Oral anti-diabetic drugs for the prevention of Type 2 diabetes

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CRD summary
Among oral anti-diabetic drugs, thiazolidinediones were associated with the greatest risk reduction in development of type 2 diabetes compared with control and were superior to biguanides. Alpha-glucosidase inhibitors and biguanides performed similarly and better than control. Sulphonylureas and glinides provided no significant benefit. The authors' conclusions reflect the evidence base and are likely to be reliable.

Authors' objectives
To compare the efficacy of different oral anti-diabetic drugs in the prevention of type 2 diabetes.

Searching
MEDLINE (from 1950), EMBASE (from 1990) and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restriction up to February 2010; search terms were reported. The reference lists of retrieved articles and reviews were searched for relevant studies.

Study selection
Randomised controlled trials (RCTs) of oral anti-diabetic drugs as monotherapy in patients at high risk of developing diabetes with data on the incidence of developing new onset type 2 diabetes were eligible for inclusion. High risk for diabetes was defined as impaired glucose tolerance, impaired fasting glucose, HbA1c 39 to 46 mmol/mol (5.7-6.4%), history of gestational diabetes or obesity. Oral anti-diabetic drugs included thiazolidinediones, biguanides, alpha-glucosidase inhibitors, sulphonylureas, glinides or dipeptidyl peptidase-4 inhibitors. The controls in the eligible trials had to be placebo, an active control or no treatment. Studies that enrolled patients with polycystic ovarian syndrome, cystic fibrosis or HIV and studies which enrolled less than 20 participants per treatment group or with treatment duration less than three months and studies using treatments such as lifestyle modification or angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins and fibrates were excluded.

Participant age ranged from 34 to 64 years, the proportion of male participants ranged from 0 to 100% and body mass index (BMI) ranged from 21 to 34 kg/m², where reported. Definitions of diabetes risk included elevated BMI, elevated random blood glucose, impaired fasting glucose and impaired glucose tolerance. Most trials used definitions of diabetes based on criteria set by the World Health Organisation or the American Diabetes Association.

Three reviewers independently selected studies for the review, with disagreement resolved by discussion.

Assessment of study quality
Studies were assessed for quality with the Jadad scale; criteria included randomisation, double-blinding and patient withdrawals.

Three investigators independently assessed studies for quality, with disagreement resolved by discussion.

Data extraction
Data were extracted on event rates and relative risks (RRs), together with 95% confidence intervals (CIs) were calculated.

Three investigators independently extracted data, with disagreement resolved by discussion.

Methods of synthesis
Studies were pooled in meta-analyses to estimate the incidence of new onset diabetes with a random-effects model. Mixed treatment comparison analyses were undertaken with a Bayesian Markov Chain Monte Carlo method and fitted in WinBUGS with a random-effects model; residual deviance was also calculated. Summary effect measures, relative risks and risk differences (RDs), with 95% CIs were calculated for both types of analysis and numbers need to treat (NNT) were also calculated, where possible. Statistical heterogeneity was assessed using I² and publication bias was...
Subgroup analyses were undertaken to assess the effects of various factors such as forced lifestyle modification or lifestyle advice, duration of follow-up (less than one year and one to five years) and control risk per person year (0.09 or below) on the findings. Sensitivity analyses were undertaken to assess the effects of different definitions of high risk (including only studies with a specified definition of impaired glucose tolerance and/or impaired fasting glucose), definition of diabetes (excluding studies with non standard definition of diabetes), type of drugs (excluding studies of oral anti-diabetic drugs no longer available for use), quality (exclusion of studies with Jadad score less than 3) and interim results (including interim results with thiazolidinedione data).

**Results of the review**

Twenty RCTs (23,230 participants) were included in the review. The quality of the studies ranged from a Jadad score of 1 to a Jadad score of 5, with more than half having a Jadad score less than 2. Follow-up ranged from 0.3 to seven years (median 2.7 years).

**Traditional meta-analysis:** Compared to control, use of any oral antidiabetic drug was associated with a significantly reduced risk of developing type 2 diabetes (RR 0.61, 95% CI 0.48 to 0.77; I² 75% or above; 19 studies). Compared with control, biguanides, thiazolidinediones and alpha-glucosidase inhibitors were associated with a significantly decreased risk (and risk difference) of developing diabetes (biguanides: RR 0.77, 95% CI 0.69 to 0.86; NNT: 37 to 74; 7 studies; thiazolidinediones: RR 0.37, 95% CI 0.25 to 0.53; NNT: 16 to 31; 4 studies; alpha-Glucosidase inhibitors: RR 0.58, 95% CI 0.41 to 0.82; I²=50 to 75%; NNT: 20 to 39; 6 studies). There was no evidence of a significant difference between sulphonylureas or glinides and control.

**Mixed treatment meta-analysis:** Compared to control, biguanides, thiazolidinediones and alpha-glucosidase inhibitors were associated with a significantly decreased risk (and risk difference) of developing diabetes (biguanides: RR 0.73, 95% CI 0.49 to 0.98; thiazolidinediones: RR 0.36, 95% CI 0.21 to 0.52; alpha-glucosidase inhibitors: RR 0.60, 95% CI 0.40 to 0.81), confirming the results of the traditional meta-analysis. There was no evidence of a significant difference between sulphonylureas or glinides and control. Compared to biguanides, thiazolidinediones were associated with a significantly decreased risk of developing diabetes (RR 0.49, 95% CI 0.28 to 0.94) and compared to alpha glucosidase inhibitors, there was a trend favouring thiazolidinediones in reducing diabetes risk (RR 0.60, 95% CI 0.34 to 1.02).

Results were not markedly changed as a result of subgroup and sensitivity analyses. There was no evidence of significant publication bias.

**Authors' conclusions**

Thiazolidinediones were associated with the greatest risk reduction in development of type 2 diabetes compared with control and associated with greater risk reduction than biguanides. Alpha-glucosidase inhibitors and biguanides performed similarly and better than control, while sulphonylureas and glinides provided no significant benefit.

**CRD commentary**

The review addressed a clear research question. Inclusion criteria appear appropriate. A range of relevant sources was used to identify studies for the review without language restriction, thus minimising the chance of language bias. Appropriate methods were used to select studies, extract data and assess studies for quality, minimising the chance of reviewer error and bias during these processes. A standardised tool was used for quality assessment (although allocation concealment was not assessed) and composite scores indicated that the studies varied in quality. Synthesis of studies and assessment of heterogeneity and publication bias were all appropriate. There was no evidence of publication bias but significant heterogeneity was identified in some analyses. Use of mixed treatment analysis enabled the comparison of different anti-diabetic drug classes by incorporating both direct comparisons within trials and indirect comparisons from two trials that had one treatment in common. Subgroup and sensitivity analyses enabled the assessment of the influence of potential factors on the results, such as concurrent lifestyle modification, lower quality and variable follow up. The authors' conclusions reflect the evidence base and were likely to be reliable.

One of the authors of the review was employed by a pharmaceutical company that manufactures thiazolidinediones.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice. Safety was not assessed in the review, but the authors acknowledged the adverse events associated with different types of oral anti-diabetic drugs in the discussion of the review.

Research: The authors stated that future research may be needed to compare the effects of combination therapy and monotherapy.

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