Therapeutic efficacy of different antihypertensive drugs in human diabetic nephropathy: an updated meta-analysis

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Authors' objectives
To assess the efficacy of antihypertensive drugs in diabetic nephropathy.

Searching
MEDLINE, publications, and abstracts of major congresses held during the review period were searched.

Study selection
Study designs of evaluations included in the review
Clinical trials, mostly uncontrolled, although some were double-blinded with a parallel placebo control.

Specific interventions included in the review
Diuretics and/or beta-blockers (conventional treatment), angiotensin-converting enzyme (ACE) inhibitors, calcium ion antagonists (except nifedipine), and nifedipine.

Participants included in the review
Patients (n=2,151) with a mean age of 46 years were included in the review: 39% were type 1 diabetics, 40% type 2, 14% were a mixture of both types, and in 7% of the trials diabetes type was not specified. Age, gender and type of diabetes did not differ significantly between the treatment groups.

Outcomes assessed in the review
Blood-pressure (BP), urine albumin or total protein excretion, and glomerular filtration rate (GFR) were measured.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection. The studies had to meet defined inclusion and exclusion criteria.

Inclusion criteria: diabetic patients receiving conventional antihypertensive drugs or monotherapy with ACE inhibitors or calcium ion antagonists; measurements of albuminuria or total proteinuria (PR, and BP before and after therapy lasting 4 or more weeks; and pre-treatment of those patients with albumin excretions greater than or equal to 30 mg/day.

Exclusion criteria: combination therapy if patients were on ACE inhibitors or calcium antagonists; normal albumin excretion of less than 30 mg/day at the beginning of the study; studies lasting less than 4 weeks; and repetitive reports of partly similar patient groups.

Assessment of study quality
The authors do not report the criteria used to assess validity, or how the validity assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The percentage change between baseline and final assessment was calculated for each of the end points under evaluation. Treatment effects were weighted by the number of patients in each trial, and mean values with 95% confidence intervals (CIs) were calculated. Analysis of variance was used to test for statistical differences between groups.

How were differences between studies investigated?
Multiple regression was used to determine the influence of different independent variables on the end points, namely type of medication, initial mean BP, initial urinary albumin or total protein excretion, type of diabetes, duration of the study and number of patients investigated.

Results of the review
One hundred and four studies:
conventional therapy, 24 treatment groups with 307 patients;
ACE inhibitors, 72 treatment groups with 1,392 patients;
calcium antagonists, 18 treatment groups with 284 patients; and
nifedipine, 12 treatment groups with 166 patients.

Urine albumin or total protein excretion and BP changes. Results reported as treatment-associated % change.
Diuretics and/or beta-blockers: BP -10 (95% CI: -12, -13), PR -23 (95% CI: -33, -13).
ACE inhibitors: BP -11 (95% CI: -17, -5), PR -37 (95% CI: -53, -22).
Calcium antagonists except nifedipine: BP -11 (95% CI: -14, -8), PR -33 (95% CI: -44, -23).
Nifedipine: BP -9 (95% CI: -12, -7), PR 5 (95% CI: -18, 28).

Statistical significance was achieved for the following groupings:
Nifedipine versus other groups (p<0.001 by ANOVA).
ACE inhibitors versus conventional therapy (p<0.001 by ANOVA).

GFR Results reported as treatment-associated % change in GFR per month.
Placebo: 0.7 (95% CI: -1.3, 0.0).
Diuretics and/or beta-blockers: 0.8 (95% CI: -1.6, 0.1).
ACE inhibitors: -0.1 (95% CI: -1.3, 1.1).
Calcium antagonists except nifedipine: 0.2 (95% CI: -0.6, 0.9).
Nifedipine: 4.0 (95% CI: -7.4, -0.7).

GFR decrease was smaller with ACE inhibitors than with nifedipine (p<0.001, unpaired t-test).

Authors’ conclusions
ACE inhibitors are the preferred first line drug in the treatment of incipient or clinical diabetic nephropathy. Their effect relies on complementary direct intrarenal as well as systemic BP-dependent mechanisms. Diuretics and/or beta-blockers, and probably calcium ion antagonists other than nifedipine, can also reduce diabetic proteinuria, but only with
ACE inhibitors tend to preserve GFR better than diuretics and/or beta-blockers or nifedipine. There is now sufficient evidence to support large-scale use of ACE inhibitors at the earliest stage of diabetic nephropathy.

**CRD commentary**
A well-presented review that would have been improved by addressing the following methodological issues: the description of the search strategy is very poor, and there is no information on the time period searched, the search terms used or the publication languages included. The lack of validity criteria prevents a real assessment of how robust the authors' conclusions are. There were 3 times more studies on ACE inhibitors included, describing data from 5 times the patients of the other interventions; this will favour a statistically-significant effect occurring in the ACE group, and may make the authors' conclusions unsound.

**Implications of the review for practice and research**
From the literature reviewed, ACE inhibitors, calcium antagonist except nifedipine, and diuretics and/or beta-blockers are effective drugs for diabetic nephropathy when compared with nifedipine. However, there were relatively few trials which assessed the effectiveness of nifedipine. The data suggesting ACE inhibitors are the treatment of choice should be viewed with caution since there is a disproportionate number of studies included.

**Bibliographic details**

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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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.