Effect of inhibition of the renin-angiotensin system on development of type 2 diabetes mellitus (meta-analysis of randomized trials)

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CRD summary
The authors concluded that the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may prevent the development of type 2 diabetes mellitus. Given the poor reporting of the review methods and differences between the studies, the reliability of the results, and hence the authors’ conclusions, should be treated with caution.

Authors’ objectives
To determine if angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) prevent the development of diabetes mellitus (DM).

Searching
MEDLINE and the Cochrane CENTRAL Register were searched from 1966 to May 2006; the search terms were reported. Only studies published in the English language were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Prospective, randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of ACE inhibitor or ARB therapy comparing placebo or active treatment were eligible for inclusion. Studies of captopril, beta blockers/thiazide, enalapril/losinopril, calcium-channel blockers, ramipril, losartan, atenolol, chlorthalidone, amlodipine, candesartan, valsartan, trandolapril, amiodipine/periopril, atenolol/bendroflumethiazide were included in the review. The studies also included a range of concurrent medications including those listed plus diuretics, reserpine, anti-arrhythmics and alpha-blockers.

Participants included in the review
Studies of adults that included subgroups of participants without DM at randomisation and that reported rates of new-onset DM during follow-up were included. DM was diagnosed according to criteria defined by the American Diabetes Association and the World Health Organization. The participants’ ages ranged from 52 to 76.4 years; the proportion of men ranged from 32 to 94%. Participants experiencing hypertension ranged from 10 to 100%. Where reported, coronary artery disease was present in between 1.2% and 92% of the population and between 0.7% and 92% of the participants had experienced a previous myocardial infarction. Diabetes was present in between 0% and 38.9% of the participants in each group. The mean body mass index ranged from 26.7 to 29.8 kg/m2, where reported.

Outcomes assessed in the review
Studies assessing the number of new cases of DM were eligible for inclusion. Event rates at the end of follow-up were used in the analysis.

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
Validity was assessed on the basis of adequate blinding of randomisation, blinding of treatment assignment, completeness of follow-up and objectivity of outcome assessment, based on published criteria. The authors did not state how the validity assessment was performed.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

In studies with more than one control arm, control-arm event rates were combined.

Methods of synthesis
How were the studies combined?
The pooled odds ratio (OR) and 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel random-effects model. The data were analysed according to intention-to-treat. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. Sensitivity analyses were conducted to assess the contribution of individual studies to the pooled estimate. Subgroup analyses were conducted which assessed the impact factor of moderator variables on the development of DM, including the type of renin-angiotensin system (RAS) inhibitor used (ACE inhibitor or ARB), the type of control treatment (active control or placebo), the type of patient population enrolled (hypertensive or nonhypertensive), the predominant gender of the study participants and the age of the study participants (over 65 years, or 65 years or less).

Results of the review
Thirteen RCTs (n=92,408) were included.

All studies used blinded end point assessment. Randomisation methods were reported in 10 of the 13 included trials. Follow-up of the participants exceeded 90% in all studies. There was no evidence of publication bias (data not presented).

Incidence of DM.
The pooled analysis of 13 studies demonstrated that DM developed in 7.1% of patients treated with ACE inhibitors or ARBs, compared with 9% treated with placebo or other agents (OR 0.73, 95% CI: 0.66, 0.81, p<0.001). The number of patients needed to treat for 4.8 years to prevent 1 case of DM was 46. However, there was significant heterogeneity between the studies. A sensitivity analysis found that the exclusion of any single study from the analysis did not alter the overall findings of the meta-analysis.

Subgroup analyses.
Nine studies which randomised hypertensive participants found that RAS inhibition was associated with a reduction in the risk of developing DM (OR 0.73, 95% CI: 0.66, 0.82, p<0.001). Four studies which randomised patients with vascular disease or left ventricular dysfunction found that RAS inhibition reduced the risk of developing DM (OR 0.67, 95% CI: 0.50, 0.90, p=0.008). In 8 studies of participants randomised to ACE inhibitors (n=1,801), DM developed in 6.5% compared with 8.4% randomised to placebo or active control (n=3,039) (OR 0.72, 95% CI: 0.63, 0.84, p<0.001).

In 5 studies, DM developed in 8.2% of patients treated with ARBs (n=1,188) compared with 10.5% treated with placebo or other agents (n=1,489) (OR 0.73, 95% CI: 0.64, 0.84, p<0.001).

The ability of RAS inhibition to prevent DM was unaffected by the treatment of the control group. In 8 studies with active controls, RAS inhibitors reduced the odds of developing DM by 26% (OR 0.74, 95% CI: 0.67, 0.83, p<0.001). In 5 studies of placebo controls (n=902) compared with treatment (n=702), inhibition of the RAS reduced the development of DM (OR 0.72, 95% CI: 0.58, 0.88, p=0.002).

Neither the predominant gender nor the mean age of the participants affected the ability of RAS inhibitors to prevent DM (data not presented).

Authors' conclusions
The evidence strongly suggests that inhibition of the RAS may prevent the development of DM.

**CRD commentary**
The review addressed a clear question in terms of the participants, intervention, outcomes and study design. Two databases were searched but no attempt was made to locate unpublished studies, which might have resulted in studies being missed. The restriction to English language studies might also have introduced language bias. The authors reported no evidence of publication bias, but did not present the data. They did not describe the methods used to select the studies, assess validity and extract the data, so it is not known whether they made efforts to reduce reviewer error and bias. Validity was assessed using specified criteria but only limited results of the assessment were reported, making it difficult to judge study validity.

The characteristics of the included studies were tabulated. A formal assessment of heterogeneity was undertaken and subgroup analyses were conducted to explore differences between the studies. However, as differences between the study populations were apparent, it might not have been appropriate to combine these studies in a meta-analysis. Given the lack of complete reporting of the review methods and heterogeneity between the studies, the reliability of the results, and hence the authors’ conclusions, are uncertain.

**Implications of the review for practice and research**
**Practice:** The authors stated that until definitive safety and efficacy data from randomised trials are available, RAS inhibitors should not be recommended solely for the purpose of preventing DM. They also stated that in nondiabetic patients with other indications for RAS inhibition, such as hypertension, these treatments should be considered as a secondary benefit; they will prevent the development of DM.

**Research:** The authors stated that randomised trials are required to determine the safety and efficacy of RAS inhibitors.

**Bibliographic details**
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**Other publications of related interest**

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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.