Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials
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CRD summary
This review evaluated the role of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) for the prevention of type 2 diabetes. The authors concluded that ACE inhibitors or ARBs should be considered in those with pre-diabetic conditions. Limited reporting of the review process and the lack of a validity assessment mean that this conclusion may not be reliable.

Authors' objectives
To determine the role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in the prevention of new-onset type 2 diabetes mellitus.

Searching
MEDLINE (from 1990 to 2004), the Cochrane Database of Systematic Reviews, ACP Journal Club, DARE and the Cochrane CENTRAL Register were searched; the search terms were reported. The reference lists of retrieved articles were also checked. Abstracts presented at national meetings were also eligible.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a minimum duration of 1 year were eligible for inclusion.

Specific interventions included in the review
Studies that compared an ACE inhibitor or an ARB with placebo or another antihypertensive agent were eligible for inclusion. The ACE inhibitors evaluated in the included studies were captopril, ramipril, enalapril, lisinopril and trandolapril. The ARBs evaluated in the included studies were losartan, candesartan and valsartan. Comparator antihypertensive agents were diuretics, beta-blockers or calcium-channel antagonists.

Participants included in the review
Studies of patients with a history of hypotension, or at least one cardiovascular risk factor, were eligible for inclusion. Some studies included patients with a diagnosis of diabetes at baseline, while some included those with conditions associated with high morbidity and mortality.

Outcomes assessed in the review
Studies that reported the incidence of new-onset diabetes were eligible for inclusion. Most of the studies used the American Diabetes Association's criteria to defined new-onset diabetes.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they formally assessed validity, although the use of double-blinding was reported.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Risk ratios (RRs) and confidence intervals (CIs) for a new diagnosis of diabetes were extracted from each
included study. If a study did not report an RR then it was assumed that the hazard ratio or odds ratio provided a reasonable approximation of the RR.

**Methods of synthesis**

**How were the studies combined?**

A pooled RR with 95% CI was calculated using a random-effects meta-analysis (DerSimonian and Laird) for all studies combined, and separately for studies that evaluated ACE inhibitors and those that evaluated ARBs.

**How were differences between studies investigated?**

Statistical heterogeneity in the meta-analysis of all studies was assessed using the Cochran test. Differences in the results were also apparent from the graphical presentation of the results.

**Results of the review**

Twelve RCTs (116,220 patients, 72,333 of whom did not have diabetes) were included in the review. The mean duration of follow-up ranged from 1 to 6.1 years.

Nine RCTs were double-blind.

ACE inhibitors and ARBs (12 RCTs) were associated with a 25% reduction in the risk of developing type 2 diabetes compared with placebo or conventional treatment (RR 0.75, 95% CI: 0.69, 0.82). Overall, the reduction in the incidence of new-onset diabetes ranged from 4 to 87%. Significant statistical heterogeneity was found (P=0.008).

ACE inhibitors (7 RCTs) were associated with a 27% reduction in the risk of developing type 2 diabetes compared with placebo or conventional treatment (RR 0.73, 95% CI: 0.63, 0.84).

ARBs (5 RCTs) were associated with a 23% reduction in the risk of developing type 2 diabetes compared with placebo or conventional treatment (RR 0.77, 95% CI: 0.71, 0.83).

**Authors' conclusions**

ACE inhibitors and ARBs should be considered in those with pre-diabetic conditions such as metabolic syndrome, hypertension, impaired fasting glucose, obesity, congestive heart failure or coronary heart disease.

**CRD commentary**

The review addressed a clear question, with inclusion criteria defined for the population, intervention, study design and outcome. Relevant sources were searched for eligible studies and attempts were made to locate unpublished studies. No details of the methods used in the review process (study selection or data extraction) were reported, thus the possibility of reviewer error and bias cannot be assessed. The quality assessment appears to have been limited to blinding, which means it is not possible to comment on the validity of studies included in the review.

There were limited details on the individual included studies. Most notably, the use of adjunctive treatments, which may have influenced outcomes, were not reported. The authors stated that the included studies differed in the types of drugs evaluated, comparator drugs (placebo and active agents), study design and methods. This made it difficult to determine whether the methods used to analyse and combine the studies were appropriate. Consequently, the limitations detailed above mean that the authors' conclusion may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice, although they did highlight that no pharmacological agent is currently approved for this particular indication.

**Research:** The authors stated that additional research is needed to confirm the role of ACE inhibitors and ARBs in the prevention of diabetes, and prospective trials are currently underway.
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Other publications of related interest
This additional published commentary may also be of interest. Padwal R. Review: Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers prevent type 2 diabetes. ACP J Club 2006;144:64.

Indexing Status
Subject indexing assigned by NLM

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.