Antihypertensive Agents for Primary Prevention of Diabetic Nephropathy

Giovanni F.M. Strippoli, Maria Craig, Francesco P. Schena, and Jonathan C. Craig
Centre for Kidney Research, Cochrane Renal Group, The Children’s Hospital at Westmead, School of Public Health, University of Sydney, Sydney, Australia

The objective of this study was to evaluate the comparative effects of antihypertensive agents in patients with diabetes and normoalbuminuria. Randomized, controlled trials that compared any antihypertensive agent with placebo or another agent in hypertensive or normotensive patients with diabetes and normoalbuminuria (albumin excretion rate <30 mg/d) were identified on Medline, in Embase, on the Cochrane Controlled Trials Register, in conference proceedings, and by contacting investigators. Two authors independently extracted data on renal outcomes and other patient-relevant outcomes (e.g., mortality, serious cardiovascular events) and assessed quality of trials. Analysis was by a random-effects model, and results were expressed as relative risk (RR) and 95% confidence intervals (CI). Sixteen trials (7603 patients) were identified, six of angiotensin-converting enzyme inhibitors (ACEi) versus placebo, six of ACEi versus calcium antagonists, one of ACEi versus calcium antagonists or combined ACEi and calcium antagonist, and three of ACEi versus other agents. Compared with placebo, ACEi significantly reduced the development of microalbuminuria (six trials, 3840 patients; RR 0.60; 95% CI 0.43 to 0.84) but not doubling of creatinine (three trials, 2683 patients; RR 0.81; 95% CI 0.24 to 2.71) or all-cause mortality (four trials, 3284 patients; RR 0.81; 95% CI 0.64 to 1.03). Compared with calcium antagonists, ACEi significantly reduced progression to microalbuminuria (four trials, 1210 patients; RR 0.58; 95% CI 0.40 to 0.84). A significant reduction in the risk for developing microalbuminuria in normoalbuminuric patients with diabetes has been demonstrated for ACEi only. It seems that the effect of ACEi is independent of baseline BP, renal function, and type of diabetes, but data are too sparse to be confident that these are not important effect modifiers, and an individual patient data meta-analysis is required.


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Address correspondence to: Dr. Giovanni F.M. Strippoli, Editor and Regional Coordinator of the Cochrane Renal Group, Centre for Kidney Research, Locked Bag 4001, Children’s Hospital at Westmead, Westmead, NSW 2145, Australia. Phone: +39-349-5705864; Fax: +39-080-5980776; E-mail: gfstrippoli@aliceposta.it

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Materials and Methods
Inclusion Criteria
We included data from trials (adult or pediatric) in which any antihypertensive agent was given for at least 6 mo, compared with placebo.

D iabetes is a global epidemic with >150 million people affected, a number that is expected to double by 2025. It is a progressively debilitating condition; a major cause of death in the world; and a leading cause of heart disease, adult blindness, and amputations of the lower extremities (1). Diabetes also represents the most common single cause of ESRD in the United States and Europe (2,3).

Renal involvement in patients with diabetes is defined by the appearance of low but abnormal levels (≥30 mg/d, or 20 μg/min) of albumin in the urine (microalbuminuria). This occurs in 40 to 80% of patients with diabetes 20 to 25 yr after the onset of diabetes (4). Without specific interventions, microalbuminuria (also called “incipient” nephropathy) progresses to the next stage of diabetic nephropathy—macroalbuminuria, or “overt” nephropathy—which is characterized by urinary albumin excretion ≥300 mg/d, or ≥200 μg/min. This stage generally develops over a period of 10 to 15 yr. If a patient has microalbuminuria, then the risk for progression to ESRD is 20 to 40% within 15 to 20 yr (5–9). If a patient has macroalbuminuria, then ESRD develops in approximately 50% of cases within 10 yr and in >75% within 20 yr. In parallel, there is a two- to four-fold increased risk for cardiovascular events and death for both conditions (9).

