悪化する心不全においてトロンビン阻害薬は無効である(Abstract 3238)

COMMANDER HF：抗トロンビン薬は冠動脈疾患を伴う洞調律の心不全において無効である

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

抗トロンビン薬リバーロキサバンは、冠動脈疾患を有する洞調律の心不全患者における心不全悪化後の生存率、心筋梗塞（MI）および脳卒中から成る複合エンドポイントのリスクを減少させない、との COMMANDER HFトライアルの結果がESC Congress 2018 で発表され、*New England Journal of Medicine* に掲載された。追跡期間中央値21.1か月の間に、主要評価項目が発現したのは、リバーロキサバン群の25.0% に対しプラセボ群では26.2% であった（p=0.27）。総死亡または非致死性MIにおいて群間差はなかったが、非致死性脳卒中はリバーロキサバン群においてプラセボ群よりも有意に低かった（p=0.023）。

Full Text

The antithrombin drug rivaroxaban does not reduce the risk of a composite endpoint of survival, myocardial infarction (MI) 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 in a Hot Line Session at ESC Congress 2018 and with simultaneous publication in the *New England Journal of Medicine*.

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 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, MI 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, MI, 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 hemoglobin 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 hospitalization. Whether a higher dose of rivaroxaban could have led to a more favorable result is unknown."

SOURCES OF FUNDING: Janssen Research and Development.

DISCLOSURES: Full disclosure available on the paper.

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