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Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in people with stroke or transient ischaemic attack.
Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD010693.
DOI: 10.1002/14651858.CD010693.pub4.

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[Intervention Review]

Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in people with stroke or transient ischaemic attack

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Editorial group: Cochrane Stroke Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2017.

Citation: Liu J, Wang LN. Peroxisome proliferator-activated receptor gamma agonists for preventing recurrent stroke and other vascular events in people with stroke or transient ischaemic attack. *Cochrane Database of Systematic Reviews* 2017, Issue 12. Art. No.: CD010693. DOI: 10.1002/14651858.CD010693.pub4.

ABSTRACT

Background

Peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists are insulin-sensitising drugs used for the treatment of insulin resistance. In addition to lowering glucose in diabetes, these drugs may also protect against hyperlipidaemia and arteriosclerosis, which are risk factors for stroke. This is an update of a review first published in January 2014 and subsequently updated in October 2015.

Objectives

To assess the efficacy and safety of PPAR-γ agonists in the secondary prevention of stroke and related vascular events for people with stroke or transient ischaemic attack (TIA).

Search methods

We searched the Cochrane Stroke Group Trials Register (16 May 2017), the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 5), MEDLINE (1949 to 16 May 2017), Embase (1980 to 16 May 2017), CINAHL (1982 to 16 May 2017), AMED (1985 to 16 May 2017), and 11 Chinese databases (16 May 2017). In an effort to identify further published, unpublished, and ongoing trials, we searched ongoing trials registers, reference lists, and relevant conference proceedings, and contacted authors and pharmaceutical companies. We did not impose any language restrictions.

Selection criteria

We included randomised controlled trials (RCTs) evaluating PPAR-γ agonists versus placebo for the secondary prevention of stroke and related vascular events in people with stroke or TIA, with the outcomes of recurrent stroke, vascular events, and adverse events.

Data collection and analysis

Two review authors independently screened the titles and abstracts of identified records, selected studies for inclusion, extracted eligible data, cross-checked the data for accuracy, and assessed methodological quality and risk of bias. We evaluated the quality of evidence for each outcome using the GRADE approach.

Main results

We identified five RCTs with 5039 participants; two studies had a low risk of bias for all domains. Four studies evaluated the drug pioglitazone, and one study evaluated rosiglitazone. The participants in different studies were heterogeneous.

Recurrent stroke

Three studies evaluated the number of participants with recurrent stroke (4979 participants, a single study contributing 3876 of these). Peroxisome proliferator-activated receptor gamma agonists probably reduce the recurrence of stroke compared with placebo (risk ratio (RR) 0.66, 95% confidence interval (CI) 0.44 to 0.99; moderate-quality evidence).

Adverse events

Evidence that adverse events occurred more frequently in participants treated with PPAR-γ agonists when compared with placebo was uncertain due to wide confidence interval and high levels of statistical heterogeneity: risk difference 10%, 95% CI -8% to 28%; low-quality evidence).

Data were available on additional composite outcomes reflecting serious vascular events (all-cause death and other major vascular events; all-cause mortality, non-fatal myocardial infarction or non-fatal stroke) from one study in 984 people. This study provided low-quality evidence that PPAR-γ agonists led to fewer events (data not meta-analysed).

Vascular events

Peroxisome proliferator-activated receptor gamma agonists given over a mean duration of 34.5 months in a single trial of 984 participants may reduce serious vascular events expressed as a composite outcome of total events of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (RR 0.73, 95% CI 0.54 to 0.99; low-quality evidence).

Other outcomes

One study in 20 people measured insulin sensitivity, and one study in 40 people measured the ubiquitin-proteasome activity in carotid plaques. Our confidence in the improvements observed with PPAR-γ agonists were limited by small sample sizes and risk of bias. None of the studies reported the number of participants with disability due to vascular events or improvement in quality of life.

Authors' conclusions

Peroxisome proliferator-activated receptor gamma agonists probably reduce recurrent stroke and total events of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, and may improve insulin sensitivity and the stabilisation of carotid plaques. Their effects on adverse events are uncertain. Our conclusions should be interpreted with caution considering the small number and the quality of the included studies. Further well-designed, double-blind RCTs with large samples are required to assess the efficacy and safety of PPAR-γ agonists in the secondary prevention of stroke and related vascular events in people with stroke or TIA.

PLAIN LANGUAGE SUMMARY

Diabetes drugs for preventing stroke and other blood vessel disease in people who have had a previous stroke or transient ischaemic attack

Question

We wanted to evaluate the effectiveness and safety of new diabetes drugs (peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists) in the prevention of stroke and related blood vessel disease in people who have already had a stroke or transient ischaemic attack.

Background

Peroxisome proliferator-activated receptor gamma agonists are drugs that improve the way insulin works in the human body. They are widely used in the treatment of adult type diabetes (type 2 diabetes). Moreover, they may also protect against the presence of excess fats in the blood and disease of the artery walls, which are both risk factors for stroke.

Study characteristics

We identified five studies to 16 May 2017 including a total of 5039 participants. Four studies evaluated the drug pioglitazone, and one study evaluated rosiglitazone. Four studies included participants who had no history of diabetes, and one study included only participants with diabetes.

Key results

Compared with placebo tablets, PPAR-γ agonists reduced recurrent strokes and other blood vessel disease, improved the body's response to insulin, and stabilised fatty deposits in artery walls. The drugs also appeared to be well tolerated, but the evidence for this was inconclusive.

Quality of the evidence

Our conclusions should be interpreted with caution considering the small number of included studies and the limited quality of some of the studies. Further well-designed randomised controlled trials with large sample sizes are required.