Recently, much attention has been given to secondary prevention strategies for patients with diabetes and nephropathy by attempting to prevent the progression of micro and macroalbuminuria to ESRD (10). Using available trial data, most national guideline groups have recommended angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) in preference to other antihypertensive agents in patients who have diabetes with micro- or macroalbuminuria (Table 1) (11–16). In comparison, these same guidelines generally do not preferentially recommend any class of antihypertensive agents in patients who have diabetes without microalbuminuria or any antihypertensive agent in patients who have diabetes without hypertension.

This systematic review was undertaken to evaluate the relative effects of antihypertensive agents in the primary prevention of nephropathy in patients who have diabetes without microalbuminuria. We also sought to determine whether the effects of these agents varied with baseline BP, renal function, and type of diabetes.
(or no treatment) or with other antihypertensive agents directly, in
patients with diabetes and no diabetic nephropathy (defined as the
absence of micro- or macroalbuminuria, i.e., urinary albumin excretion
<30 mg/d). These data were extracted from three groups of trials:

Table 1. Guidelines on pharmacologic management of hypertension in patients with diabetes

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Country</th>
<th>Year</th>
<th>Indication</th>
<th>Recommended Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC-7</td>
<td>United States</td>
<td>2003</td>
<td>Hypertension</td>
<td>X X X X X X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 1 diabetes)</td>
<td>X X</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 2 diabetes)</td>
<td></td>
</tr>
<tr>
<td>ADA</td>
<td>United States</td>
<td>2003</td>
<td>Hypertension</td>
<td>X X X X^b X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 1 diabetes)</td>
<td>X X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 2 diabetes)</td>
<td></td>
</tr>
<tr>
<td>K-DOQI</td>
<td>United States</td>
<td>2003</td>
<td>Hypertension</td>
<td>X X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 1 diabetes)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 2 diabetes)</td>
<td></td>
</tr>
<tr>
<td>Canadian Diabetes Association</td>
<td>Canada</td>
<td>2003</td>
<td>Hypertension</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 1 diabetes)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 2 diabetes)</td>
<td></td>
</tr>
<tr>
<td>European Society of Hypertension</td>
<td>Europe</td>
<td>2003</td>
<td>Hypertension</td>
<td>X X^d X X X X X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 1 diabetes)</td>
<td>X X</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 2 diabetes)</td>
<td></td>
</tr>
<tr>
<td>British Hypertension Society</td>
<td>United Kingdom</td>
<td>2004</td>
<td>Hypertension</td>
<td>X^e X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 1 diabetes)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 2 diabetes)</td>
<td></td>
</tr>
<tr>
<td>CARI Guidelines</td>
<td>Australia</td>
<td>2000</td>
<td>Hypertension</td>
<td>X X X^f X X^f</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 1 diabetes)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetic nephropathy (type 2 diabetes)</td>
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</tr>
</tbody>
</table>

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CA, calcium antagonists; JNC-7, Joint National Committee on Prevention, Diagnosis and Management of Hypertension; ADA, American Diabetes Association; K-DOQI, Kidney Disease Outcome Quality Initiative; CARI, Caring for Australians with Renal Impairment; X, suggested agent.

^bSecond-line agent.
^cEither ACEi or ARB but ARB only if creatinine clearance is \( \leq 60 \text{ ml/min}\).
^dUse CA for hypertension when can be managed with monotherapy; use any agent for hypertension that requires combination treatment.
^eIf intolerant to other agents.
^fOnly if intolerant to ACEi.
primarily hypertensive patients, including some patients with diabetes, when the data of the patients with diabetes and without diabetic nephropathy could be extracted or obtained.

To compare the consistency of these findings with results obtained in large-scale, randomized trials of different antihypertensive agents conducted in general population settings, we searched for trials using the criteria of the Blood Pressure Lowering Treatment Trialists Collaboration (n > 4000 with a planned minimum of 1000 patient-years of follow-up; http://www.thegeorgeinstitute.org/bpttc/resources.html). These trials were analyzed separately because data on baseline albuminuria for the patients with diabetes were not provided (i.e., the outcomes for normoalbuminuric patients with diabetes could not be isolated). A separate systematic review of the relative effects of antihypertensive agents in patients with established diabetic nephropathy has been published elsewhere (10).

