Pharmacology Watch

Evidence-based updates in clinical pharmacology

By William T. Elliott, MD, FACP

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New Research Weighs Benefits of Triple Therapy for Patients Who Have Undergone PCI

One of the most difficult clinical dilemmas is when to initiate "triple therapy" — the use of oral anticoagulation (OAC) with dual antiplatelet therapy (DAPT) in patients who have undergone percutaneous coronary intervention and have concurrent indications for OAC, such as atrial fibrillation or a mechanical heart valve. The need for triple therapy seems to be increasing as new risk scores (CHA_2DS_2-VASc) have expanded the number of atrial fibrillation patients recommended for OAC and DAPT now recommended for a least a year after percutaneous coronary intervention. But a new study suggests that more is perhaps not better. The study evaluated nearly 5000 patients age 65 or older with acute myocardial infarction and atrial fibrillation who underwent coronary stenting. Outcomes included major adverse cardiac events, including death, myocardial infarction, or stroke, while the primary outcome was bleeding. Triple therapy was used on 27.6% of patients, while the rest were on DAPT. Major adverse cardiac events occurred at about the same rate in both groups (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.86-1.16), while bleeding occurred much more frequently in the triple therapy group (HR 1.61 [95% CI :1.31 to 1.97]). Intracranial hemorrhage was twice as common in the triple therapy group (HR, 1.61; 95% CI, 1.31-1.97). The authors conclude that older atrial fibrillation patients who needed percutaneous coronary intervention had no better outcomes with triple therapy but had significantly higher bleeding rates (*J Am Coll Cardiol* 2015;66:616-627).

An accompanying editorial suggests it is not yet time to abandon triple therapy, but the optimal antiplatelet and anticoagulation therapy is not known. A recent study suggests that warfarin plus clopidogrel may lower major adverse cardiac events and bleeding rates. (*Lancet* 2013;381:1107-1115).

Complicating the issue is the role of the newer anticoagulants, which is still unknown. Although most evidence argues against triple therapy, more research is needed before we make a change (*J Am Coll Cardiol* 2015;66:628-630). Fortunately, ongoing studies may soon answer this difficult clinical dilemma. ■

FDA Actions

The FDA has fast-tracked approval of a new drug combination for the treatment of heart failure. Sacubitril, a neprilysin inhibitor that prevents metabolism of natriuretic peptides, is combined with the angiotensin receptor antagonist valsartan. The efficacy of sacubitril/valsartan was established in a study of some 8400 patients with symptomatic chronic heart failure (PARADIGM-HF) in which the combination was compared to enalapril. The study stopped early when sacubitril/valsartan was shown to be superior to enalapril with regard to cardiovascular death and heart failure-related hospitalization. Side effects include hypotension, hyperkalemia, and renal impairment. Sacubitril/valsartan is marketed by Novartis as Entresto. The company is currently recruiting subjects in a clinical trial evaluating the effect of sacubitril/valsartan on morbidity and

mortality in heart failure patients with preserved ejection fraction (PARAGON-HF).

The FDA is warning prescribers about a number of medication errors involving two drugs with similar brand names — Brintellix and Brilinta. Brintellix (vortioxetine) is an antidepressant while Brilinta (ticagrelor) is an antiplatelet drug. The errors have occurred because of the similarity of the names of the drugs, especially the first three letters that position the drugs together in "pick lists" on computer order entry screens. The FDA has reviewed 50 reports of medication errors, although none of them were administered to a patient. The FDA suggests prescribers reduce the risk of name confusion by including the generic name of the medication and the indication when prescribing.

The FDA has approved the first monoclonal antibody as second-line treatment for high cholesterol levels in adults. Alirocumab is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor that is approved to lower low-density lipoprotein (LDL) cholesterol in patients with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who have not been able to lower their LDL adequately with statins. Blocking the PCSK9 protein allows the liver to clear more LDL from the blood stream. Alirocumab was approved on the strength of five placebo-controlled trials of individuals who were at high risk and were already on statins, in which the drug lowered LDL cholesterol from 36% to 59%. Whether that translates to lower cardiovascular risk is the subject of ongoing studies. The drug is given by subcutaneous injection once every 2 weeks. Alirocumab is marketed by Sanofi-Aventis and Regeneron Pharmaceuticals as Praluent. The drug is expected to cost more than $14,000 per year.

The FDA has approved sonidegib, an oral medication for the treatment of locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or for patients who are not candidates for surgery or radiation. Sonidegib inhibits the Hedgehog pathway, which is active in basal cell carcinomas. Efficacy was established in a double-blind trial in which 66 patients with locally advanced basal cell carcinoma were randomly assigned to receive sonidegib 200 mg daily and 128 patients were assigned to receive sonidegib 800 mg daily. The lower dose was effective with 58% of patients, with tumors shrinking or disappearing. The higher dose was no more effective but did have more side effects. Half the patients had the response last 6 months or longer. Sonidegib is given as a 200 mg pill once daily. Common side effects were muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus. The drug also has the potential to cause rhabdomyolysis. Sonidegib is marketed by Novartis and Genentech as Odomzo. The drug is expected to cost approximately $100,000 per year.

The FDA has approved two new hepatitis C (HCV) treatments for specific genotypes. Ombitasvir/paritaprevir/ritonavir as a single pill has been approved for the treatment of HCV genotype 4 infections in patients without cirrhosis or scarring. The combination is given with ribavirin but does not require interferon and is the first interferon free treatment for HCV genotype 4 infections. The drug combination was highly effective in a clinical trial of 135 patients with the endpoint of no detectable virus 12 weeks after treatment (sustained viral response [SVR]). Ombitasvir/paritaprevir/ritonavir with ribavirin achieved a SVR of 100% while the combination without ribavirin achieved a SVR of 91%. Ombitasvir/paritaprevir/ritonavir is manufactured by AbbVie and is the same drug combination found in AbbVie's HCV genotype 1 drug combination Viekira Pak. The combination for treatment of HCV genotype 4 is marketed as Technivie and is expected to cost more than $76,000 for the 12-week course.

The FDA has also given the greenlight for the combination of a new drug, daclatasvir, to be used with sofosbuvir for the treatment of genotype 3 HCV infections. This combination is the first for this indication that does not require interferon or ribavirin. Twelve weeks of daclatasvir plus sofosbuvir was evaluated in a study of 152 treatment-naïve and treatment-experienced patients with genotype 3 HCV infection. The endpoint was SVR at 12 weeks after treatment. In the treatment-naïve group, 98% of those without cirrhosis and 58% with cirrhosis achieved SVR. In the treatment-experienced group, 92% without cirrhosis and 69% with cirrhosis achieved SVR. Daclatasvir is marketed by Bristol-Myers Squibb as Daklinza. Cost of the combination is not available at this time. ■

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Customer Service: 1-800-688-2421
Email Address: jonathan.springston@ahcmedia.com
World Wide Web: AHCMedia.com

Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.