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## Heart Risk Seen in Drug for Diabetes

By [STEPHANIE SAUL](#)

An article in a leading medical journal yesterday raised serious safety questions about the widely used [diabetes](#) pill Avandia and renewed skepticism about the vigilance of federal drug regulators.

The analysis, based on a review of more than 40 existing clinical studies involving nearly 28,000 patients, showed that Avandia significantly increased the risk of heart attacks, compared with other diabetes drugs or a placebo.

Both the study's lead author and the editors of The [New England Journal of Medicine](#), in which the article appeared, cautioned that the research method used left the findings open to interpretation. But they said the study nevertheless raised important concerns.

And the publication of [the study on the journal's Web site](#) prompted the [Food and Drug Administration](#) to issue a public safety alert and advise users of the drug — an estimated million people in this country and two million worldwide — to consult their doctors about the potential cardiovascular risks.

The journal's editor in chief, Dr. Jeffrey M. Drazen, said: "We view this as the best publicly available data on a very important question. It shows what we regard as a preliminary, but worrisome, signal about cardiovascular toxicity of this drug."

The drug's maker, [GlaxoSmithKline](#), issued a news release defending Avandia's safety and saying it "strongly disagrees" with the conclusions of the journal article, which it said was based on incomplete evidence.

Glaxo's stock fell by nearly 8 percent on the news.

While the analysis took Wall Street and many doctors by surprise, Glaxo and the F.D.A. disclosed yesterday that they had known about the signs of potential cardiovascular risk since last August, when the company, on its own initiative, submitted a similar analysis to the agency. That disclosure prompted questions on Capitol Hill about why patients and doctors had not been informed earlier.

Explaining its delay, the F.D.A. said the significance of the studies had not been confirmed and in fact was contradicted by some other studies of the drug.

"We decided we needed to reanalyze the complex dataset ourselves to make a better informed decision," Dr. Robert J. Meyer, a director of the agency's office of drug evaluation, said in a news conference yesterday.

Dr. Meyer said that the agency was close to completing its analysis and would convene an advisory panel as soon as possible to review the drug. The F.D.A. is conducting an estimate of excess heart attacks that might be attributed to the drug, but Dr. Meyer said that the results were not final, declining to disclose the number.

He noted that Avandia's label already carries a warning of cardiovascular risks.

Meanwhile, the F.D.A. advised Avandia patients to check with their doctors.

"We're expecting dozens if not hundreds of phone calls tomorrow," said Dr. John B. Buse, chief of endocrinology at the [University of North Carolina](#) in Chapel Hill. "I've told our staff to tell people who call that this is not cause for panic. We can discuss it further at their next visit."

But Dr. Buse, a president-elect of the American Diabetes Association, said he would not be surprised if some doctors ultimately switched patients to an alternative drug unless additional details were released supporting Avandia's safety.

The New England Journal of Medicine posted the paper on its Web site, ahead of its planned print publication on June 14. Early Web postings are made by the journal's editors in matters that they consider to have public health importance.

The study was not supposed to be released until 5 p.m. yesterday, after the closing bell on Wall Street, but it was inadvertently published yesterday morning by two wire services. The company's stock began falling almost immediately and was down more than 8 percent by midafternoon, before finishing down 7.85 percent, at \$53.18.

The research method employed by the lead author, Dr. Steven E. Nissen of the Cleveland Clinic, was a so-called meta-analysis, which combines the data of various studies. Such analyses, generally used to develop hypotheses, are seen as less reliable than uniform controlled studies.

In an interview, Dr. Nissen said that the average diabetic has a 20.2 percent risk of a heart attack over a seven-year period. A diabetic taking Avandia has a 28.9 percent risk during that same seven-year period, according to his analysis.

"It's a huge risk," he said, estimating that "tens of thousands of people" had heart attacks as a result of taking the drug.

An editorial that accompanied the article questioned why doctors would continue to prescribe Avandia, which is known generically as rosiglitazone. But the editorial cautioned patients not to stop taking the medication without discussing it with their doctors.

In its news release, Glaxo defended Avandia's safety.

"The totality of the data show that Avandia has a comparable cardiovascular profile to other oral antidiabetic medicines," the release said. "GSK stands firmly behind the safety of Avandia when used appropriately, and we believe its significant benefits continue to outweigh any treatment risks."

