Main Results
Insulin Resistance Intervention after Stroke (IRIS) Trial

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February 17, 2016
Presenter Disclosure Information
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**Topic**
IRIS Trial Results

**Conflict of Interest**
None

**Unlabeled Use**
Pioglitazone for stroke secondary prevention
IRIS Funding

U.S. National Institute of Neurological Disorders and Stroke
(Grant # U01NS044976)

Pioglitazone, Matching Placebo and Funds for Blood Storage Provided by Takeda Pharmaceuticals International, Inc.
Dr. Lawrence M. Brass 1956-2006
Professor of Neurology, Yale School of Medicine
Insulin resistance

A physiological state in which a normal amount of insulin produces a subnormal cellular response.

Consequences:
- Hyperinsulinemia
- Hyperglycemia
- Dyslipidemia
- Inflammation
- VSMC Proliferation
- Endothelial Dysfunction

WN Kernan *Neurology* 2002;59:809
Insulin resistance

- Is associated with increased risk for:
  - Stroke
  - Myocardial infarction
  - Diabetes
- Affects > 50% non-diabetic stroke patients
- Affects almost all patients with Type 2 DM
Treatments for Insulin Resistance

- Weight loss
- Diet
- Exercise
- Drugs
Thiazolidinediones (TZD): Nuclear Transcription Factors

TZD

PPARγ

↑ FFA uptake + storage
↑ Insulin sensitivity
↑ Adiponectin

Inflammatory cytokines
NF-κB
Adhesion molecules

Gene transcription
Gene suppression

RNA
Among insulin resistant, non-diabetic patients with a recent ischemic stroke or TIA, to determine if the TZD, pioglitazone, compared with placebo, reduces risk for:

**Primary Aim**
- Stroke or MI

**Secondary Aims**
- Stroke alone
- Acute Coronary Syndrome
- Stroke, MI, or heart failure
- Diabetes
- Cognitive decline
- All-cause mortality
Design:
Randomized Clinical Trial

Eligibility:  
- Ischemic stroke or TIA within 6 months
- Age ≥ 40 years
- Insulin resistance
- No diabetes
- No heart failure
- No bladder cancer

Randomize

Placebo 5 years

Pioglitazone 15mg → 45 mg 5 years

Outcomes
Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)

HOMA-IR =

\[
\frac{\text{Fasting insulin (\(\mu\text{U/ml}\)) \times Fasting glucose (mmol/L)}}{22.5}
\]

For IRIS, insulin resistance = HOMA-IR > 3.0
RESULTS

Lauren Golden, MD
7634 Screened with HOMA Blood Test

2796 (37%) Not Insulin Resistant

4865 (63%) Insulin Resistant

564 Retracted consent
379 Excluded other reasons

3895 Randomized

1948 Pioglitazone
- 9 excluded
  - 1939 Analyzed

1947 Placebo
- 10 excluded
  - 1937 Analyzed

1937 Analyzed

9 excluded
## Baseline Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>63.5</td>
<td>63.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>Black race</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Stroke at entry (vs. TIA)</td>
<td>87%</td>
<td>87%</td>
</tr>
<tr>
<td>NIHSS ≥ 5</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Mean BMI, mean kg/m^2</td>
<td>29.9</td>
<td>30.0</td>
</tr>
<tr>
<td>Event to rand, median d.</td>
<td>81</td>
<td>79</td>
</tr>
</tbody>
</table>
### Primary Outcome

<table>
<thead>
<tr>
<th></th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke or MI</strong></td>
<td>% (No.)</td>
<td>% (No.)</td>
<td>Hazard Ratio</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>9.0 (175)</td>
<td>11.8 (228)</td>
<td>0.76 (0.62, 0.93)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Primary Outcome

Cumulative Event-Free Survival Probability

HR, 0.76; 95% CI, 0.62 to 0.93; P=0.007
## Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>6.5 (127)</td>
<td>8.0 (154)</td>
<td>0.82</td>
<td>0.19</td>
</tr>
<tr>
<td>ACS</td>
<td>5.0 (96)</td>
<td>6.6 (128)</td>
<td>0.75</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke/MI/HF</td>
<td>10.6 (206)</td>
<td>12.9 (249)</td>
<td>0.82</td>
<td>0.11</td>
</tr>
<tr>
<td>DM</td>
<td>3.8 (73)</td>
<td>7.7 (149)</td>
<td>0.48</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Death</td>
<td>7.0 (136)</td>
<td>7.5 (146)</td>
<td>0.93</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*ACS=Acute coronary syndrome (unstable angina or MI). HF=heart failure
Three Glucose-Related Subgroups (Out of 13 total subgroups examined)

