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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The IRIS Trial: Reviewing Results & Taking a Look at Pioglitazone

Dr. Buse:
Prediabetes is associated with risk to developing diabetes but also cardiovascular complications, including stroke and heart attack, but can pioglitazone mitigate these risks? And how does adherence affect outcomes? One clinical trial aimed to answer just that.

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse. And joining us to talk about the Insulin Resistance Intervention after Stroke trial, or IRIS for short which explored the impacts of pioglitazone in people who had a history of stroke and evidence of insulin resistance, is Dr. David Spence, a Professor Emeritus of Neurology and Clinical Pharmacology at Western University and the Director of the Stroke Prevention and Atherosclerosis Research Center in London, Ontario.

Dr. Spence, thanks for being here today.

Dr. Spence:
It's my pleasure.

Dr. Buse:
So, to begin with, Dr. Spence, can you tell us about the IRIS trial? What was the rationale behind it?

Dr. Spence:
The rationale was that pioglitazone is the most powerful therapy against insulin resistance, and it was well known that insulin resistance affects atherosclerosis and increases cardiovascular risk. So, in the IRIS trial, we randomized patients who had insulin resistance defined by a HOMA score, a homeostasis model score greater than three, which identifies insulin resistance. In that study the analysis was an intention-to-treat analysis, so the effect in the IRIS trial was not as impressive as it was in the study that I subsequently conducted in patients with prediabetes defined by an A1c level. The reason I did that was I was trying to persuade the Ontario Government to pay for pioglitazone for my patients, and they said, "Well, doctors don't measure HOMA score, so it's not relevant," so that's why we did this study that was in *JAMA Neurology*, 2019, was that we analyzed people who had prediabetes as opposed to people with insulin resistance, and in that study the primary analysis was an analysis of people who actually took the medication. And the reason for that is that it is really not appropriate to do an intention-to-treat analysis of a drug that many people stop because of adverse effects.

Dr. Buse:
Great. So, with that background in mind, let's dive into the results. Can you share some of your key findings?

Dr. Spence:
Yeah. And among people who took 80 percent of the protocol dose and—and something that is not well understood, the protocol dose did not have to be the full 45 mg dose because people could be down-titrated if they had adverse effects from the full dose. And in that study, among people who took 80 percent of the protocol dose, there was an 82 percent reduction in new-onset diabetes over five years and a 43 percent reduction in stroke and myocardial infarction over five years, and there was also a reduction of all the other endpoints that we looked at, such as heart failure, hospitalization and so on.

The problem is that the 45 mg dose has fairly significant adverse effects. About 20 percent of people get leg swelling, and about 10 percent of people get weight gain, so there's a lot of pushback against this medication on the part of pharmacists and physicians. There, is also a myth about pioglitazone causing bladder cancer. There were some studies that showed that it did and some that showed it didn't, but in the big meta-analysis, I went through it and calculated that if there were a risk of bladder cancer—and that's not for sure—if

there were a risk of bladder cancer, the risk would be 0.006 percent per year, which pales in comparison to an 80 percent reduction in the new-onset diabetes and a 43 percent reduction in stroke and MI.

Now, what we went on and did was, was a paper that was published in Diabetes, Obesity and Metabolism where we analyzed the effects of different doses of pioglitazone, and what we found was that the 15 mg dose provided virtually all of the benefit of pioglitazone without the adverse effects, so I think pioglitazone should be much more widely used in people with prediabetes and stroke. And something that's useful to identify insulin resistance without doing a HOMA score, is that we published in Lipidology a paper reporting that a high ratio of triglycerides to HDL identifies metabolic syndrome and insulin resistance. So, if you've got a patient who's prediabetic with a high triglyceride and a low HDLC, that person is going to benefit from pioglitazone.

Dr. Buse:
That's extraordinary. For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. John Buse, and today I'm speaking with Dr. David Spence about the IRIS trial and pioglitazone in prediabetes.

Dr. Spence, so what you've told us so far is, in this trial, whether you identified people with diabetes risk based on A1c or the HOMA score or the triglyceride to HDL ratio, that there's this extraordinary benefit of pioglitazone on the risk of stroke, cardiovascular events and the development of diabetes.
So there's two parts to the story. One is the dose part, whether we use 15 or 30 mg versus 45 mg, and the other part is the adherence part. You know, one thing that's fascinating is your adherence analysis, compared to people that were adherent with placebo, and people who were adherent to placebo generally do quite well. So, what do you think the right story is with regards to encouraging adherence and dose selection when using pioglitazone for diabetes prevention or cardiovascular risk reduction?

Dr. Spence:
That's why I think it's important to use the low dose, because people are more likely to be adherent to it.

Dr. Buse:
Wonderful. And to bring it all together, as a clinician, what do you think the role of pioglitazone should be in patients with cardiovascular disease, and/or prediabetes?

Dr. Spence:
Well, it's an off-label use in prediabetes, but our results in the JAMA Neurology paper are so striking that I think it's something that clinicians should consider doing. And they could identify prediabetes by an A1c; they could identify insulin resistance by a high triglyceride/HDL ratio; and that's going to find the patients that will benefit most from this medication.

Dr. Buse:
Before we close, do you have any final thoughts or takeaways you'd like to share with our audience?

Dr. Spence:
Yes. I think pioglitazone is tremendously underutilized because there's such a, impression of its adverse effects, and if we can get around those adverse effects with a low dose, it should make it much more easy to use.

Dr. Buse:
Well, with those thoughts in mind, I want to thank my guest, Dr. David Spence, for sharing his research and insights with us today on pioglitazone in prediabetes. Dr. Spence, it was really a pleasure speaking with you today.

Dr. Spence:
My pleasure.

Dr. Buse:
For ReachMD, I'm Dr. John Buse. To access this episode and others from our series, visit ReachMD.com/DiabetesDiscourse where you can be Part of the Knowledge. Thanks for listening.