**Literature Search**

Electronic searches were performed in Medline (1966 through September 2003) and Embase (1988 through September 2003) using optimally sensitive search strategies developed by the Cochrane Collaboration for the identification of trials (17). The Cochrane Renal Group Specialized Register and the Cochrane CENTRAL registry of randomized trials were also searched. The following medical subject heading terms and text words were used: AT 2 receptor blockers, angiotensin II receptor antagonist(s), angiotensin receptor antagonist(s), chlorothiazide, chlorthalidone, hydralazine, hydrochlorothiazide, indapamide, minoxidil, losartan, imidazole, irbesartan, candesartan, eprosartan, valsartan, olmesartan, telmisartan, angiotensin converting enzyme inhibitors, captopril, enalapril, cilazapril, enalaprilat, fosinopril, lisinopril, perindopril, ramipril, saralasin, tetrodide, calcium channel blockers, amiodipine, diltiazem, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrrendipine, verapamil, adrenergic β-antagonists, alprenolol, atenolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, adrenergic α-antagonists, labetalol, prazosin, beta blocker, diuretics, spironolactone, triamterene, bumetanide, furosemide, combined with diabetes mellitus or diabetic nephropathy.

Trials were considered without language restriction. The results of the searches were analyzed in title and abstract form by two independent authors (G.F.M.S., M.C.) according to the inclusion criteria. Reference lists from identified articles were also searched. Information about unpublished or additional trials were sought from experts in the field (authors of identified trials) and the Internet (international medical societies web sites, on-line guidelines, and health promotion organizations).

**Data Extraction, Definition of Outcomes, and Quality Assessment**

Each trial was assessed by two independent authors (G.F.M.S., M.C.). From all included trials, data were extracted on characteristics of the participants, interventions, comparisons, and outcomes (progression from normo- to micro- or macroalbuminuria, ESRD, doubling of creatinine, all-cause mortality, fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, cough, headache, and hyperkalemia). Whenever data were not reported in the publications, authors were contacted by at least two methods from the primary investigator (G.F.M.S.) and the Cochrane Renal Group editorial office. Authors were also contacted when trials enrolled mixed populations of normo- and micro-/macroalbuminuric patients with diabetes to obtain individual data of the normoalbuminuric individuals only, as per the inclusion criteria and objectives of this analysis. The quality of included randomized trials was assessed using standard criteria (allocation concealment, intention-to-treat analysis, loss to follow-up, and blinding). Any differences in data extraction were resolved by discussion among authors.

**Statistical Analyses**

Treatment effects were summarized as relative risks (RR) with 95% confidence intervals (CI) and pooled using the DerSimonian and Laird random-effects model (18). Heterogeneity of treatment effects between studies was examined using Cochran Q and the F' statistics (19). Subgroup analysis and random-effects meta-regression were planned to explore the influence of possible sources of heterogeneity (duration of follow-up, type of diabetes, type of drug, baseline renal function and hypertension, and specific trial quality items) on treatment effect, provided that a sufficient number of trials were identified.

In trials of populations with mixed-causation hypertension, the raw data were used whenever available to summarize treatment effect with the RR measure and its 95% CI. Estimates of treatment effect were obtained for the overall population, the patients with diabetes, and the patients without diabetes. Differences in the estimate of effect of treatment between patients with and without diabetes were tested with a formal test of interaction whenever these data were available.

**Results**

**Literature Search**

The literature search identified 4723 articles, 4424 of which were excluded after title and abstract review (Figure 1). The
major reasons for exclusion were a nonrandomized design, nonantihypertensive interventions, nondiabetic study populations, patients with diabetes and established nephropathy (either micro- or macroalbuminuria), and duplicate publications. Full-text assessment of 299 potentially eligible studies identified 16 eligible trials (25 publications) that enrolled 7603 patients (20–35).

Supplemental data on design features and outcomes were asked of all authors of the trials. Authors of the 10 trials that enrolled both patients with and without nephropathy were also asked for the data sets of the normoalbuminuric patients only, with seven replying to our requests (23–28,32).

Study Characteristics
The characteristics of the populations and interventions of the studies included in this systematic review are presented in Table 2. Of the 16 trials, seven trials or trial arms (4925 patients) compared ACEi with placebo or no treatment, seven trials or trial arms (1161 patients) compared ACEi with calcium antagonists, and four trials or trial arms compared ACEi with β-blockers, combined ACEi and calcium antagonists, α-blockers, or “conventional” treatment (note: one trial had four arms and so contributed data to more than one group of trials).

