Pharmacology Watch

Evidence-based updates in clinical pharmacology

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Aspirin Matches Xarelto Efficacy Regarding VTE Prophylaxis After Knee or Hip Surgery

Aspirin is as effective as rivaroxaban (Xarelto) for venous thromboembolism (VTE) prophylaxis after knee or hip surgery, according to a new study. About 1,800 patients undergoing hip arthroplasty and 1,600 patients undergoing knee arthroplasty were treated with five days of rivaroxaban postoperatively. The hip patients were randomized to 30 days of continued rivaroxaban or aspirin 81 mg, while the knee patients were randomized to nine days of rivaroxaban or aspirin. All patients were followed for 90 days for symptomatic VTE and bleeding complications. Venous thromboembolism occurred in 0.64% of subjects in the aspirin group and in 0.70% of subjects in the rivaroxaban group (95% confidence interval [CI], -0.55 to 0.66; $P < 0.001$ for noninferiority and $P = 0.84$ for superiority). Major bleeding occurred in 0.47% of the aspirin patients and 0.29% of rivaroxaban patients (95% CI, -0.65 to 0.29; $P = 0.42$) while clinically important bleeding occurred in 1.29% of the aspirin group and 0.99% of the rivaroxaban group (95% CI, -1.07 to 0.47; $P = 0.43$). The authors concluded that among hip or knee arthroplasty patients who receive five days of postoperative rivaroxaban, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic VTE (*N Engl J Med* 2018;78:699-707). An accompanying editorial suggested that the very low rates of bleeding and thrombosis seen with the "relatively inexpensive and user-friendly aspirin-based strategy" has established "a prophylaxis regimen against which all strategies to prevent thromboembolism after joint replacement will be compared." (*N Engl J Med* 2018;378:762-763)

Comparing Treatments for Cancer-associated VTE

Edoxaban appears to be as effective as low-molecular-weight heparin for the treatment of cancer-associated VTE. Researchers randomized just over 1,000 cancer patients who had acute symptomatic or incidental VTE to low-molecular-weight heparin for at least five days. The researchers followed with oral edoxaban 60 mg once a day or with subcutaneous dalteparin 200 IU/kg of body weight once daily for one month followed by dalteparin 150 IU/kg once daily. Patients were treated for at least six months and up to 12 months. The primary outcome was a composite of recurrent VTE or major bleeding.

A primary outcome event occurred in 12.8% of subjects in the edoxaban group compared with 13.5% of subjects in the dalteparin group (hazard ratio [HR], 0.97; 95% CI, 0.70-1.36; $P = 0.006$ for noninferiority and $P = 0.87$ for superiority). Recurrent VTE occurred in 7.9% of subjects in the edoxaban group and 11.3% of subjects in the dalteparin group (difference in risk, -3.4%; 95% CI, -7.0 to 0.2). Major bleeding occurred in 6.9% of the edoxaban patients compared with 4.0% of the dalteparin patients (difference in risk, 2.9%; 95% CI, 0.1-5.6). The authors concluded that edoxaban was noninferior to dalteparin regarding the composite outcome of recurrent VTE or major bleeding, although recurrent VTE was lower and bleeding was higher with edoxaban (*N Engl J Med* 2018;378:615-624).

What About Aspirin for PCI Patients?

Should clinicians continue using aspirin for patients with prior percutaneous coronary intervention (PCI) who are undergoing noncardiac surgery? The answer appears to be yes based on the results of a new study from Canada. Researchers excluded those who had received a bare-metal stent within six weeks, placement of a drug-eluting stent within one year, or nonstudy aspirin within 72 hours of surgery. About 470 patients with previous PCI were randomized to aspirin or placebo, initiated four hours before surgery and continued throughout the perioperative period. The outcomes death or nonfatal myocardial infarction were reduced by 5.5% by aspirin therapy (absolute risk reduction, 5.5%; 95% CI, 0.4-10.5; HR, 0.50; 95% CI, 0.26-0.95; *P* for interaction = 0.036). The risk for myocardial infarction was reduced by more than half (absolute risk reduction, 5.9%; 95% CI, 1.0-10.8; HR, 0.44; 95% CI, 0.22-0.87; *P* for interaction = 0.021). The effect on bleeding was "uncertain," with an absolute risk increase of 1.3% (*Ann Intern Med* 2018;168:237-244).

An accompanying editorial stated that this study is an "important contribution to the field of cardiovascular management of patients who require noncardiac surgery. In the absence of a very high bleeding risk, low-dose aspirin should be continued or resumed during the perioperative period among patients with previous coronary stents." (*Ann Intern Med* 2018;168:289-290)

Influenza A Renders This Year's Flu Vaccine Ineffective

This year's flu vaccine was only 36% effective, according to the CDC. Data on nearly 4,600 patients showed that of patients testing positive for influenza, about 43% had received the flu vaccine. The high prevalence of influenza A (H3N2) was the primary culprit, as the vaccine was only 25% effective against this virus. It is notoriously difficult to create a vaccine against H3N2 because of its tendency to mutate during the flu season. Still, the vaccine reduced severe H3N2 illness in children by more than half. The vaccine was more effective against the other circulating viruses this year — H1N1 and influenza B strains (*MMWR Morb Mortal Wkly Rep* 2018;67:180-185). The FDA has approved the makeup of the 2018-2019 vaccine. It is very similar to this year's vaccine. For the trivalent vaccine, the FDA Vaccines and Related Biological Products Advisory Committee has approved H1N1 as well as A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, which is a different H3N2 from the 2017-2018 vaccine. One influenza B virus was included in the trivalent vaccine and a second B virus was included in the quadrivalent vaccine. Additionally, the CDC's Advisory Committee on Immunization Practices gave a lukewarm endorsement to FluMist, the live-attenuated influenza vaccine. The vaccine was not marketed the last two seasons because of poor effectiveness against the H1N1 strain. However, the manufacturer reports it has reformulated the H1N1 component of the vaccine, improving efficacy. FluMist will appear on the recommended vaccine list this fall.

FDA Actions

The FDA has approved apalutamide for the treatment of non-metastatic castration-resistant prostate cancer. The drug is a nonsteroidal androgen receptor inhibitor and is the first androgen receptor inhibitor that is approved for non-metastatic disease. Also, this is the first oncolytic drug to be approved using metastasis-free survival as an endpoint, which the FDA touts as one of several new "novel endpoints to expedite important therapies to the American public." Safety and efficacy of apalutamide was based on a randomized, clinical trial of 1,207 patients with non-metastatic, castration-resistant prostate cancer. All patients had received gonadotropin-releasing hormone analog therapy or undergone surgical castration. Median metastasis-free survival was 40.5 months with apalutamide vs. 16.2 months for placebo. The agency granted the drug priority review. Apalutamide is marketed as Erleada.

The FDA has expanded the indication for durvalumab (Imfinzi) to include treatment of patients with stage III non-small cell lung cancer (NSCLC) whose tumors are unresectable and whose cancer has not progressed after chemoradiation, the first drug approved for this niche indication. Durvalumab binds PD-1/PD-L1 and is approved for certain patients with locally advanced or metastatic bladder cancer. Approval was based on a trial of 713 patients with unresectable NSCLC whose cancer had not progressed after completing chemoradiation. The median progression-free survival for patients taking durvalumab was 16.8 months compared to 5.6 months for patients receiving a placebo. ■

Author's Note: This will be the last Pharmacology Watch. I'd like to thank editors at Relias who have helped with this publication and Pharmacology Alert before that spanning more than 25 years.

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