Apixaban plus P2Y12 inhibitor and no aspirin safest for patients with both AFib and ACS

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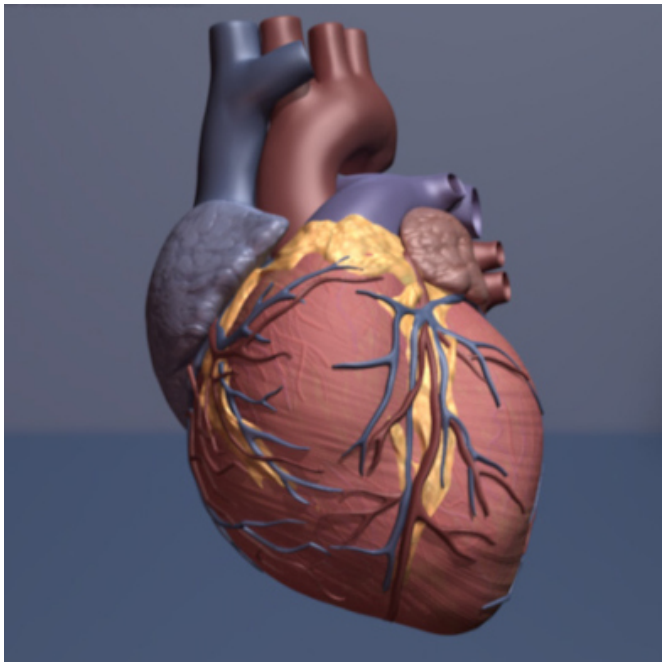

Human heart. Credit: copyright American Heart Association

Patients at high risk for heart attacks, strokes and blood clots who were treated with a novel blood thinner (apixaban) and an antiplatelet drug such as clopidogrel had a significantly lower risk of bleeding and being hospitalized compared with patients who received an older blood-thinning medication such as warfarin, according to research presented at the American College of Cardiology's 68th Annual Scientific Session. In addition, patients who received clopidogrel without concurrent aspirin, which has been standard for these patients, had an additional 47 percent reduction in bleeding events with no increase in heart attacks, strokes or blood clots when compared with patients who received aspirin.

The lowest rates of bleeding, with no increase in deaths or hospitalizations, were seen in patients who did not receive aspirin and were treated with apixaban plus a drug such as clopidogrel. In addition to the significant reduction in risk for bleeding and lower rates of stroke, patients treated with these two medications had no increase in heart attacks or blood clots.

"We have shown that when it comes to treating this high-risk patient population, less may be more," said Renato D. Lopes, MD, Ph.D. of the Duke Clinical Research Institute at Duke University School of Medicine in Durham, North Carolina, and the study's lead author. "Our findings show that the combination of apixaban and a drug such as clopidogrel—without aspirin—is the safest treatment regimen for this difficult-to-treat group of patients, without significantly increasing ischemic events such as heart attacks, strokes and blood clots. These results should reassure clinicians that it's okay not to treat most of these patients with aspirin."

Patients in the trial, known as AUGUSTUS, had both atrial fibrillation (AFib), a rapid, irregular heart beat that can increase risk for stroke, heart failure and other heart complications, and acute coronary syndrome (ACS), which occurs when blood flow to the heart is suddenly blocked. ACS may take the form of a heart attack or chest pain (unstable angina) that may signal an imminent heart attack. ACS is often treated by inserting a small metal tube, or stent, into a blocked artery to keep the artery open, a procedure known as an angioplasty.

Choosing the optimal treatment for patients with both AFib and ACS is challenging, Lopes said. These patients need to take a blood thinner to prevent stroke and blood clots, but blood thinners have not been shown to prevent blood clots in

stents (stent thrombosis) and are usually not recommended for patients with ACS. Treatment with aspirin plus clopidogrel or a similar drug—known as dual antiplatelet therapy (DAPT)—has been shown to reduce heart attacks and stent thrombosis in patients with ACS but not stroke associated with AFib. Moreover, combining a blood thinner with DAPT increases the risk of potentially life-threatening bleeding.

Most AFib treatment trials have excluded patients with ACS, while most ACS treatment trials have excluded patients with AFib, Lopes said, creating a gap in researchers' understanding of how best to treat patients who have both conditions. Among the unanswered questions: whether a next-generation blood thinner such as apixaban is more effective than warfarin, the standard treatment, for reducing episodes of bleeding in this group of patients and whether these patients fare better if they take aspirin plus a medication such as clopidogrel in addition to a blood thinner.

The AUGUSTUS trial was designed to answer both questions. It is the first randomized, double-blinded, placebo-controlled trial to test the effect of withdrawing aspirin from the treatment regimen for a patient population at high risk for bleeding as well as for heart attacks, strokes and blood clots, Lopes said.

The trial enrolled 4,614 patients in 33 countries, including the United States, Canada, Mexico, the United Kingdom, and other countries in Europe, Asia and South America. Patients' median age was 70 years and 71 percent were men. All patients had AFib requiring long-term treatment with a blood thinner, had experienced a recent episode of ACS and/or were having a stent inserted in a blocked artery.

All the patients had an indication to take medications to reduce the risk of blood clots in the arteries by inhibiting platelets (blood cells that help the body form clots and stop bleeding). More than 92 percent were taking clopidogrel at baseline; the rest were taking one of the similar drugs (e.g., prasugrel, ticagrelor).

Within 14 days of an ACS episode or stent insertion, patients underwent random assignment twice: first, to receive either apixaban or warfarin and, second, to receive either a daily baby aspirin or a matching placebo. The aspirin-or-placebo treatment assignments were double blinded, meaning that neither the patients nor their doctors knew who was receiving which treatment. The apixaban-or-warfarin treatment assignments were not blinded because of the need for patients taking warfarin to get regular blood tests to check the drug's effect on blood clotting.

All patients were treated for six months. This follow-up period was selected because most bleeding episodes, heart attacks, strokes and blood clots occur during the first six months after an ACS episode, insertion of a stent or initiation of a blood-thinning medication, Lopes said.

The trial's primary endpoint was major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). The ISTH definition includes bleeding that results in death; occurs in a critical organ; or results in hospitalization, medical treatment or surgery for bleeding or a change in the patient's anti-blood-clotting treatment. Secondary endpoints included a composite of death or hospitalization and a composite of death or stroke, heart attack, stent thrombosis or urgent treatment to unblock an artery.

Results for the primary safety endpoint showed that patients taking apixaban had a 31 percent reduction in risk compared with patients taking warfarin and that patients taking a placebo instead of aspirin had a 47 percent reduction in risk compared with those taking aspirin. The proportion of patients who had a bleeding episode was highest among patients treated with clopidogrel, warfarin and aspirin (18.5 percent), and lowest among those treated with clopidogrel, apixaban and placebo (7.3 percent).

The proportion of patients who died or were hospitalized was highest for patients treated with clopidogrel, warfarin and aspirin (27.5 percent) and lowest for those treated with clopidogrel, apixaban and placebo (22 percent). Patients treated with apixaban also had 50 percent lower risk of stroke

compared with those taking warfarin.

A limitation of the study, Lopes said, is that it was not large enough to detect potential small differences in clinically important but rare outcomes such as stent thrombosis for individual patients.

The study was funded by Bristol-Myers Squibb and Pfizer, Inc.

It was simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

More information: Renato D. Lopes et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation, *New England Journal of Medicine* (2019). DOI: 10.1056/NEJMoa1817083