News and Views from the Literature

Stroke

Choices for Stroke Prevention

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A Comparison of Warfarin and Aspirin for the Prevention of Recurrent Ischemic Stroke

Mohr JP, Thompson JLP, Lazar RM, et al.
N Engl J Med. 2001:345:1441–1451.

An issue that primary care providers, cardiologists, and neurologists commonly deal with is the approach to preventing recurrent ischemic stroke in patients with noncardioembolic stroke. Choices that are currently available include aspirin (at a variety of doses), warfarin (at a variety of international normalized ratios [INRs]), clopidogrel, dipyridamole with aspirin, and a variety of combinations of these. Of the 450,000 strokes that will occur in the United States this year, in 300,000 of these cases the patients will have no identifiable cardiac source and will not be candidates for carotid endarterectomy.[1,2]

In this multicenter, double-blind, randomized trial by the Warfarin–Aspirin Recurrent Stroke Study (WARSS) Group, the effect of warfarin (at an INR of 1.4–2.8) was compared to that of 325 mg aspirin in 2206 patients who had noncardioembolic stroke within 30 days of the index event. Patients in whom a severe carotid stenosis was presumed to be the cause of the stroke or in whom carotid artery endarterectomy was planned were excluded. The primary endpoint of death or recurrent stroke was reached in 17.8% of patients assigned to warfarin and in 16% of patients assigned to aspirin (P = ns). The mean follow-up period was 10.2 months. The rates of major hemorrhage were low and similar in both groups (2.22 per 100 patient-years in the warfarin group and 1.49 per 100 patient-years in the aspirin group). In patients with presumed cryptogenic stroke, there was a nonsignificant trend toward a benefit with warfarin. A nonsignificant trend toward benefit with aspirin was observed in those patients with presumed small vessel or lacunar cause or large artery, severe stenosis, or occlusion. In the warfarin group, those patients who had events were more likely to have had subtherapeutic INRs (< 1.5) prior to the event.

In an excellent editorial by Powers, the results of the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) comparing the efficacy of oral anticoagulant therapy (with goal INR of 3.0–4.5) to 30 mg aspirin are shown to complement the WARSS trial.[3] There was no significant change in the non-hemorrhagic endpoints. This trial was stopped prematurely because of excessive bleeding. Powers concludes that there is no evidence supporting an anticoagulant strategy over antiplatelet therapy in patients with noncardioembolic stroke. Whether characteristics such as the presence of antiphospholipid antibody, intracranial large-artery stenosis, or aortic arch atheroma, which have been described in nonrandomized, observa-

tional studies to respond better to an anticoagulation strategy, actually do respond better to such therapy is the subject of current study.[4] ■

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Aortic Aneurysms

Immediate Repair Versus Surveillance of Small Abdominal Aortic Aneurysms

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Abdominal aortic aneurysms (AAAs) are relatively common, particularly among older persons.[1] In the Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study, 1031 out of 73,451 persons (1.4%), 50–79 years of age, were found to have an AAA ≥ 4.0 cm.[2] In the Cardiovascular Health Study, AAAs ≥ 3.0 cm were detected in 451 out of 4741 persons (9.5%), 65–90 years of age.[1]

Approximately 9000 deaths from the rupture of AAAs occur each year.[3] Elective surgical repair of AAAs > 4.0 cm has been advocated by professional vascular surgery organizations to reduce the risk of rupture and prolong survival.[4] There are compelling reasons to repair large AAAs, particularly those > 5.0 cm, where the 5-year risk of rupture is 25%–50%.[5] The risk of rupture for AAAs < 5.0 cm, however, is considerably lower.[4,6,7] The majority of patients with AAAs die from other cardiovascular diseases. Although operative mortality ranges from 2% at some high volume academic centers to 5%–8% at many other institutions, operative repair of small AAAs may not confer survival benefit.[8]

Two large studies that examined the effects of immediate repair versus surveillance of AAAs 4.0 to 5.5 cm in diameter have been reported recently. In each study, operative repair was performed in the surveillance group if the AAA enlarged to 5.5 cm, expanded at a rate of at least 1 cm per year (or 0.7 cm over 6 months), or became symptomatic.

