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[Intervention Review]

Pioglitazone for type 2 diabetes mellitus

Bernd Richter[1], Elizabeth Bandeira-Echtler[1], Karla Bergerhoff[1], Christine Clar[2], Susanne H Ebrahim[3]

[1]Department of General Practice, Universitaetsklinikum Duesseldorf, Heinrich-Heine University, Duesseldorf, Germany. [2]Researcher in Systematic Reviews , Cochrane Metabolic and Endocrine Disorders Group, Berlin, Germany. [3]Institute for Quality and Efficiency in Health Care, Cologne, Germany

Contact: Bernd Richter, Department of General Practice, Universitaetsklinikum Duesseldorf, Heinrich-Heine University, PO Box 101007, Duesseldorf, 40001, Germany. richterb@uni-duesseldorf.de.

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ABSTRACT

Background

Diabetes has long been recognised as a strong, independent risk factor for cardiovascular disease, a problem which accounts for approximately 70% of all mortality in people with diabetes. Prospective studies show that compared to their non-diabetic counterparts, the relative risk of cardiovascular mortality for men with diabetes is two to three and for women with diabetes is three to four. The two biggest trials in type 2 diabetes, the United Kingdom Prospective Diabetes Study (UKPDS) and the University Group Diabetes Program (UGDP) study did not reveal a reduction of cardiovascular endpoints through improved metabolic control. Theoretical benefits of the newer peroxisome proliferator activated receptor gamma (PPAR-gamma) activators like pioglitazone on endothelial function and cardiovascular risk factors might result in fewer macrovascular disease events in people with type 2 diabetes mellitus.

Objectives

To assess the effects of pioglitazone in the treatment of type 2 diabetes.

Search methods

Studies were obtained from computerised searches of MEDLINE, EMBASE and *The Cochrane Library*.

Selection criteria

Studies were included if they were randomised controlled trials in adult people with type 2 diabetes mellitus and had a trial duration of at least 24 weeks.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. Pooling of studies by means of random-effects meta-analysis could be performed for adverse events only.

Main results

Twenty-two trials which randomised approximately 6200 people to pioglitazone treatment were identified. Longest duration of therapy was 34.5 months. Published studies of at least 24 weeks pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient-oriented outcomes like mortality, morbidity, adverse effects, costs and health-related quality of life are positively influenced by this compound. Metabolic control measured by glycosylated haemoglobin A1c (HbA1c) as a surrogate endpoint did not demonstrate clinically relevant differences to other oral antidiabetic drugs. Occurrence of oedema was significantly raised. The results of the single trial with relevant clinical endpoints (Prospective Pioglitazone Clinical Trial In Macrovascular Events - PROactive study) have to be regarded as hypothesis-generating and need confirmation.

Authors' conclusions

Until new evidence becomes available, the benefit-risk ratio of pioglitazone remains unclear. Different therapeutic indications for pioglitazone of the two big U.S. and European drug agencies should be clarified to reduce uncertainties amongst patients and physicians.

PLAIN LANGUAGE SUMMARY

Pioglitazone for type 2 diabetes mellitus

Diseases of the heart and blood vessels account for approximately 70% of all mortality in people with diabetes. Compared to their non-diabetic counterparts the relative risk of mortality caused by disorders of the heart and blood vessels is two to three for men and three to four for women with diabetes. Type 2 diabetes is mainly characterised by a reduced ability of the hormone insulin to stimulate glucose uptake in body fat and muscles (insulin resistance) and affects most people suffering from diabetes. Several medications are on the market to treat diabetes, amongst them pioglitazone as a member of the 'glitazones' reduced risk factors for diseases of the heart and blood vessels. Since the two biggest trials in people with type 2 diabetes showed that improved blood glucose alone is not enough to reduce the risk of the above mentioned diseases we looked for longer-term studies investigating 24 weeks as a minimum of pioglitazone treatment on patient-oriented outcomes. As patient-oriented outcomes we defined mortality, complications of diabetes, side effects of the medication, health-related quality of life, costs and metabolic control (lowering of blood glucose to near normal levels).

Twenty-two trials randomised approximately 6200 people to pioglitazone treatment. The longest duration of pioglitazone therapy was 34.5 months. Unfortunately, the published studies of at least 24 weeks pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient-oriented outcomes are positively influenced by this compound. The occurrence of oedema was significantly raised. The results of the single trial with relevant endpoints (Prospective Pioglitazone Clinical Trial In Macrovascular Events - PROactive study) have to be confirmed by other independent investigations. Until new evidence becomes available (several large trials are ongoing) the place of pioglitazone in the treatment of type 2 diabetes mellitus remains unclear.

Furthermore, confusion arises due to different labelling of pioglitazone, for example in Europe and the USA. Consumers and physicians need clear guidance and transparent information about which studies exactly are used for the decisions of the relevant drug authorities.