Antithrombin drug not effective in heart failure with sinus rhythm and coronary disease

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The antithrombin drug rivaroxaban does not reduce the risk of a composite endpoint of survival, myocardial infarction and stroke after an episode of worsening heart failure in patients with heart failure, sinus rhythm, and coronary artery disease, according to late breaking results from the COMMANDER HF trial presented today in a Hot Line Session at ESC Congress 2018 and with simultaneous publication in *NEJM*.

After an episode of worsening heart failure, patients experience high rates of hospital readmission and death, particularly in the first few months. Previous studies have suggested that the enzyme thrombin may contribute to these poor outcomes by inducing inflammation, endothelial dysfunction, and clot formation (thrombosis) in blood vessels.

Rivaroxaban is an oral, direct factor Xa inhibitor that reduces thrombin generation. Higher doses (10-20 mg daily) are approved to treat and prevent venous thromboembolism, and prevent stroke or systemic embolism in patients with atrial fibrillation. Lower doses (2.5 mg twice daily), combined with antiplatelets, reduce cardiovascular mortality, myocardial infarction and stroke in patients with acute coronary syndromes or stable coronary artery disease.

The COMMANDER HF trial tested whether, compared to placebo, rivaroxaban 2.5 mg twice daily could reduce thrombin generation and thereby lower rates of death and cardiovascular events in patients with

recent worsening of chronic heart failure, who had reduced ejection fraction (40% or less), coronary artery disease and no atrial fibrillation.

Professor Faiez Zannad, study author, University of Lorraine, Nancy, France, said: "COMMANDER HF is not just another trial of oral anticoagulation in heart failure. The aim is to interfere with disease processes that rely on thrombin using a targeted antithrombin drug."

The trial enrolled 5,022 patients from 628 sites in 28 countries. Patients were randomly assigned to rivaroxaban 2.5 mg, taken orally twice daily, or matching placebo. The use of guideline recommended therapies for heart failure and coronary artery disease was well balanced between groups and included diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists. Background therapy included aspirin in virtually all patients and a substantial number were also receiving dual antiplatelet agents at the time either rivaroxaban or placebo was initiated in the trial.

The median age of participants at the start of the study was 66 years, 23% were women, and the median ejection fraction was 34%. Patients were followed-up for the primary efficacy outcome of all-cause mortality, myocardial infarction, or stroke. The primary safety outcome was the composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability.

During a median follow-up of 21.1 months, the primary efficacy outcome occurred in 626 (25.0%) of 2,507 patients assigned to rivaroxaban compared to 658 (26.2%) of 2,515 on placebo (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.84-1.05, p=0.27). There were no differences between groups in all-cause mortality (HR 0.98, 95% CI 0.87-1.10, p=0.74) or nonfatal myocardial infarction (HR 0.83, 95% CI 0.63-1.08, p=0.17) but there was a significantly lower rate of nonfatal stroke in the rivaroxaban, compared to placebo, group (HR 0.66, 95% CI

0.47-0.95, p=0.023).

The principal safety outcome occurred in 18 (0.7%) patients assigned to rivaroxaban and 23 (0.9%) assigned to placebo (HR 0.80, 95% CI 0.43-1.49, p=0.48). Patients taking rivaroxaban had a significantly higher risk of major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) compared to those on placebo (HR 1.68, 95% CI 1.18-2.39, p=0.003). This result was mainly driven by the ISTH criterion of bleeding causing a fall in haemoglobin of 2 g/dL (1.24 mmol/L) or more.

Serious adverse events were reported in 479 (19.2%) patients taking rivaroxaban and 451 (18.0%) on placebo. The percentage of patients who permanently discontinued study medication due to an adverse event was 7.1% in the rivaroxaban group and 5.8% in the placebo group.

Professor Zannad said: "The most likely reason rivaroxaban failed to improve the primary efficacy outcome is that thrombin-mediated events are not the major driver of cardiovascular events in patients with recent heart failure hospitalisation. Whether a higher dose of rivaroxaban could have led to a more favourable result is unknown."

More information: "COMMANDER HF - Randomized Study Comparing Rivaroxaban with Placebo in Subjects with Heart Failure and Significant Coronary Artery Disease Following an Episode of Decompensated Heart Failure" ESC Congress 2018.

Faiez Zannad et al. Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and signi, *European Journal of Heart Failure* (2015). DOI: 10.1002/ejhf.266

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