Immediate Repair Compared with Surveillance of Small Abdominal Aortic Aneurysms

Lederle FA, Wilson SE, Johnson GR, et al, for the Aneurysm Detection and Management Veterans Affairs Cooperative Study Group

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The ADAM Veterans Affair Cooperative Study was designed to determine whether elective surgical repair of small abdominal aortic aneurysms improved survival. The study randomized 5038 patients, aged 50–79 years, with AAAs of 4.0 to 5.4 cm in diameter, to immediate open surgical repair of the AAA or to surveillance with ultrasound or computed tomography every 6 months. In the surveillance group, operative repair was to occur for aneurysms that reached at least 5.5 cm in diameter, enlarged by at least 0.7 cm in 6 months, or by 1.0 cm in 1 year, or became symptomatic. A total of 569 patients were randomly assigned to immediate repair, and 567 patients to surveillance. The patients were followed for an average of 4.9 years (3.5–8.0 years). Total mortality, the primary end point, was not significantly different between the two groups. There were 143 deaths (25.1%) in the immediately repaired group, and 122 deaths (21.5%) in the surveillance group. The relative risk of death for the immediately repaired group compared to the surveillance group was 1.21 (95% CI, 0.95–1.54). Operative mortality in the immediately repaired group was 2.7%. In the surveillance group, rupture of AAAs occurred in 11 patients (0.6%) causing 7 deaths. The authors concluded that a strategy of immediate repair of an AAA, compared with surveillance by computed tomography or ultrasonography, did not improve the rate of survival among patients with low surgical risk who had AAAs of 4.0 to 5.4 cm.

Long-Term Outcomes of Immediate Repair Compared with Surveillance of Small Abdominal Aortic Aneurysms

The United Kingdom Small Aneurysm Trial Participants

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The United Kingdom Small Aneurysm Trial, initially reported in 1998,[9] found that elective repair of AAAs

measuring 4.0 to 5.5 cm did not improve 5-year survival compared to a surveillance strategy. This recent study extends the findings to 8 years of follow-up. In this trial, 1090 persons with AAAs 4.0 to 5.5 cm were randomized to early elective surgery versus surveillance with surgery

The authors concluded that a strategy of immediate repair of an AAA, compared with surveillance by computed tomography or ultrasonography, did not improve the rate of survival among patients with low surgical risk who had AAAs of 4.0 to 5.4 cm.

to occur if the aneurysm exceeded 5.5 cm in diameter, expanded by more than 1 cm per year, or became symptomatic. There were 563 patients assigned to early elective surgery and 527 patients to surveillance. In the early surgery group, there were 242 deaths (7.1 per 100 patient years), and in the surveillance group there were 252 deaths (8.3 per 100 patient years). The adjusted hazard ratio for death from any cause in the early surgery group compared to that for the surveillance group was 0.83 (95% CI, 0.69–1.00; $P = .05$). Neither age nor sex nor the initial size of the aneurysm modified the hazard ratio. The mean duration of survival was 6.7 years among patients in the early surgery group and 6.5 years among patients in the surveillance group ($P = .29$). The 30-day operative mortality rate was unexpectedly high (5.5%) in the early surgery group. This accounted, in part, for the apparent increase in mortality in those undergoing early surgery. However, the survival curves crossed at 3 years and at 8 years, such that mortality in the early surgery group was approximately 7% lower than that in the surveillance group. Rupture of the AAA occurred in 21 persons (8%) in the surveillance group. Death secondary to a ruptured AAA occurred in 5% of men who died and in 14% of women who died. Interestingly, there was a greater rate of smoking cessation among patients who underwent early repair of the AAA than in the surveillance group. The authors concluded that among patients with small AAAs, there was no difference in mean survival between early surgery and surveillance, although after 8 years, total mortality was lower in the early surgery group. They attributed the difference, at least in part, to beneficial changes in lifestyle that occurred in the early surgery group.

Comment

These studies provide a strong rationale for reconsidering the guidelines for operative repair of AAAs < 5.5 cm. It is reasonable to defer surgery until the maximal diameter of the AAA is 5.5 cm or larger, or if its rate of expansion is at least 0.7 cm over 6 months or at least 1 cm over 1 year, or if symptoms develop. This course of action assumes that both the physician and the patient will be extremely vigilant about ensuring that an examination and imaging study, such as abdominal ultrasound or computed tomography, are performed every 6 months. Moreover, it assumes that operative repair will be undertaken by a skilled surgeon whose operative mortality rates are low. Comorbid conditions such as congestive heart failure, chronic lung disease, renal insufficiency, and other life-limiting diseases should be taken into consideration. A less invasive strategy to treat AAAs with stent grafts has engendered considerable enthusiasm and could potentially redirect the decision analysis regarding treatment of small AAAs in favor of earlier treatment. There is, however, insufficient data regarding periprocedural morbidity and mortality rates and long-term durability to recommend a paradigm shift at this time. One recent trial compared outcomes between open surgical and endovascular repair of AAAs.[10] The initial morbidity was less and the length of stay in the hospital was shorter after endovascular repair with stent grafts than with open conventional repair, but long-term complications requiring rehospitalization were more common. Regardless of the approach, the prevalence of AAAs begs the question as to whether all persons over the age of 50, particularly smokers and those with known atherosclerosis or a family history of AAA, should have a screening abdominal ultrasound.