All Participants

IFG (≥100 mg/dL)
   Present
   Absent

HOMA
   ≥4.6
   < 4.6

Glycated Hgb
   ≥5.7%
   <5.7%

Pioglitazone Better  Placebo Better

P-Value For Interaction

0.11
0.10
0.85
## Serious Adverse Events*

<table>
<thead>
<tr>
<th>Event</th>
<th># Participants</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pioglitazone (N=1939)</td>
<td>Placebo (N=1937)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Bone fracture†</td>
<td></td>
<td>5.1</td>
<td>(99)</td>
<td>3.2</td>
<td>(66)</td>
</tr>
<tr>
<td>Heart failure†</td>
<td></td>
<td>2.6</td>
<td>(51)</td>
<td>2.2</td>
<td>(42)</td>
</tr>
<tr>
<td>Incident cancer</td>
<td></td>
<td>6.9</td>
<td>(133)</td>
<td>7.7</td>
<td>(150)</td>
</tr>
</tbody>
</table>

*Serious = life threatening or resulting in death, hospitalization, or persistent disability.
†Previously reported to be associated with pioglitazone or drugs in its class.
## Non-Serious Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Weight Gain†</td>
<td>% (No. Participants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Year 4, mean</td>
<td>2.6 kg</td>
<td>-0.5 kg</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>New or worse edema†</td>
<td>36 (691)</td>
<td>25 (483)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>New or worse SOB†</td>
<td>18 (342)</td>
<td>15 (292)</td>
<td>0.03</td>
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†Previously reported to be associated with pioglitazone or drugs in its class.
Summary

Among insulin resistant, non-diabetic patients with ischemic stroke or TIA, pioglitazone prevented:

- Stroke or MI
  Absolute Risk Reduction = 2.9%
  Relative Risk Reduction = 24%
- Diabetes
  Absolute Risk Reduction = 3.9%
  Relative Risk Reduction = 52%

However, bone fracture requiring surgery or hospitalization was more common with pioglitazone:
5.1% vs. 3.2% over 5 years
Insulin resistance affects the majority of non-diabetic patients with ischemic stroke or TIA.

For the first time, a therapy directed at insulin resistance has been shown to prevent cardiac and cerebrovascular events for these patients.
Important next steps include research to:

- Optimize use of pioglitazone
  - Strategies to minimize weight gain and assure bone health
- Identify other therapies that work on the same biological pathways.
## Acknowledgements

<table>
<thead>
<tr>
<th>NINDS Scientists</th>
<th>Members of the DSMB</th>
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<tr>
<td>Robin Conwit</td>
<td>Michael Walker (Chair)</td>
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<tr>
<td>Laurie Gutmann</td>
<td>John Buse</td>
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<td>Scott Janis</td>
<td>Lloyd E. (Woody) Chambless</td>
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<td>Walter J. Koroschetz</td>
<td>David P. Faxon</td>
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<td>John Marler</td>
<td>Jennifer K. Pary</td>
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<td>Claudia S. Moy</td>
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<td>Barbara Radziszewska</td>
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## Acknowledgements

### Neurology Review Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
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<td>Scott E. Kasner (Chair)</td>
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<td>Joseph P. Broderick</td>
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<td>Carlos S. Kase</td>
<td>Boston University</td>
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<td>Mark J. Alberts</td>
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### External Scientific Advisory Group

<table>
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<tr>
<th>Name</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Philip B. Gorelick (Chair)</td>
<td>Michigan State University</td>
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<td>Eugene J. Barrett</td>
<td>University of Virginia</td>
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<td>Mark L. Dyken</td>
<td>Indiana University</td>
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<td>Richard W. Nesto</td>
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<td>William T. Longstreth</td>
<td>University of Washington</td>
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<td>DeJuran Richardson</td>
<td>Lake Forest College</td>
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Acknowledgements

Robert G. Hart, MD
Professor of Medicine (Neurology)
McMaster University
Many More to Thank

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<thead>
<tr>
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<tr>
<td>179</td>
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<td>238</td>
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<tr>
<td>372</td>
<td>Coordinators</td>
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<tr>
<td>3876</td>
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Thank You