first described this phenomena in 1957 from autopsy cases, the association between aortic arch and stroke has been a topic of great interest. A strong association with cerebral ischemic events was established by a landmark postmortem study of 500 patients with neurological symptoms; aorta atherosclerotic disease was present in 28% of the patients who perished from a cerebrovascular insult compared with 5% in patients who died from another neurological process. Subsequent studies, including prospective cohorts evaluated with transesophageal echocardiography, established the presence of aortic arch atheroma (especially plaques >4 mm or mobile plaques) as a risk factor for cerebrovascular disease and a high risk factor for recurrent stroke.

Until now, however, retrospective studies and subgroup analysis of larger trials have provided the sole source of guidance for treating patients with severe aortic arch disease and cryptogenic stroke. In fact, the latest guidelines from the American College of Cardiology Foundation and the American Heart Association state that for significant aortic arch atherosclerosis (>4 mm) there is no definitive therapeutic regimen for this high-risk patient group because no randomized trial has been completed. These guidelines proceed to state that either oral anticoagulation or antiplatelet therapy is a reasonable option for antithrombotic therapy. In this issue of Stroke, Amarenco et al describe the first prospective randomized trial addressing antithrombotic therapy options for secondary stroke prevention in this understudied population. The Aortic Arch-Related Cerebral Hazard (ARCH) was an open-labeled, blind end point evaluation trial that compared a dual antiplatelet regimen (aspirin plus clopidogrel) to antiocoagulation (dose adjusted warfarin, target INR 2–3) in hopes of determining which treatment was superior for subsequent stroke prevention after an initial ischemic stroke or transient ischemic attack in patients found to have significant aortic arch atherosclerosis and no alternative pathogenesis.

Unfortunately, because of substantially lower than expected event rates and slow recruitment, the trial was stopped prematurely, limiting its power to detect differences in the primary end point of cerebral infarction, myocardial infarction, peripheral embolism, vascular death, or intracranial hemorrhage. However, vascular death, one of the secondary end points, was significantly reduced in the dual antiplatelet arm.

A total of 349 patients were enrolled during a period of 8.3 years and followed up for a median of 3.4 years, yet the primary events rate was <3% per year. As seen in several other recent trials, the recurrent stroke rate was remarkably lower than expected; only 9 ischemic strokes occurred in the dual antiplatelet arm and 11 in the warfarin arm. This finding highlights the fact that sample size estimates based on historical cohorts are typically undersized, most likely because modern risk factor management strategies are having a substantial impact on stroke rates.

So what conclusions can we draw about the agents evaluated in ARCH? The results suggest that combination of clopidogrel and aspirin may have an efficacy advantage compared with adjusted dose warfarin for prevention of vascular death in this patient population; however, recurrent ischemic stroke rates seem to be low on either therapy. Whether the combination antiplatelet therapy is superior to either aspirin or clopidogrel alone for this patient population cannot be determined from ARCH because an assumption made during trial design was that dual antiplatelet therapy would likely be superior to single antiplatelet treatment. Based on this assumption and limited resources, no aspirin-only or clopidogrel-only arm was included in the trial. Since the time when ARCH was designed, large studies involving other stroke patient populations, such as Aspirin and Clopidogrel Compared With Clopidogrel Alone After Recent Ischemic Stroke or Transient Ischemic Attack in High-Risk Patients (MATCH), Clopidogrel and Aspirin Versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA), and Effects of Clopidogrel Added to Aspirin in Patients With Recent Lacunar Stroke (SPS3), have shown that extended therapy with the combination of aspirin and clopidogrel was not superior to single agent antiplatelet therapy, especially when both ischemic and hemorrhagic complications are considered. However, short durations of dual antiplatelet therapy (3 weeks to 3 months) such as used in the Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) and Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) trials may be safe and potentially more beneficial than aspirin alone for patients with certain stroke pathogenesis or presentations. Additional studies are needed to confirm these observations.
An interesting trial to compare and contrast to ARCH is Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W), which evaluated aspirin plus clopidogrel versus warfarin for primary stroke prevention in patients with atrial fibrillation plus an additional stroke risk factor. This large study randomized ≈7000 patients. In the ACTIVE W trial, vascular deaths were similar in the dual antiplatelet and anticoagulation groups (2.87% versus 2.52%, respectively); these results differ from the statistically significant difference reported in the ARCH trial. The 2 trials were similar; however, in the finding that number of outcome events in the warfarin arms of the trials was correlated with the time in therapeutic range (TTR). In the ACTIVE W trial, among the patients at the centers where maintenance of therapeutic anticoagulation was below the median TTR (65%), no difference in treatment effect was noted; however, for patients at centers with a TTR above the study median, warfarin therapy had a marked benefit compared with the dual antiplatelet strategy for stroke prevention. A similar analysis in ARCH revealed trends favoring the antiplatelet strategy among patients in the lower tertile of warfarin TTR, and opposite trends (favoring warfarin) among patients in the upper tertile of TTR. This finding provides impetus for initiation of new stroke prevention trials in noncardioembolic stroke populations to assess the efficacy of the newer direct oral anticoagulants (thrombin and Xa inhibitors) that have the potential to provide more stable anticoagulation as well as a lower risk of intracranial hemorrhage.

Despite this future potential for the newer oral anticoagulants, the ARCH results suggest that in general, patients with stroke or transient ischemic attack with aortic arch atherosclerosis should be treated with antiplatelet therapy rather than warfarin. The primary reason for this is not because antiplatelet agents have been shown to have superior efficacy for prevention of subsequent ischemic stroke, but rather because warfarin therapy is more cumbersome and typically carries a higher bleeding liability. Whether the antiplatelet therapy for patients with aortic atheroma who experience a stroke should be single agent or dual remains unresolved. As the authors indicate, ARCH clearly provides the impetus for further hypothesis formation and additional trials that will not only clarify the stroke mechanisms associated with this form of atherosclerosis but also more definitely establish optimal prevention regimes. In addition, ARCH highlights the challenges involved in completing an adequately powered trial in this patient population in an era of excellent risk factor modification.

We congratulate the ARCH Trial investigators for providing the first randomized data to help address a common clinical conundrum. However, despite the new data from ARCH, it remains unclear whether aortic atheroma is merely an indicator of atherosclerotic disease contributing to large vessel pathogenesis of stroke or a unique entity requiring different treatment algorithms. In essence, the color of this horse continues to be elusive.

Disclosures

None.

References


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