Most trials enrolled only patients with type 2 diabetes (12 trials, 3381 patients). Three trials (645 patients) of ACEi versus placebo/no treatment enrolled only patients with type 1 diabetes, and one trial (3577 patients) of ACEi versus placebo enrolled both patients with type 1 and type 2 diabetes (24). Ten trials enrolled mixed populations of normo- and micro-/macroalbuminuric patients. Fourteen trials enrolled hypertensive individuals, and BP equalization between the experimental and control group of the trials was obtained in eight by administration of additional antihypertensive co-interventions besides the randomized intervention. Follow-up of the studies ranged from 6.0 to 63.6 mo.

Co-interventions for blood glucose control were administered in all but one trial, but the agents used were often not specified. In general, tight control of blood glucose was addressed with end-of-treatment values of HbA1c reported in 10 trials and ranging between 5 and 9%.

Study Quality
Trial quality was variable. Allocation concealment was adequate in four (25%) of 16 trials and unclear in the remaining trials. Participants were blinded in nine (56%) of 16 trials, investigators were blinded in seven (44%) of 16 trials, and outcome assessors were blinded in two (13%) of 16 trials. Intention-to-treat analysis was used in six (38%) of 16 trials. The percentage of patients who were lost to follow-up ranged between 0.0 and 20.0%.

Quantitative Data Synthesis
ACEI versus Placebo/No Treatment. Compared with placebo/no treatment, ACEI significantly reduced the risk for microalbuminuria (six trials, 3840 patients; RR 0.60; 95% CI 0.43 to 0.84). A test of interaction did not demonstrate any difference in the effect of ACEI versus placebo in hypertensive and nonhypertensive patients ($\chi^2 = 0.854, P = 0.36$), type 1 and type 2 diabetes ($\chi^2 = 0.3408, P = 0.56$), and normal and abnormal renal function ($\chi^2 = 1.4158, P = 0.23$), but given the relatively sparse data, dominated by three trials, important quantitative interactions have not been excluded (Figure 2).

For other outcomes, trial data were sparse, with the MICRO-HOPE trial dominating all analyses. There was no significant difference in the risk for doubling of creatinine with ACEi compared with placebo (three trials, 2558 patients; RR, 0.81; 95% CI, 0.24 to 2.71; Figure 3). This analysis presented significant heterogeneity (heterogeneity $\chi^2 = 2.84, P = 0.09, I^2 = 64.8\%$), which may be explained by competing risks between the different trial outcomes (Table 1). ESRD (one trial, $n = 2683$; RR, 2.35, 95% CI, 0.46 to 12.10) and all-cause mortality (three trials, 2683 patients; RR, 0.80; 95% CI, 0.63 to 1.02) were not significantly different with ACEI compared with placebo (Figure 4).

The risk for cough was significantly increased with ACEI compared with placebo/no treatment (four trials, 3725 patients; RR, 1.79; 95% CI, 1.19 to 2.69), whereas there was no significant difference in the risk for headache (one trial, 2438 patients; RR, 1.25; 95% CI, 0.44 to 3.61) or hyperkalemia (two trials, 2594 patients; RR, 2.95; 95% CI, 0.31 to 28.18). There were no data on other cardiovascular end-points.

ACEI versus Calcium Antagonists. Compared with calcium antagonists, ACEI reduced the risk for micro- or macroalbuminuria (four trials, 1210 patients; RR, 0.58; 95% CI, 0.26 to 2.73) and all-cause mortality with ACEI compared with calcium antagonists (six trials, 1286 patients; RR, 0.84; 95% CI, 0.26 to 2.73) and no data on other cardiovascular end points.

ACEI versus Other Agents. There was no statistically significant difference in risk for nephropathy with ACEI compared with β-blockers (one trial, 299 patients; RR, 1.01; 95% CI, 0.74 to 1.37) and with combination ACEI and calcium antagonist therapy compared with ACEI alone (one trial, 901 patients; RR, 1.03; 95% CI, 0.59 to 1.80).

