Study finds no link between diabetes drug rosiglitazone and increased rate of heart attack

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The diabetes drug rosiglitazone has been under intense scrutiny since a 2007 study in the New England Journal of Medicine looked at more than 40 clinical trials and linked the drug's use with increased risk of heart attack and death from heart disease.

Now, in a post-trial analysis of results from an international clinical trial of 2,368 diabetes patients with cardiovascular disease, researchers at Washington University School of Medicine in St. Louis and several major centers across the country report no increased rate of heart attack or death in patients taking rosiglitazone. In fact, this analysis found a lower combined rate of death, heart attack and stroke associated with patients taking rosiglitazone compared with those who were not taking a thiazolidinedione drug (rosiglitazone or pioglitazone).

Richard G. Bach, MD, a Washington University researcher and medical director of the Cardiac Intensive Care Unit at Barnes-Jewish Hospital, presented this research June 29 in a late-breaking clinical studies session at the American Diabetes Association's Scientific Sessions in Orlando, Fla.

These new results are relevant in the debate over rosiglitazone's cardiovascular safety, according to Bach. In an advisory panel scheduled to meet next month, the U.S. Food and Drug Administration (FDA) will reassess the safety of rosiglitazone and determine whether it should

remain on the market.

"As a result of the questions raised by the meta-analysis in the New England Journal and certain other studies, some have cautioned that rosiglitazone should not be used in patients with coronary heart disease and diabetes," says Bach, also associate professor of medicine in the Cardiovascular Division at the School of Medicine. "Our data carefully examine use of rosiglitazone in a large cohort of patients with established coronary artery disease and suggest that treatment with rosiglitazone was not associated with an increased risk of ischemic cardiovascular events, like heart attack and stroke, and in a number of analyses it was associated with a lower rate of those events," he says.

Rosiglitazone, made by GlaxoSmithKline under the brand name Avandia, is an insulin-sensitizing drug. In type 2 diabetes, the pancreas continues to make insulin, but the body's tissues can't use it well. Rosiglitazone and other thiazolidinediones (TZDs) do not provide more insulin but reduce insulin-resistance, helping the body regulate blood sugar with the insulin it already makes.

Rosiglitazone was one of several drugs used to control blood sugar in the BARI 2D clinical trial (Bypass Angioplasty Revascularization Investigation 2 Diabetes). Between 2001-08, BARI 2D was a multi-center trial directed by the University of Pittsburgh that investigated treatment strategies for patients with both type 2 diabetes and cardiovascular disease. The trial was designed to determine the best strategies for treating patients with both conditions.

To address their cardiovascular disease, patients in BARI 2D were randomly assigned to receive either intensive medical therapy plus revascularization treatment (such as angioplasty or bypass surgery) or intensive medical therapy alone (with the possibility of revascularization treatment later if their symptoms did not improve).

To address their diabetes, the same patients were randomly assigned to receive either insulin-providing drugs (such as insulin itself) or insulin-sensitizing drugs (such as rosiglitazone or another drug, metformin). As a result, a large number of patients were treated with rosiglitazone during approximately five years of follow up in the trial. This aspect of BARI 2D provided a way to investigate rosiglitazone's cardiovascular safety after it came under scrutiny in 2007. In addition, Bach notes the importance of this new analysis because it looks at a population of patients already at high risk of cardiovascular events like heart attack and stroke.

Compared with patients not receiving a TZD, those who did take rosiglitazone showed a 28 percent lower combined rate of death, heart attack and stroke. In addition, the rate of stroke on its own was 64 percent lower in patients receiving rosiglitazone. Both of these differences were statistically significant. Rates of heart attack and death on their own showed no significant difference between those who took rosiglitazone and those who did not. In line with other studies, rosiglitazone was associated with increased risk of bone fracture, especially in women.

While these results support rosiglitazone's safety in patients with existing heart disease, Bach points out a weakness in the new analysis. Because BARI 2D was designed to assess treatment strategies, not the safety of rosiglitazone, the drug was not randomly assigned. It was the treating physician who decided whether to prescribe rosiglitazone to a particular patient, in line with the study protocol.

"It's not a pure randomly assigned trial of rosiglitazone versus a different drug," Bach says. "Our post-trial analysis compared patients treated with rosiglitazone to patients not receiving any TZD drug. That included patients in both arms - the insulin-providing and insulin-sensitizing arms," he says.

Like many diabetes drugs, rosiglitazone's FDA approval in 1999 was based on the fact that it improves glucose control, Bach explains. "We also have to be very careful about any additional adverse consequences or side effects of those drugs," he says. "We're always balancing risk versus benefit. Our particular data do not suggest that harm exceeds the potential benefit for rosiglitazone in patients with diabetes and established coronary artery disease."

Provided by Washington University School of Medicine