Diabetes drug drives down fatal heart attacks, strokes, study finds

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A new drug drives down the likelihood that diabetic patients with established cardiovascular disease will suffer or die of heart attack, stroke or heart failure, a new study finds.

Compared with clinical trial subjects who took a placebo medication, those who added the drug empagliflozin - marketed as Jardiance - to their regimen of diabetes medications were 38 percent less likely to suffer a fatal or nonfatal "cardiovascular death" (heart attack, stroke or heart failure) during the roughly three years subjects were tracked.

The study found that those taking Jardiance were 35 percent less likely to be hospitalized for heart failure than were subjects who took a placebo pill instead. And they were 32 percent less likely to die of any cause.

The results of the clinical trial astonished physicians, who have been pummeled in recent years by a litany of disappointing findings about diabetes treatments. Four major clinical trials involving other diabetes medications in recent years have shown that those treatments improve patients' metabolic function. But in each case, that improvement has failed to translate into fewer heart attacks, strokes or cardiovascular deaths.

In some cases, those medications were linked to higher death rates from heart attack and stroke.

"It's an amazing result, very unexpected and wonderful news," said Dr. Christopher P. Cannon, a cardiologist at Brigham & Women's Hospital in Boston, who was not involved with the study.

Cleveland Clinic cardiologist Steven Nissen hailed the new findings as a "blockbuster result."

"This is the first time ever that a diabetes drug has shown evidence of cardiovascular benefit," said Nissen, who eight years ago prodded the Food and Drug Administration to change its standards for evaluating diabetes medications and require them to undergo cardiovascular safety trials. "Obviously, this is an important finding."

Empagliflozen is the third of a new class of diabetes drugs that reduce blood sugar in diabetics by facilitating its excretion in urine. It won U.S. marketing approval in August 2014 from the FDA and is one of about 40 medications approved for the treatment of diabetes.

Its cost, close to $800 per year, has raised some doubts however. Calling into question its cost effectiveness, Britain's National Health Service has said it will not pay for the medication.

Jardiance's sponsors - Boehringer Ingelheim Pharmaceuticals Inc. and Eli Lilly and Co. - conducted the new study, called the EMPA-REG outcome trial, on orders from the FDA. The results were presented Thursday to a meeting of the European Association for the Study of Diabetes in Stockholm, Sweden, and published simultaneously in the *New England Journal of Medicine*.

The latest trial results suggest that for every 39 diabetic patients with established cardiovascular disease who are treated with Jardiance, one death might be averted.

The participants in the EMPA-REG outcome trial were at unusually high risk of early cardiovascular death, so it's hard to draw clear comparisons with other drugs. But the "number-to-treat" figure calculated by the study's authors puts the drug's effectiveness in preventing cardiovascular death close to that of lipid-lowering statin medications, introduced in the 1980s, and possibly ahead of ACE inhibitors, a widely used class of hypertension medications, said Dr. Silvio E. Inzucchi, a Yale Medical School endocrinologist who is among the paper's authors.

Since such medications are already in wide use among diabetes patients, physicians had begun to fear they would be hard-pressed to drive heart attacks and strokes much lower, said Inzucchi. The results of the trial - that adding Jardiance to a diabetic's existing treatment regime could do so - has sparked jubilation among study investigators, he said.

"It's almost like, how much more benefit can you get?" said Inzucchi in a telephone interview from Stockholm. "Personally, I was shocked by the findings."

The need for such improvements couldn't be clearer. About 23.6 million American adults have diabetes, a disease that is closely tied to the nation's epidemic of obesity. People with Type 2 diabetes are five to eight times likelier than the general population to develop cardiovascular disease, and hence, to suffer a fatal heart attack or stroke. Four in five with diabetes will die of coronary heart disease, the accumulation of plaque in the arteries.

Nissen noted that some of the study's findings were less than stunning. Compared with subjects taking a placebo pill, those taking empagliflozin were only slightly less likely to suffer a nonfatal heart attack. And they were, in fact, slightly more likely to suffer a nonfatal stroke.

But when deaths from strokes, heart attacks and heart failure were combined, the group taking empagliflozin was unmistakeably better off. In some trials where a medication is found to reduce nonfatal "events," researchers suspect that patients are saved only to die of something else a little later.

Only a few months into the trial, however, it became clear that subjects taking the study drug were much less likely to die than those on the placebo.

In the hierarchy of outcomes, said Nissen, "death trumps everything else."

"When you have an effect on death, you have to pay attention. Of all the things we do in medicine, averting death is high among them."

In all, 194 of 2,333 subjects (8.3 percent) taking the placebo died of any cause during the roughly three years most were tracked. Among those taking empagliflozin, 269 of 4,687 subjects (5.7 percent) died. The rates of "cardiovascular death" were 5.9 percent for those taking placebo and 3.7 percent for those taking empagliflozin.

Those on empagliflozen also were found to lose more weight and more inches around their waists, as well as to see their blood pressure and levels of "bad cholesterol" go down more steeply. Genital infections were a more common side effect in those taking the drug than those on placebo.

Beyond its ability to lower blood glucose, the range of the medication's effects has prompted broad speculation about how it could succeed where so many other diabetes medications have failed.

Coauthor Inzucchi suggested that empagliflozin's diuretic effect - one

means by which it lowers blood sugar - may have an unforeseen benefit, especially for diabetics whose hearts are nearing the point of failure. At the same time, he and the paper's other authors acknowledged they are unsure of how the medication may work to forestall fatal and nonfatal cardiovascular events.

"It's a reminder that controlling all these things - blood pressure, weight, cholesterol - is part of the mix," said Cannon of Brigham & Womens' Hospital. "This looks like a terrific way to do that, adding this drug."

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