CLOSER LOOK

MEMORANDUM

IRIS Trial finds pioglitazone reduces risk of stroke and MI in high-risk patients without diabetes - February 17, 2016

Executive summary

- TZD pioglitazone (Takeda, now generic) treatment reduced relative risk of stroke and MI by 24% (p=0.007) and new diabetes incidence by 52% (p<0.001) compared with placebo in patients without diabetes but with insulin resistance
- Dr. Silvio Inzucchi (Yale School of Medicine, New Haven, CT) points out that pioglitazone is now the only glucose-lowering medication to be shown to reduce atherosclerosis-mediated CV events
- The potential of a pioglitazone/empagliflozin (SGLT-2) combination is suddenly of quite enormous interest ….

Today, Dr. Walter Kernan (Yale School of Medicine, New Haven, CT) presented extremely exciting results from the Insulin Resistance Intervention after Stroke (IRIS) trial at the American Heart Association's International Stroke Conference in Los Angeles, CA. These results were simultaneously published in NEJM. The five-year, placebo-controlled trial investigated the TZD pioglitazone in patients without diabetes but with insulin resistance (n=3,876), and a history of recent stroke or transient ischemic attack (TIA). At baseline, patients were in the highest quartile of insulin resistance among populations without diabetes, as measured by a HOMA-IR index (a measure of insulin resistance based on a simple equation that incorporates the fasting glucose and insulin level) of 3.0 or higher. However, patients with existing diabetes were excluded from the trial and average baseline A1c of trial participants was 5.8%. The study found that treatment with pioglitazone reduced the relative risk of a combined primary endpoint (fatal and non-fatal stroke and MI) by an impressive 24% (p=0.007) compared with placebo - 9.0% of patients in the pioglitazone-treated group experienced a stroke or MI during the trial period, compared to 11.8% of those in the placebo-treated group. Furthermore, the secondary outcome of new diabetes diagnosis was reduced by 52% (p<0.001 vs placebo) in the pioglitazone-treated group. However, other secondary endpoints (stroke, acute coronary syndrome, three-point MACE [stroke, MI, and heart failure], and death) were not significantly reduced with pioglitazone when compared with placebo. That said, study co-author Dr. Silvio Inzucchi (Yale School of Medicine, New Haven, CT) emphasized that this is fairly typical in such trials, driven by the lower number of events in these secondary endpoints. He pointed out that, while not statistically significant, each of these endpoints were less frequent in pioglitazone-treated patients.

Dr. Silvio Inzucchi (Yale School of Medicine, New Haven, CT), a co-author of the study, pointed out that TZD pioglitazone (formerly Takeda/Lilly's Actos, now generic) is now the only glucose-lowering medication to be shown to reduce atherosclerosis-mediated CV events. He expressed strong confidence that these results are pioglitazone-specific, and may not extend to rosiglitazone. While we have see TZDs fall out of favor with patients due to side effects, these exciting results suggest that, in the right patient population, with the right dose, pioglitazone could have significant benefits in preventing type 2 diabetes onset and reducing cardiovascular outcomes. We consider these landmark results that could increase some use of generic pioglitazone, though the drug has been unpopular due to the side effect profile (which may be reduced using a lower dose though most patients in this trial used a full dose as we understand it). Especially for those populations for whom other classes of medications are difficult to access due to cost, these results are very exciting. Like Dr. Inzucchi, we are very eager to see the TZD/empa (SGLT-2) combination used over the long term, since these are now the only two agents used in type 2 diabetes that have been proven to improve CV outcomes in high-risk patients.

- **To put the results into perspective, treating 100 patients with pioglitazone over five years would prevent three patients from having a stroke or MI.** On the flipside, two patients would be expected to experience bone fractures requiring surgery or hospitalization. While acknowledging that little is known about the relationship between TZD dose and bone fractures, Dr. Inzucchi suggested that lower doses may be just as effective at reducing stroke and MI and may have less adverse events. In IRIS, patients were treated with up to 45 mg of pioglitazone, but were able to down-titrate the dose in response to adverse events. Thus, the actual median dose ranged from 29-40 mg/day and Dr. Inzucchi noted that he suspects 30 mg of pioglitazone would have been just as efficacious.
- **Adverse events associated with pioglitazone were as expected, including weight gain, edema, and bone fractures.** The study observed the greatest difference in weight change after four years, at which point the pioglitazone-treated group experienced a mean weight gain of 2.6 kg and the placebo-treated group experienced a mean weight loss of 0.5 kg ($p<0.001$). That said, Dr. Inzucchi argued that the weight gain can be mitigated with optimal dosing and careful attention to diet. 35.6% of participants in the pioglitazone-treated group experienced edema while 24.9% of participants in the placebo group did ($p<0.001$). Bone fracture risk was also significantly higher in the pioglitazone-treated group, with 5.1% of patients reporting a bone fracture requiring hospitalization or surgery compared to 3.2% with placebo ($p=0.003$). An increase in heart failure with pioglitazone use was not observed in the trial, though this may be attributed to the trial excluding participants with a history of heart failure.
- **Dr. Silvio Inzucchi shared his view that TZDs are "without question" the most potent drugs to prevent diabetes -** this potential was overshadowed in the past by the negative effects associated with the class, including weight gain, edema, possibly heart failure, bone fractures, and the controversial bladder cancer concerns - later findings of which showed no association between the drug and bladder cancer. He acknowledged that providers found it difficult to prescribe TZDs, especially with the rise of alternative medications with fewer side effects such as DPP-4 inhibitors although the potential to reduce strokes and reduce diabetes diagnosis may bring this drug back for those with pre-diabetes. While there is no current FDA pathway, we hope to see this changed in the near future.
- **Dr. Inzucchi said he was "tantalized" by the potential of a pioglitazone/empagliflozin combination** - calling empagliflozin's effect on heart failure and pioglitazone's effect on stroke and MI an "awesome one-two punch to address cardiac disease in diabetes." He also suggested that empagliflozin may attenuate the weight gain and edema seen with pioglitazone. We know that there is a strong association between obesity and type 2 diabetes, so preventing weight gain is a major goal with glucose-lowering medications.

Close Concerns Questions

Q: Lilly is partnered with Takeda to market Actos (though since it has gone generic this is not a commercial priority) and also manufactures SGLT-2 inhibitor Jardiance (empagliflozin). Will Lilly consider investigating a combination product of pioglitazone/empagliflozin?

Q: Given that pioglitazone is already generic, will Takeda or Lilly find it worthwhile to pursue an expanded label or indication for Actos?

Q: How will ADA/EASD and AACE/ACE consider these results in the next iteration of their diabetes treatment guidelines?

Q: Will the IRIS results be able to overcome the negative publicity surrounding pioglitazone following the bladder cancer risk controversy?

Q: Is there potential for a metformin/pioglitazone combination therapy for prediabetes?

Q: What is the mechanism of action behind the cardioprotective effect?

Q: Do the IRIS results apply to patients with insulin resistance but who have not experienced a stroke? What about patients who have preexisting diabetes?

Q: Will patients and providers deem the increased bone fracture risk an acceptable trade-off for reduced risk of stroke and MI?

Q: Will payers begin asking patients to try cheaper, generic pioglitazone before covering more expensive therapies?

-- by Helen Gao, Sarah Odeh, and Kelly Close