

Thiazolidinediones onder vuur wegens mogelijke cardiovasculaire neveneffecten : een vervolgverhaal

Context

Pioglitazone is widely used for glycemic control in patients with type 2 diabetes mellitus, but evidence is mixed regarding the influence of medications of this class on cardiovascular outcomes.

Objective

To systematically evaluate the effect of pioglitazone on ischemic cardiovascular events.

Data Sources and Study Selection

A database containing individual patient-level time-to-event data collected during pioglitazone clinical trials was transferred from the drug's manufacturer for independent analysis. Trials were included if they were randomized, double-blinded, and controlled with placebo or active comparator.

Data Extraction

The primary outcome was a composite of death, myocardial infarction, or stroke. Secondary outcome measures included the incidence of serious heart failure. A fixed-effects approach was used to combine the estimates across the duration strata and statistical heterogeneity across all the trials was tested with the I^2 statistic.

Data Synthesis

A total of 19 trials enrolling 16 390 patients were analyzed. Study drug treatment duration ranged from 4 months to 3.5 years. Death, myocardial infarction, or stroke occurred in 375 of 8554 patients (4.4%) receiving pioglitazone and 450 of 7836 patients (5.7%) receiving control therapy (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.72-0.94; $P = .005$). Progressive separation of time-to-event curves became apparent after approximately 1 year of therapy. Individual components of the primary end point were all reduced by a similar magnitude with pioglitazone treatment, with HRs ranging from 0.80 to 0.92. Serious heart failure was reported in 200 (2.3%) of the pioglitazone-treated patients and 139 (1.8%) of the control patients (HR, 1.41; 95% CI, 1.14-1.76; $P = .002$). The magnitude and direction of the favorable effect of pioglitazone on ischemic events and unfavorable effect on heart failure was homogeneous across trials of different durations, for different comparators, and for patients with or without established vascular disease. There was no evidence of heterogeneity across the trials for either end point ($I^2 = 0\%$; $P = .87$ for the composite end point and $I^2 = 0\%$; $P = .97$ for heart failure).

Conclusions

Pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.

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Context

Recent reports of serious adverse events with rosiglitazone use have raised questions about whether the evidence of harm justifies its use for treatment of type 2 diabetes.

Objective

To systematically review the long-term cardiovascular risks of rosiglitazone, including myocardial infarction, heart failure, and cardiovascular mortality.

Data Sources

We searched MEDLINE, the GlaxoSmithKline clinical trials register, the US Food and Drug Administration Web site, and product information sheets for randomized controlled trials, systematic reviews, and meta-analyses published in English through May 2007.

Study Selection

Studies were selected for inclusion if they were randomized controlled trials of rosiglitazone for prevention or treatment of type 2 diabetes, had at least 12 months of follow-up, and monitored cardiovascular adverse events and provided numerical data on all adverse events. Four studies were included after detailed screening of 140 trials for cardiovascular events.

Data Extraction

Relative risks (RRs) of myocardial infarction, heart failure, and cardiovascular mortality were estimated using a fixed-effects meta-analysis of 4 randomized controlled trials ($n = 14\ 291$, including 6421 receiving rosiglitazone and 7870 receiving control therapy, with a duration of follow-up of 1-4 years).

Results

Rosiglitazone significantly increased the risk of myocardial infarction ($n = 94/6421$ vs $83/7870$; RR, 1.42; 95% confidence interval [CI], 1.06-1.91; $P = .02$) and heart failure ($n = 102/6421$ vs $62/7870$; RR, 2.09; 95% CI, 1.52-2.88; $P < .001$) without a significant increase in risk of cardiovascular mortality ($n = 59/6421$ vs $72/7870$; RR, 0.90; 95% CI, 0.63-1.26; $P = .53$). There was no evidence of substantial heterogeneity among the trials for these end points ($I^2 = 0\%$ for myocardial infarction, 18% for heart failure, and 0% for cardiovascular mortality).

Conclusion

Among patients with impaired glucose tolerance or type 2 diabetes, rosiglitazone use for at least 12 months is associated with a significantly increased risk of myocardial infarction and heart failure, without a significantly increased risk of cardiovascular mortality.

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We zitten dus, in zoverre tenminste deze twee meta-analyses te vergelijken zijn, met een duidelijk verschil tussen rosiglitazone en pioglitazone, behalve wat het risico op hartfalen betreft!

In een editoriaal wijst men erop dat binnen het FDA een discussie alleen ging over rosiglitazone, minder of niet over pio. Een grote meerderheid van de leden was akkoord dat rosi een verhoogd cardiovasculair risico inhield, maar een even grote meerderheid was van mening dat mits een waarschuwing op de verpakking de molecule op de markt mocht blijven. Vreemde beslissing, toch?