糖尿病における心血管リスクに対する薬物研究の結果は残念なものであった

NAVIGATOR：スタディの結果、糖尿病および心血管疾患の予防に対して疑問が生じた

NAVIGATOR: Study raises questions on prevention of diabetes and cardiovascular disease

糖尿病および心血管疾患の高リスク患者においてアンジオテンシン受容体遮断薬バルサルタンは、心血管系の健康状態維持には効果がなく糖尿病発症を軽度減少させたのみであり、一方糖尿病治療薬ナテグリニドにおいては糖尿病または心疾患進行に対し有意な効果が認められなかったと第59回American College of Cardiology学会で発表され、同時にNew England Journal of Medicineに掲載された。心血管リスクファクターまたは心血管疾患を有する耐糖能異常患者9,306人を解析した。二重無作為化デザインを用いて、患者らはナテグリニド（最高60mgを1日3回食直前に内服）またはプラセボ、およびバルサルタン（最高1日160mg）またはプラセボのいずれかを内服する群に割り付けられた。全ての患者が5%の減量維持、週5日平均30分の運動、および低脂肪食を目標とした生活習慣改善プログラムに参加した。その結果、バルサルタンはプラセボと比較し、糖尿病発症リスクを14%減少させたが、心血管死、非致死性心筋梗塞、非致死性脳卒中、心不全による入院、不安定狭心症、または血行再建術の複合リスクは軽減しなかった。ナテグリニドは糖尿病発症および心血管リスクのいずれも減少させなかった。

Full Text

In patients at high risk for diabetes and cardiovascular disease, a drug used for treating the heart and blood vessels had no effect on cardiovascular health but modestly reduced progression to diabetes, while a drug for controlling blood sugar levels had no significant effect on progression of either diabetes or heart disease, according to research presented at the American College of Cardiology's 59th annual scientific session and published simultaneously in the New England Journal of Medicine.

The Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study was a large, international, randomized trial involving patients at high risk for diabetes and cardiovascular disease. The study found that, when added to a program to promote a healthy lifestyle, valsartan reduced progression to diabetes by 14 percent in high-risk patients, but nateglinide had no effect on diabetes progression. Neither medication reduced the risk of cardiovascular illness, such as myocardial infarction or stroke. "Most experts believed that nateglinide would prevent diabetes and that valsartan would reduce cardiovascular events in this population," said Robert M. Califf, M.D., Vice Chancellor for Clinical.

Research at Duke University Medical Center, Durham, NC and the lead investigator. "Interestingly, with respect to nateglidine, we found the opposite. The results with valsartan confirmed previous studies that showed a reduction in diabetes. It was disappointing that there was no reduction in cardiovascular events, but in such a large study, with patients on other therapies that are known to impact cardiovascular disease, this lack of event reduction is consistent with other studies."

Nateglinide is a diabetes medication that minimizes spikes in blood sugar after meals by stimulating the pancreas to produce more insulin. Researchers had hypothesized that nateglinide would reduce progression to diabetes by restoring a more normal insulin response after meals. It was hoped the drug would reduce the risk of cardiovascular disease.

Valsartan is an angiotensin-receptor blocker (ARB) that is used to treat high blood pressure, heart failure, and the long-term consequences of a myocardial infarction. Some studies have suggested that medications that block the renin-angiotensin system may not only help the cardiovascular system, but may also delay or prevent the development of diabetes.

For the study, researchers at 806 medical centers in 40 countries analyzed 9,306 patients with glucose intolerance and either cardiovascular risk factors or established cardiovascular disease. Using a double randomization design, patients were assigned to receive either nateglinide (up to 60 mg three times a day before meals) or a matching placebo, and valsartan (up to 160 mg daily) or a matching placebo. All patients were required to participate in a lifestyle program, with the goal of maintaining a 5 percent weight loss, increasing physical activity to an average of 30 minutes five days a week, and to follow a low-fat diet.

"Lifestyle modification remains the best choice for preventing diabetes in high-risk patients," said Rury R. Holman, MB, ChB, FRCP, professor of Diabetic Medicine, and Diabetes Trials Unit Director, University of Oxford, UK. "Eating a healthy diet, exercising regularly, and maintaining a normal body weight are critical for long-term health in patients at risk for diabetes and vascular disease."

Patients were followed for 5 years, on average, for development of diabetes and 6.5 years, on average, for cardiovascular disease. Researchers found that valsartan reduced the risk of progression to diabetes by 14 percent. When compared with the placebo, valsartan did not reduce the risk of a combination of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, unstable chest pain, or the need for a surgical or catheter-based procedure to restore blood flow through clogged arteries, nor did the ARB reduce the risk of key cardiovascular outcomes, which excluded unstable chest pain or vascular procedures. Nateglinide failed to reduce both progression to diabetes and cardiovascular risk.

Investigators speculated that the study's results may have been influenced by how effective the lifestyle program was in reducing both diabetes progression and cardiovascular risk. By the end of the study, a large number of patients were taking medications prescribed by their personal physician to inhibit the rennin angiotensin system or to treat abnormal lipid levels or high blood pressure, and this may have lowered overall risk.

The trial was sponsored by Novartis. Prof. Holman reports receiving grant support from Asahi Kasei Pharma, Bayer Healthcare, Bayer Schering Pharma, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Merck Serono, Novartis, Novo Nordisk, Pfizer and Sanofi-Aventis; consulting fees from Amylin, Eli Lilly, GlaxoSmithKline, Merck and Novartis; and lecture fees from Astella, Bayer, GlaxoSmithKline, King Pharmaceuticals, Eli Lilly, Merck, Merck Serono, Novo Nordisk, Takeda and Sanofi-Aventis. Dr. Califf reports receiving research grant support from Novartis Pharmaceuticals, Johnson & Johnson/Scios, Lilly, Merck, and Schering Plough, and consulting fees from Annenberg, Aterovax, Bayer/Ortho McNeil, BMS, Boehringer Ingelheim, GSK, WebMd/theheart.org, Johnson and Johnson/Scios, Kowa Research Institute, McKinsey & Company, Medtronic, Merck, Novartis Pharmaceuticals, Sanofi Aventis, and Schering Plough, and an equity position with NITROX, LLC. All personal income from industry relations is donated to non-profit entities.

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