

## Insulin Resistance Intervention After Stroke Trial of Pioglitazone

### Is This Perhaps the End of the Beginning?

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The completion of the Insulin Resistance Intervention After Stroke (IRIS) trial culminated a long process to design, fund, and recruit patients to test, for the first time, whether treatment with an approved antidiabetic drug at the prediabetic stage of insulin resistance (IR) improves outcomes in patients with cerebrovascular disease.<sup>1</sup> In the IRIS trial, pioglitazone, a member of the thiazolidinedione class of peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ) agonists, was compared with placebo. Nondiabetic subjects with recent (<6 months) stroke or transient ischemic attack, who met inclusion criteria for IR, defined as Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR) >3.0, were enrolled. Major exclusions included heart failure (HF) because of the known potential for thiazolidinediones to precipitate/worsen HF, active liver disease because of the association of another thiazolidinedione (troglitazone) with hepatotoxicity, and either the occurrence or risk factors for bladder cancer because of data from other trials suggesting an imbalance of bladder cancer in pioglitazone-treated diabetics.<sup>2</sup> After 5 years, pioglitazone-treated patients had 24% reduction in cardiovascular outcomes above and beyond a generally modern approach to secondary stroke prevention. Stroke reduction was entirely for the ischemic type, and interestingly, the biggest relative reduction was in the lacunar subtype although unfortunately almost 2 of 3 had no identified stroke mechanism, making this finding tentative. Consistent with previous studies in diabetics where thiazolidinediones reduced the need for insulin introduction,<sup>3</sup> in the IRIS trial, pioglitazone reduced by half the development of diabetes mellitus. Despite a higher incidence of shortness of breath and edema, HF mortality/hospitalization did not increase, potentially because of the strict definition of HF in contrast to previous studies.<sup>3,4</sup> Also, the investigators found only a slight trend for one of the most scrutinized potential complications of thiazolidinediones, urinary bladder cancer. Moreover, despite an expected overall weight gain, there was reduction in the pioglitazone group in HOMA-IR index, insulin levels, and fasting glucose levels by the end of the trial.<sup>1</sup> The findings of reduction both in cardiovascular events and

in the development of diabetes mellitus and its biochemical correlates deserve considerable attention as the longer term benefit for this potentially large population of patients may be greater than possible to detect in the IRIS trial.

Considered in various contexts for decades, the unifying concept of IR linking hyperglycemia, hypertension, hyperlipidemia, and ultimately the ravages of diabetes mellitus was put into the context of modern medicine by Reaven<sup>5</sup> in 1988. Indeed, the prediabetic syndrome, including these features as well as central obesity, called the metabolic syndrome (MetS) is sometimes referred to as Reaven syndrome. Although discussion continues on the precise relationship between IR and MetS,<sup>6</sup> many consider IR central to MetS. The population meeting modern criteria is potentially as many as one third.<sup>7</sup> Although increased physical activity is recognized as a key component in improving IR, MetS incidence continues to increase despite attempts to address a sedentary lifestyle.<sup>7</sup> Moreover, the definition of IR may have age, sex, and racial and ethnic differences, with some groups manifesting risk for MetS at lower HOMA-IR levels.<sup>8</sup>

Interest in Reaven's and others' conceptualizations anticipated the introduction of PPAR- $\gamma$  agonists to decrease IR as a hope for breakthrough. PPAR- $\gamma$  receptors have roles in fatty acid uptake and production and in glucose metabolism.<sup>1</sup> Specific PPAR- $\gamma$  receptor subtypes are concentrated in adipose tissue, but other forms are present in virtually all cells. Not surprisingly, then, PPAR- $\gamma$  may influence other conditions. Patients with acute stroke commonly manifest hyperglycemia<sup>9</sup> and IR, and because of a complex influence of thiazolidinediones on inflammation, these drugs are also undergoing study in acute ischemic and hemorrhage stroke.<sup>10</sup> These receptors have roles in cell proliferation and bone homeostasis,<sup>10</sup> perhaps contributing to side effects that have dogged these drugs to various degrees, including bladder cancer and bone fractures. The history of these concerns is well outlined in the study's accompanying editorial as is the circuitous route these drugs have taken before and during the IRIS trial.<sup>11</sup> Persistence in the face of these obstacles is a testament to the resourcefulness

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The subtitle paraphrases Winston Churchill's speech at the Lord Mayor's Luncheon, Mansion House, London, October 11, 1942.

