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# Similar efficacy, lower adverse event risk with lower doses of pioglitazone

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Both 15 mg and 30 mg pioglitazone doses have similar efficacy as 45 mg for preventing new-onset diabetes, stroke and myocardial infarction but with lower risk for adverse events, according to study findings.

In post hoc analysis of data from the Insulin Resistance Intervention after Stroke (IRIS) trial published in *Diabetes, Obesity and Metabolism*, participants taking less than 45 mg pioglitazone had lower risks for edema, weight gain and heart failure than those taking 45 mg, showing the agent may be better utilized at lower doses.

"Pioglitazone is the most potent therapy for insulin resistance, but it is underutilized, largely because of adverse effects from the 45 mg dose: leg swelling in 20% and weight gain in 10% of patients," **J. David Spence, CM, MD, FRCPC, FAHA**, professor of neurology and clinical pharmacology at Western University, and director of the Stroke Prevention Atherosclerosis Research Centre at the Robarts Research Institute in London, Ontario, Canada, told Healio. "In this study we analyzed outcomes comparing lower doses — combining those who took 15 mg or 30 mg per day — with those taking 45 mg per day. We found that lower doses provided most of the benefit, with no significant increase in leg swelling and weight gain compared to placebo, and less than the 45 mg dose. This means that pioglitazone can be used more widely, as most patients will tolerate the lower doses."

Spence and colleagues analyzed data from IRIS, a randomized, double-blind trial in which researchers compared the efficacy of pioglitazone for preventing new-onset type 2 diabetes, MI or stroke with placebo. Participants randomly assigned pioglitazone started with one 15 mg tablet daily, increased to 30 mg daily at 4 weeks and increased again to 45 mg at 8 weeks. Participants with adverse effects were down titrated to a better tolerated dose. In the ad hoc analysis, participants were

categorized based on the most frequent dose taken for each participant from pioglitazone initiation to the end of follow-up. Researchers examined pioglitazone efficacy and adverse outcomes in participants in each dosing group.

"The IRIS study demonstrated that pioglitazone not only reduced the cardiovascular complications, but also reduced the progression of prediabetes to diabetes," **Paresh Dandona, MD, PhD,** SUNY distinguished professor and chief of endocrinology in the department of medicine at the University of Buffalo and an *Endocrine Today* Editorial Board Member, told Healio. "Since most of the patients in the study were treated with the high dose of 45 mg daily, which has a frequent side effects of weight gain and edema, it was important to reanalyze the data to focus on the effects of the two lower doses of the drug."

**Efficacy maintained with lower dose**

Of 1,938 participants receiving pioglitazone in IRIS, 28.2% most frequently received less than 15 mg per day, 6.6% received 15 mg, 4.6% received 30 mg and 60.6% received 45 mg. Participants receiving 15 mg or 30 mg per day had a lower HR for MI or stroke compared with placebo (adjusted HR = 0.48; 95% CI, 0.3-0.76; $P = .002$) than the group receiving 45 mg per day (aHR = 0.74; 95%, 0.59-0.94; $P = .01$). Compared with placebo, the 15 mg and 30 mg group (aHR = 0.34; 95% CI, 0.15-0.81; $P = .01$) and the 45 mg group (aHR = 0.31; 95% CI, 0.21-0.46; $P < .0001$) had similar reduced risks for new-onset diabetes.

**Fewer adverse events with lower dose**

In an analysis of adverse events, the 15 mg or 30 mg dose group did not have a significantly increased risk for edema, weight gain or heart failure compared with placebo. By contrast, those receiving a 45 mg dose had an increased risk for edema (aHR = 1.81; 95% CI, 1.43-2.3; $P < .0001$), weight gain (aHR = 2.16; 95% CI, 1.93-2.42; $P < .0001$) and heart failure (aHR = 1.71; 95% CI, 1.03-2.86; $P = .04$) compared with placebo.

"While the two lower doses provide CV protection similar to that of the higher dose, the side effects of edema and weight gain are significantly lower," Dandona said. "This differential between the doses is important since the use of pioglitazone

has been hampered by these side effects. I have used the dose of 15 mg daily over the past decade and a half with excellent results in terms of glycemic control without the side effects of weight gain and edema."

In addition to significant improvements in both glucose level and CV complications for people with diabetes, Dandona said, pioglitazone could give patients a more affordable treatment option.

"Pioglitazone is a generic drug now, it is inexpensive," Dandona said. "This is relevant in the context of the astronomical prices of insulin. Hence, pioglitazone must be used prior to insulin, especially since subcutaneously injected insulin has no protective effect on cardiovascular complications."

Spence said the findings reveal a need for a randomized trial examining the effects of lower doses of pioglitazone. He also said more research is needed to explore ways to reduce fractures in people using pioglitazone.

"In our study, fractures were increased on all doses; most occurred in older women," Spence said. "The number needed to harm, to cause one serious fracture, was 125 vs. a number needed to treat of only 12 to prevent one case of new-onset diabetes and 24 to prevent one stroke or MI. Probably pioglitazone should be avoided in older women with osteoporosis — the group in which most fractures occurred. It would be important to test in human subjects the observation that, in a rat model, fenofibrate prevented bone loss from pioglitazone."