In the United Kingdom Small Aneurysm Trial, the survival rate was greater in those who stopped smoking than in those who continued to smoke, and even long-term benefits in patients who underwent early operative repair were attributed to lifestyle changes.

It must be emphasized that the majority of patients with AAAs die from other manifestations of atherosclerosis, including myocardial infarction and stroke. Therefore, physicians must be diligent about diagnosing and appropriately treating coronary artery disease and cerebrovascular disease. This includes risk-factor identification and modification. In the United Kingdom Small Aneurysm Trial, the survival rate was greater in those who stopped smoking than in those who continued to smoke, and even long-term benefits in patients who underwent early operative repair were attributed to lifestyle changes. ■

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Coronary Artery Disease

Prevention with Statin and Niacin

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Simvastatin and Niacin, Antioxidant Vitamins, or the Combination for the Prevention of Coronary Disease

Brown BG, Zhao XQ, Chait A, et al.
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Brown and associates report on a very important trial looking at the impact of combination statin and niacin (S+N) therapy with and without an antioxidant cocktail, compared to placebo. The patient population studied included those with known coronary artery disease and low levels of high-density lipoprotein cholesterol (HDL-C) (men < 35 mg/dL and women < 40 mg/dL); low-density lipoprotein cholesterol (LDL-C) levels < 145 mg/dL; and triglyceride levels < 400 mg/dL. The antioxidant cocktail consisted of vitamin E (800 IU), vitamin C (1000 mg) and selenium (100 μg). The "placebo" patients were given 10 mg simvastatin if their LDL-C was 140 mg/dL or higher, with a target LDL-C level of <130 mg/dL. For those patients randomized to a niacin-containing strategy, initial dosing was 250 mg twice daily of Slo-Niacin (Uppsher-Smith, Minneapolis, MN), increasing to 1000 mg twice daily over 4 weeks. Patients who did not achieve HDL-C target elevations were transitioned to a crystalline niacin preparation with titrations up to 4 g/day.

In this trial, effects on a variety of biochemical parameters, including LDL-C, HDL-C, intermediate density lipoprotein (IDL), lipoprotein (a) (Lp(a)) and homocysteine levels were measured; importantly, clinical endpoints, including the composite of coronary-related death, myocardial infarction, or stroke, or revascularization for worsening ischemic symptoms, as well as angiographic progression, were also measured.

The risk of the composite clinical endpoint was reduced by 90% in the statin-and-niacin therapy group compared to placebo.

The combination of S+N produced small but consistent increases in aspartate aminotransferase, creatine kinase, uric acid, homocysteine, and insulin levels without affecting glucose levels. Antioxidant therapy alone reduced the level of the antiatherogenic HDL_2 level and had no other lipid effect. LDL-C and triglyceride levels were reduced by 42% and 36%, respectively, by the combination S+N. HDL-C levels were increased by 26% with S+N and attenuated with the addition of antioxidants. Diene lag time, an index of LDL-C oxidative potential, was reduced by 35% with antioxidant therapy.

Measurements of changes of proximal coronary artery stenosis revealed an increase of 1.8% in patients receiving antioxidants only, decreased by 0.4% in patients receiving S+N, and increased by 0.7% in patients receiving S+N plus antioxidants when compared to "placebo."

The risk of the composite clinical endpoint was reduced by 90% in the S+N group compared to placebo (P = .03). The other groups receiving the antioxidant cocktail with and without S+N did not differ from the placebo group. The rate of event reduction in this trial was greater than could be attributed to either the LDL-C lowering (1% risk reduction for every 1 mg/dL reduction) or the increase in HDL-C (1% risk reduction for every 1 mg/dL increase). This provides support for simultaneous HDL-C and LDL-C modification for secondary risk prevention in patients with low HDL-C levels and mildly

elevated LDL-C levels, who may constitute up to 40% of patients with coronary artery disease.

The authors conclude that they see little justification for the use of antioxidants for the prevention of cardiovascular events and that the combination of S+N does have positive effects on lipid profiles, angiographic progression of coronary artery stenosis, and cardiovascular events. Whether the synergistic effect of LDL-C/HDL-C modification on reducing cardiovascular events with the combination of a S+N can be extrapolated to the combination of statin and fibric acid derivative remains to be established by randomized clinical trials. ■

Congestive Heart Failure

Doppler Imaging to Predict Beta-Blocker Performance

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Echo-Doppler Mitral Flow Monitoring: An Operative Tool to Evaluate Day-to-Day Tolerance to and Effectiveness of Beta-Adrenergic Blocking Agent Therapy in Patients with Chronic Heart Failure

Capomolla S, Pinna GD, Febo O, et al.
J Am Coll Cardiol. 2001;38:1675–1684.