Other Potentially Relevant Trials
Eight large trials that were performed in patients with mixed-cause hypertension met the criteria for analysis in this review (36–43). These trials included varying proportions of patients with diabetes (10 to 35%). Patients with renal impairment were systematically excluded from the trials, and baseline data on nephropathy were not available, so we were not able to separate out the data of patients with diabetes and normoalbuminuria and could not include these data in our main analyses. The characteristics of these trials’ interventions, a quantitative description of treatment effects in the overall trial population, and a comparison of effect estimates in the patients with and without diabetes with a formal test of interaction are reported in Table 3. In general, all trials reported that patients with diabetes had a two to three times higher rate of cardiovascular events compared with the trial population as a whole, but the relative effects of the antihypertensive agents used in the trial did not differ significantly between patients with diabetes and the entire trial population for the outcomes of death and a range of composite cardiovascular end
The only exception was the HOT study, in which patients were randomized to three diastolic BP targets (≥50, ≥85, and ≤80 mmHg) and which showed that patients with diabetes had a greater RR reduction in cardiovascular mortality and major cardiovascular events with lower target BP than patients without diabetes (38). There was no evidence of significant differences in

Table 2. Characteristics of populations and interventions in the studies of antihypertensive agents to prevent diabetic nephropathy included in this systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Albuminuria</th>
<th>Type of Diabetes</th>
<th>Baseline Renal Function (Mean ± SD)</th>
<th>Baseline Hypertension</th>
<th>BP Target Equalization</th>
<th>Experimental Intervention</th>
<th>Control</th>
<th>Antihypertensive Co-Interventionsa</th>
<th>End-of-Treatment HbA1c (%)</th>
<th>N</th>
<th>Follow-Up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI versus placebo/no treatment</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ABCD 2002 (21)</td>
<td>NA/NA</td>
<td>X</td>
<td>NA</td>
<td>X</td>
<td>Enalapril 5 to 40 mg/d</td>
<td>Placebo</td>
<td>X</td>
<td>NA</td>
<td>264</td>
<td>24</td>
<td>63.6</td>
</tr>
<tr>
<td>EUCLID 1997 (22)</td>
<td>227 (22) 34/269</td>
<td>X</td>
<td>NA</td>
<td>X</td>
<td>Lisinopril 10 to 20 mg/d</td>
<td>Placebo</td>
<td>X</td>
<td>NA</td>
<td>340</td>
<td>24</td>
<td>530</td>
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<tr>
<td>Kvetny 2001 (23)</td>
<td>89 –</td>
<td>X</td>
<td>NA</td>
<td>X</td>
<td>Perindopril 2 mg × 2/d</td>
<td>Placebo</td>
<td>X</td>
<td>NA</td>
<td>89</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>HOPE 2000 (24)</td>
<td>2438 1139/NA</td>
<td>X</td>
<td>Creatinine 1.05 ± 0.2 mg/d</td>
<td>X</td>
<td>Ramipril 10 mg/d</td>
<td>Placebo</td>
<td>X</td>
<td>2.2 versus 3.57</td>
<td>537</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Ravid 1998 (25)</td>
<td>156 –</td>
<td>X</td>
<td>Creatinine 1.3 ± 0.1 mg/d</td>
<td>X</td>
<td>Enalapril 5 to 10 mg/d</td>
<td>Placebo</td>
<td>X</td>
<td>2.0 change b</td>
<td>87 versus 8.5</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Tuominen 1998 (26)</td>
<td>26 –</td>
<td>X</td>
<td>Creatinine 1.0 ± 0.1</td>
<td>X</td>
<td>Lisinopril 15 to 20 mg/d</td>
<td>Placebo</td>
<td>NA</td>
<td>26</td>
<td>24</td>
<td></td>
<td></td>
