

**How beneficial are thiazolidinediones for diabetes mellitus?**

**EVIDENCE-BASED ANSWER** The thiazolidinediones pioglitazone (Actos) and rosiglitazone (Avandia) are effective at lowering fasting plasma glucose (FPG) and glycosylated hemoglobin (Hb A<sub>1c</sub>) in patients with type 2 diabetes when used either as monotherapy or in combination with sulfonylureas, metformin, or insulin. The glucose-lowering effects appear comparable with those of sulfonylureas and metformin alone. Currently, there are no randomized trials directly comparing patient-oriented outcomes of the thiazolidinediones with those of sulfonylureas and metformin. Grade of recommendation: B (on the basis of extrapolations from randomized trials and low quality randomized trials).

**EVIDENCE SUMMARY** Proper nutrition and exercise remain the cornerstones of diabetes therapy; medication management, however, is often necessary.<sup>1</sup> Both pioglitazone and rosiglitazone have similar glucose-lowering effects. See the tables in the online version of this Clinical Inquiry at [www.fpin.org](http://www.fpin.org) for a summary of monotherapy and combination clinical trials.

Pioglitazone has consistently been shown to decrease triglycerides and increase high-density lipoprotein and rosiglitazone increases total cholesterol, HDL, and low-density lipoprotein. The clinical significance of these effects has not been established. Both medications are generally well tolerated but have the potential to cause edema and mildly decrease hemoglobin and hematocrit.<sup>2,9</sup>

To date, there have been reports of pulmonary edema and hepatotoxicity associated with the use of rosiglitazone. In all cases, rosiglitazone was found to be a possible, not a definite, cause.<sup>10-12</sup>

**RECOMMENDATIONS FROM OTHERS** The American Diabetes Association and the American Association of Clinical Endocrinologists do not recommend one class of antidiabetic medication over another.<sup>1,13</sup> Both of the thiazolidinediones are indicated for monotherapy and in combination with a sulfonylurea and metformin. However, only pioglitazone

is indicated in combination with insulin. They are highly metabolized by the liver and should not be used in patients with liver enzymes greater than 2.5 times the upper limit of normal. Routine liver monitoring is recommended at baseline, every 2 months for the first year, and then periodically thereafter.<sup>1</sup> Patients with New York Heart Association class III or IV heart failure should not use thiazolidinediones. In addition, thiazolidinediones cost considerably more than sulfonylureas and metformin.<sup>14</sup>

**TABLE**

**Effects of rosiglitazone and pioglitazone, by dosage**

Drug and dosage	Control	Adjunct medication	Change in Hb A <sub>1c</sub> vs comparison (%)	Change in FPG vs comparison (mg/dL)
<b>Rosiglitazone</b>				
4 mg bid <sup>2</sup>	placebo	none	-1.5*	-73*
2 mg bid <sup>3</sup>	glyburide	none	+0.4	+5
4 mg bid			+0.2 <sup>†</sup>	-11
8 mg bid <sup>4</sup>	placebo	metformin	-1.3*	-54.3*
2 mg bid <sup>5</sup>	placebo	sulfonylurea	-1.1*	-43.6*
4 mg bid <sup>6</sup>	placebo	insulin	-1.3 <sup>‡</sup>	-55.8 <sup>‡</sup>
<b>Pioglitazone</b>				
45 mg qd <sup>7</sup>	placebo	none	-1.6*	-65.3*
30 mg qd <sup>8</sup>	placebo	sulfonylurea	-1.3*	-57.9*
30 mg qd <sup>9</sup>	placebo	metformin	-0.83*	-37.7*

Hb A<sub>1c</sub> denotes glycosylated hemoglobin; FPG, fasting plasma glucose; bid, twice a day; qd, every day.  
 \*P < .05 versus control.  
<sup>†</sup>P = not significant.  
<sup>‡</sup>P < .006 versus placebo plus insulin.  
 Find further details online at [www.fpin.org](http://www.fpin.org).

Therefore, thiazolidinediones are not generally considered for first-line therapy.<sup>15</sup> These agents may be most beneficial in patients with insulin resistance and patients with renal dysfunction.<sup>1</sup>

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Read a clinical commentary by Steven Zweig, MD, at [www.fpin.org](http://www.fpin.org)

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