In this study by Capomolla and colleagues, the authors assess the utility of evaluating mitral inflow parameters (restrictive and nonrestrictive patterns) for predicting the effectiveness and tolerance of β-blocker therapy with carvedilol in patients with chronic heart failure. The attractiveness of this approach lies in the ability to use parameters (such as mitral flow patterns) that are simple to measure in an office or in-patient setting to help identify patients with chronic heart failure who would respond to and tolerate β-blocker therapy.

One hundred sixteen patients were studied, with 54 patients exhibiting a "restrictive" mitral flow pattern (RMFP) and 62 patients a "nonrestrictive" mitral flow pattern (NRMFP). RMFP was defined as a ratio of maximal early to maximal late diastolic filling velocities (E/A) > 1 and a deceleration time of early diastolic filling (DT) ≤ 130. NRMFP was defined as E/A ≤ 1 or E/A > 1 and a DT > 130.

After recording MFPs at baseline, cardiac loading manipulations were performed. In the 54 patients with abnormal, restrictive pattern, intravenous nitroprusside, to pre- and afterload reduce, was titrated until a systolic pressure of 80 mm Hg or pulmonary capillary wedge pressure < 15 mm Hg was achieved. At the maximal infusion rate, repeat measures of MFP were done. Of the 54 patients, 17 (31%) had a persistent RMFP pattern and were designated as irreversible-RMFP (irr-RMFP), and the 37 patients (69%) who had reverted to a normal, nonrestrictive pattern were designated reversible-RMFP (rev-RMFP). Those who did not convert to the normal nonrestrictive pattern with unloading would be considered most ill.

In the 62 patients with the nonrestrictive pattern, passive leg-raising to 45 degrees to increase pre-load was performed and MFP re-measured. Fifty patients (81%) remained with a NRMFP and were categorized as irreversible-NRMFP (irr-NRMFP), and 12 patients (19%) developed the abnormal restrictive pattern and were designated as reversible-NRMFP (r-NRMFP). In this group, patients who reverted to the restrictive pattern would constitute the more ill cohort.

Carvedilol therapy was administrated to all patients by the physician responsible for titration, who was blinded to the results of the echo-Doppler. The mean daily dose of carvedilol was 44 mg. Baseline parameters showed, to no surprise, that patients with the normal, nonrestrictive patterns had lower pulmonary capillary wedge pressures and were in a better New York Heart Association Class. There was no difference in measures of left ventricular ejection fraction and diastolic and systolic dimensions or cardiac outputs between the two groups.

Beta-blocker therapy with carvedilol was able to convert chronic heart failure patients from the abnormal, restrictive mitral flow pattern to the more normal, nonrestrictive pattern. This was predictive of tolerance and clinical benefit.

The response of the MFP to loading and unloading were predictive of tolerance to β-blocker treatment, effectiveness of β-blocker treatment, and clinical outcomes. Those patients with irr-RMFP had a high rate of treatment interruption compared to the patients with r-RMFP (47% vs 8%). Conversely, those patients with r-NRMFP had a higher interruption rate than those with irr-NRMFP (17% vs 2%). Of the patients with a baseline RMFP, 31/43 (72%) moved to the more normal nonrestrictive pattern

after chronic therapy with carvedilol, and 12/43 (18%) did not change. Of the 31 patients who became nonrestrictive after β-blocker treatment, 30 had a r-RMFP with unloading at the time of the original study. Only one patient with irr-RMFP at baseline changed to a nonrestrictive mitral flow pattern with β-blocker therapy. Patients who either maintained the restrictive mitral flow or were initially nonrestrictive and became restrictive despite treatment with carvedilol had much higher event rates than those who remained nonrestrictive and those who were originally restrictive and improved to the nonrestrictive mitral flow pattern. These may be patients for whom more aggressive treatment strategies, such as earlier consideration for transplant, might be considered.

The conclusions of the authors were that "echo-Doppler monitoring of mitral flow at baseline, during loading manipulations is an operative tool for managing β-blocker therapy in patients with congestive heart failure and for redefining therapeutic strategies including heart transplantation in those patients on chronic β-blocker therapy." Beta-blocker therapy with carvedilol was able to convert chronic heart failure patients from the abnormal, restrictive pattern to the more normal, nonrestrictive pattern and provide a substantial clinical benefit. This is consistent with the fact that a good part of the benefit from β-blocker therapy is mediated by positive effects on diastolic function in addition to its known effects on systolic function. ■