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<tr>
<td>ACEI versus calcium channel blocker</td>
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</tr>
<tr>
<td>Baba 2001 (27)</td>
<td>NA/NA</td>
<td>X</td>
<td>Creatinine 0.7 ± 0.3 mg/d</td>
<td>X</td>
<td>Enalapril 5 to 20 mg/d</td>
<td>Nifedipine 20 to 60 mg/d</td>
<td>X</td>
<td>No difference</td>
<td>464</td>
<td>24</td>
<td>24</td>
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<tr>
<td>Chan 2000 (28)</td>
<td>44 36/NA</td>
<td>X</td>
<td>Creatinine clearance 62.0 ± 23.0 ml/min</td>
<td>X</td>
<td>Enalapril 10 to 40 mg/d</td>
<td>Nifedipine SF 40 to 80 mg/d</td>
<td>X</td>
<td>7.6 versus 7.1</td>
<td>102</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Crepaldi 1995 (29)</td>
<td>55 24/NA</td>
<td>X</td>
<td>Creatinine clearance 120 ± 10 ml/min per 1.73 m²</td>
<td>X</td>
<td>Lisinopril 10 to 20 mg/d</td>
<td>Nifedipine 20 to 60 mg/d</td>
<td>X</td>
<td>−0.4 versus 0.6</td>
<td>82</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>FACET 1998 (30)</td>
<td>42 –</td>
<td>X</td>
<td>Creatinine 1.0 ± 0.1 ml/min</td>
<td>X</td>
<td>Fosinopril 20 mg/d</td>
<td>Amlodipine 10 mg/d</td>
<td>X</td>
<td>6.8 versus 7.0</td>
<td>103</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Raggenbachi 2004 (23)</td>
<td>1204 –</td>
<td>X</td>
<td>Creatinine 0.8 ± 0.2 mg/d</td>
<td>X</td>
<td>Trandolapril 2 mg/d</td>
<td>Verapamil SR 240 mg/d</td>
<td>X</td>
<td>NA</td>
<td>1204</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Scognamiglio 1997 (31)</td>
<td>73 –</td>
<td>X</td>
<td>NA</td>
<td>X</td>
<td>Captopril 50 to 100 mg/d</td>
<td>Nitrendipine 20 to 40 mg/d</td>
<td>X</td>
<td>6.6 versus 6.8</td>
<td>73</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Velussi 1996 (32)</td>
<td>26 18/0</td>
<td>X</td>
<td>Creatinine 1.2 ± 0.1 mg/d</td>
<td>X</td>
<td>Cilazapril 2.5 mg/d</td>
<td>Amlodipine 5 mg/d</td>
<td>X</td>
<td>8.0 versus 8.0</td>
<td>44</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>ACEI versus other</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>UKFDS 1998 (33)</td>
<td>NA/NA</td>
<td>X</td>
<td>NA</td>
<td>X</td>
<td>Captopril 25 to 50 mg</td>
<td>Atenolol 50 to 100 mg/d</td>
<td>X</td>
<td>8.3 versus 8.4</td>
<td>758</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Josiakar 1998 (34)</td>
<td>NA/NA</td>
<td>X</td>
<td>NA</td>
<td>X</td>
<td>Enalapril 5 to 10 mg/d</td>
<td>Prazosin CTS 2.5–5 mg/d</td>
<td>NA</td>
<td>89</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin 1995 (35)</td>
<td>NA/NA</td>
<td>X</td>
<td>Creatinine 1.2 ± 0.1 mg/d</td>
<td>X</td>
<td>Captopril 25 to 150 mg/d</td>
<td>Conventional f</td>
<td>X</td>
<td>7.0 versus 7.6</td>
<td>60</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

aNA, not available; X, presence of the factor.
bCo-interventions were calcium antagonists, β-blockers, α-blockers, or diuretics.
cThis trial included not only a placebo/no treatment control arm but also an additional treatment arm (non-ACEi, non–angiotensin receptor antagonist).
dFrom baseline value.
eThis trial included not only a calcium antagonist control arm but also two additional arms, one of placebo and one of the combination of an ACEI and a CA.
fUnclear; the term conventional was not defined.
all-cause mortality or cardiovascular end points among the classes of antihypertensive agents trialled (Table 3). The only exception was the CAPPP trial, which showed a significant reduction in the risk for all-cause mortality with captopril compared with conventional treatment only in the subgroup of patients with diabetes.