In a conference call with reporters yesterday, the company's chief medical officer, Dr. Ronald L. Krall, said that Glaxo had submitted similar data to the F.D.A. last August after noticing a signal of increased cardiovascular risk. Its data indicated a 31 percent increased risk, based on a similar meta-analysis. That information was also posted on the company's Web site last year, Glaxo said.

But the company submitted its analysis along with another study that supported the drug's safety — a look at 30,000 patients taking Avandia and other diabetes drugs enrolled in an unidentified insurer's managed care plan. And the company also said that a drug safety monitoring committee overseeing a continuing study of the drug's cardiovascular risks had not raised any red flags.

Avandia, a pill on the market since 1999, is used for the treatment of Type 2, or adult-onset, diabetes. It is sold alone as Avandia and in combination with other drugs as Avandamet and Avandryl. With \$3 billion in worldwide sales last year, it was Glaxo's second-biggest product after the [asthma](#) inhalant Advair.

Patients who are newly discovered to have Type 2 diabetes generally receive another oral drug, metformin, as the first-line treatment, with Avandia among several medications recommended when metformin alone no longer works. If those treatments fail, patients typically move to insulin injections.

Some doctors contend that another drug that works by a similar mechanism to Avandia — Actos, made by the Takeda Pharmaceutical Company and jointly marketed by [Eli Lilly](#) — has been shown in studies to have a superior cardiovascular risk profile.

The journal editorial, by Dr. Bruce M. Psaty of the [University of Washington](#) and Dr. Curt D. Furberg of [Wake Forest University](#), said that they could see no reason doctors would prescribe Avandia, given the alternative treatments available.

“In view of the potential cardiovascular risks,” the editorial said, “and in the absence of evidence of other related advantages, except for laboratory measures of glycemic control, the rationale for prescribing rosiglitazone at this time is unclear.” Glycemic refers to blood sugar.

The editorial said that problems with Avandia had once again spotlighted flaws in the nation's drug approval and monitoring system. They asserted that those problems had not been fully addressed by legislation recently passed by the Senate that is meant to strengthen the agency's powers. Both Dr. Psaty and Dr. Furberg have been critical of the F.D.A.'s drug approval process in the past.

On Capitol Hill, several lawmakers questioned whether Avandia could be another Vioxx — a painkiller that [Merck](#) pulled off the market in 2004 after it was shown to cause heart attacks in some patients.

Rep. [John D. Dingell](#), the Michigan Democrat who is chairman of the House Energy and Commerce Committee, said the agency's handling of questions about Avandia might reflect dangerous shortcomings in its drug safety monitoring. Those questions, he said, would figure in his committee's efforts to force the agency to be a tougher regulator.

“We learned from an F.D.A. briefing that the agency has known about this problem for at least eight months and perhaps even longer,” Mr. Dingell said in a prepared statement yesterday. “What we don't know is why diabetics and their doctors haven't been notified of the substantial risk to the heart from a drug prescribed to protect the cardiovascular system.”

[Henry A. Waxman](#), the California Democrat who is chairman of the Committee on Oversight and Government Reform, said yesterday that he had started an investigation of Avandia and would call Glaxo officials and Dr. Andrew C. von Eschenbach, the F.D.A. commissioner, to testify at a hearing on June 6.

The finding — that Avandia raises the risk of heart attack by 43 percent — was based on a review of 44 studies of the drug. The review was conducted by Dr. Nissen and Kathy Wolski of the Cleveland Clinic, where Dr. Nissen is the chief of cardiovascular medicine.

Dr. Nissen, who had been among the first doctors to raise questions about the cardiovascular safety of Vioxx, first publicly raised concerns about Avandia in a letter published last December in the British medical journal *Lancet*.

Dr. Nissen's letter noted increased cardiovascular problems in a 5,000-patient clinical study, called Dream. Glaxo had sponsored the Dream trial in an effort to expand the product beyond a treatment for diabetes by using it to prevent the disease.

In the Dream trial, intended to determine if Avandia could prevent diabetes, patients taking Avandia had 66 percent more heart attacks, 39 percent more strokes and 20 percent more deaths from cardiovascular-related problems compared with a placebo. That outcome, Dr. Nissen wrote, "virtually precludes the possibility of an overall benefit and suggest an unexpected mechanism for harm."

Both Avandia and Actos, the Takeda drug, are members of a class of compounds with a troubled history. One drug in the group, Rezulin, was withdrawn in 2000 because it caused liver problems.

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