薬剤により糖尿病患者の狭心症は軽減する（Abstract # 13-LB-15927）

TERISA: Ranolazineの狭心痛軽減作用は血糖コントロール不良の患者において最も顕著であった

TERISA: Angina pain reduction effects of ranolazine most pronounced in patients with poor glucose control

Ranolazineは2型糖尿病患者の狭心症を軽減し、この効果は血糖コントロール不良な患者においてより顕著なようであるとの研究結果が第62回American College of Cardiologyで発表された。Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina（TERISA）トライアルには927人の患者（男性61%）が組み入れられ、ranolazine 1,000mgを1日2回内服群またはそれに匹敵させたプラセボを8週間内服する群に無作為に割り付けられた。全ての患者が2型糖尿病を有し、冠動脈疾患の確定診断を受け、1週間に1回以上の狭心発作を伴う安定狭心症を有していた。患者はすでに、他の狭心症治療薬を1または2剤内服していた。一次エンドポイントは第2～8週の自己報告の狭心症頻度であった。その結果、週当たりの胸痛発作はranolazine群において3.8回/週であり、プラセボ群の4.3回/週よりも少なかった（*P*=0.008）。重要な二次エンドポイントは、同じ時間枠内のニトログリセリン使用頻度であった。これもまたプラセボ群よりもranolazine群で低く、週当たり1.7回対2.1回であった（*P*=0.003）。このスタディ結果は*Journal of the American College of Cardiology*オンライン版に掲載されており、5月21日号の印刷版に掲載予定である。

Full Text

A commonly used anti-anginal drug reduces chest pain in patients with type 2 diabetes and appears to have a more pronounced effect in those with poorer glucose control, according to research presented at the American College of Cardiology's 62nd Annual Scientific Session.

Ranolazine is approved by the U.S. Food and Drug Administration for the treatment of chronic angina, or chest pain, both as first line therapy and as an add-on when symptoms are not relieved with other anti-anginal drugs, including beta-blockers, calcium channel blockers and nitrates. However, this randomized, double-blind, placebo-controlled trial is the first to evaluate the drug in patients with diabetes, coronary artery disease and angina.

People with diabetes are at increased risk for coronary artery disease. Patients with diabetes and coronary artery disease also tend to have a higher burden of chest pain or angina than those without diabetes.

The Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) trial included 927 patients, randomized to receive either 1000 mg ranolazine twice daily or matching placebo for eight weeks. To qualify for the study, patients had to have type 2 diabetes, established coronary artery disease and stable angina with at least one angina episode per week. Patients were already taking one or two other anti-anginal drugs.

The primary endpoint was self-reported angina frequency between weeks two and eight. Weekly episodes of chest pain were lower in the ranolazine arm at 3.8 episodes per week compared to 4.3 episodes per week with the placebo (*P*=0.008). A key secondary endpoint was how often people used sublingual nitroglycerin during the same timeframe. This was also lower in the ranolazine arm compared with placebo, 1.7 vs. 2.1 doses per week (*P*=0.003).

"Angina is associated with worse quality of life, increased risk of hospitalization and higher health care costs and appears to be more prevalent in patients with diabetes," said Mikhail Kosiborod, M.D., associate professor of medicine at the University of Missouri, Kansas City, cardiologist at St. Luke's Mid America Heart Institute and the study's lead author. "While ranolazine was shown to be effective in reducing angina in prior studies, this is the first time it has been prospectively evaluated in patients with diabetes—a high-risk and therapeutically challenging group."

Each patient was given an electronic diary in which to record angina episodes, sublingual nitroglycerin use and other information. This unique feature was a strength of the study, Dr. Kosiborod said.

"Patient-reported outcomes done with usual methods, such as paper entry, may result in a hoarding effect," he said. "Patients fill out a lot of information at one sitting, and there can be issues with data validity. In this study, they had daily prompts to use the electronic diary and were constantly monitored for compliance. There was 98 percent compliance with the diary in both arms."

The patient population was 61 percent male. Nearly all (96 percent) had hypertension, and 74 percent had a history of myocardial infarction. Most patients were taking statins (82 percent) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (88 percent). Sixteen percent were smokers.

The researchers also found that ranolazine was especially effective in patients with worse glucose control, as measured by hemoglobin a1c (Hba1c) levels. The therapeutic superiority of ranolazine vs. placebo on reducing weekly angina frequency was more pronounced in patients with higher baseline Hba1c, regardless of the cut-point used. Prior data show that the drug may lower fasting glucose levels in people with diabetes, thus lowering Hba1c.

"Ranolazine is an effective anti-anginal drug in patients with diabetes and may also have a glucose-lowering effect," Dr. Kosiborod said. "If the glucose-lowering action of ranolazine is confirmed in future studies, patients with diabetes and angina may derive a dual benefit from this drug."

Researchers also completed a subgroup analysis of patients by geographic region. Angina frequency was not different between the ranolazine and placebo arms among patients enrolled in Russia, Ukraine and Belarus. Among patients enrolled in other countries, those treated with ranolazine experienced a significant reduction in angina frequency as compared with placebo (3.1 vs. 4.1 episodes per week; *P*=0.002).

"The reasons for this geographic difference are not clear," Dr. Kosiborod said. "It wasn't explained by differences in baseline characteristics but was driven by several sites located in Russia. We're exploring it."

Diabetes affects more than 347 million people worldwide. About 90 percent of diabetes is type 2 diabetes, in which the body does not use insulin effectively. Excess weight and a lack of physical activity are thought to be the main causes of type 2 diabetes. The U.S. Centers for Disease Control estimates that one in three American adults could have the condition by the year 2050.

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The study was simultaneously published online in the *Journal of the American College of Cardiology*, and will appear in the May 21 print edition.

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