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and dedication of the study's prime movers exemplified by Kernan et al.<sup>1</sup>

How should we implement the IRIS trial in our daily clinical practice? As always, we need to find the balance between the estimated benefit and the potential harms taking also into account the preferences and values of patients and proxies. On one hand, the IRIS trial did show beneficial effects on stroke/myocardial infarction and diabetes mellitus progression; however, the size of this effect is modest given that it would take >500 patient-years of pioglitazone treatment to prevent just 3 strokes/myocardial infarctions.

This modest benefit, however, did not come without a cost: during the same period, 2 patients more compared with the placebo group would have to be operated or hospitalized for bone fracture.<sup>1</sup> Simultaneously, many more pioglitazone-treated patients would increase considerably their weight compared with placebo-treated patients; in view of the graded association between obesity and disability,<sup>12</sup> this could potentially lead to impairment in activities of daily living in pioglitazone-treated patients. A cautious interpretation of these results would emphasize that in combination with the negative effect of bone fractures/surgery on activities of daily living, these 2 side effects could cancel any benefit on activities of daily living, which may result from the lower stroke incidence in pioglitazone-treated patients. However, a different view might consider that the medical profession has not been particularly successful in increasing activity levels of our patients and the incidence of MetS is on the rise. Because the pioglitazone group, despite weight gain and bone fractures, had a reduction in diabetes mellitus and many of its biochemical correlates, there may be a longer-term benefit that may emerge over time.

One certainly needs to take into consideration also the pioglitazone controversy about its association with bladder and other cancers.<sup>13</sup> Animal-model research associated pioglitazone with bladder cancer,<sup>13</sup> a finding reproduced also in humans.<sup>3</sup> In 2011, the French Medicines Agency withdrew pioglitazone in view of a French-based study, which confirmed the association between pioglitazone and bladder cancer.<sup>14</sup> Soon, German authorities followed and recalled pioglitazone from the market, as India did later on,<sup>15</sup> whereas Food and Drug Administration updated the pioglitazone drug label to include a statement that its use for >1 year may be associated with increased risk of bladder cancer.<sup>16</sup> The pioglitazone–bladder cancer association was not confirmed by recent studies or the IRIS trial (although the latter was not powered to address this question), so the jury is still out.<sup>13,17</sup>

Given these ongoing concerns, if the treating physician and the patient finally decide to start pioglitazone, the former needs to make sure that the patient profile is similar to the IRIS patient, that is, HOMA-IR >3 and free of HF, transaminasemia, active liver disease, anemia, bladder cancer, or related risk factors.<sup>2</sup> However, as we get a better understanding of strengths and limitations of the HOMA-IR in different populations,<sup>8</sup> it may be worth adjusting inclusion criteria, but only if the risk/benefit of this medication and versions under development is further clarified.

From a stroke physician's perspective, further analysis of the data set to address specific questions is welcomed, for example, is there any way to retrospectively confirm stroke

subtypes? If the relative reduction in lacunar stroke is real, it would be one of the first add-on interventions to demonstrate such an effect. Was there a relationship between cardiovascular event reduction and change in HOMA-IR or other metabolic parameters? Could a threshold of IR reduction and stroke prevention be identified?

In conclusion, IRIS identified a modest beneficial effect of pioglitazone in preventing diabetes mellitus and stroke/myocardial infarction in patients with cerebrovascular disease and IR at the expense of higher rates of bone fractures and weight gain. The risk of pioglitazone's aforementioned side effects should be carefully weighed during treatment decisions. Ideally, embarking on treatment would involve collaboration between the stroke physician, primary care, and endocrinology in an ongoing assessment for benefit and emergence of complications.

## Disclosures

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# Stroke

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