### Discussion

In currently available randomized trials, only one class of antihypertensive agents—ACEI—has been found to be effective for the primary prevention of nephropathy in patients with diabetes. With ACEI, an RR reduction of 42% has been demonstrated (95% CI, 16 to 60%). Given a 10% risk for the development of microalbuminuria in hypertensive patients with diabetes over 3 to 4 yr, approximately 25 people would need to be treated to prevent one new case of microalbuminuria (2). Comparing the effects of ACEI against other classes of antihypertensive agents is more difficult because of the relative sparseness of data, except for calcium antagonists. Compared with these agents, ACEI reduce the risk for nephropathy and by a similar degree than for the placebo-comparison trials (40%).

### Figure 2

Effect of angiotensin converting enzyme inhibitors (ACEi) versus placebo/no treatment on development of micro- or macroalbuminuria in patients with diabetes and normoalbuminuria (note: data on normoalbuminuric patients only were not provided from the authors of the EUCLID trial).

### Figure 3

Effect of ACEi versus placebo/no treatment on doubling of creatinine in patients with diabetes and normoalbuminuria.

### Figure 4

Effect of ACEi versus placebo/no treatment on all-cause mortality in patients with diabetes and normoalbuminuria.
What our review also shows is considerable areas of residual uncertainty regarding the effects of antihypertensive agents in normoalbuminuric patients with diabetes. The existing uncertainties cluster around four main areas: the comparative effects of different antihypertensive agents; the presence of hypertension, type of diabetes, and renal function as potential effect modifiers of ACEi therapy; the other renal and nonrenal effects of ACEi in this population; and the identification and reporting of renal disease as a relevant outcome for microvascular disease.

First, there are few available trial data comparing β-blockers or other antihypertensive agents for patients with diabetes and no renal disease. There are no trial data on the relative effects of ARB and ACEi, even though these agents are recommended interchangeably by most guidelines groups once nephropathy has occurred (Table 1).

Second, patients with diabetes, even without microalbuminuria, are a heterogeneous population, most have hypertension but some do not, most have type 2 diabetes but some have type 1 diabetes, the level of renal function is variable, and patients have different diabetes-associated comorbidities. Is the beneficial effect of ACEi on preventing nephropathy constant across these groups, or is there a qualitative (different effect but only in terms of the size of the effect, not direction) or quantitative (different effect in terms of direction) interaction? Here, the variability in design of the ACEi versus placebo trials is moderately informative. In our analysis, the point estimates for all trials favored ACEi, irrespective of design, and we could not detect statistically significant interactions between ACEi and differences in baseline characteristics across trials. However, given the small number of trials, our power to detect significant differences is low, and because comparisons are made across trials and not within trials, these comparisons are potentially confounded. Given such uncertainty, we may conclude at best that there is no evidence that the effect of ACEi varies with baseline BP, renal function, or type of diabetes and that any variability is likely to be quantitative and not qualitative. This uncertainty could be reduced by an individual patient data meta-analysis.

Third, these trials are relatively uninformative about outcomes other than the development of microalbuminuria and macroalbuminuria, such as side effects, effects on cardiovascular end points, and mortality. Clinicians and patients would want to know the effect of ACEi on all patient-centered outcomes, not just surrogate outcomes, such as urinary protein excretion. Only three (of six) trials reported these outcomes, and no statistically significant reduction in the risk for ESRD, doubling of creatinine, or all-cause mortality was demonstrated. There was considerable imprecision around these estimates as a result of low event rates and low sample sizes, except for the micro-HOPE trial, which dominates all analyses. The lack of beneficial effect on ESRD and doubling of serum creatinine shown in micro-HOPE could be explainable by the competing risks of these renal outcomes and overall survival (which was improved in HOPE with ramipril therapy). It is plausible that fewer patients developed ESRD in the ramipril arm because fewer patients survived long enough. A reduction in these outcomes is plausible given that microalbuminuria is an independent risk factor for kidney failure and cardiovascular deaths, ACEi have been shown to reduce microalbuminuria more than other antihypertensive agents, and a reduction in these outcomes with ACEi treatment has also been demonstrated in patients with diabetes and overt nephropathy (10). However, summarizing the nonalbuminuria outcomes of these trials, we conclude that no statistically significant benefit of ACEi on ESRD, doubling of serum creatinine, and all-cause mortality has been demonstrated.

Fourth, as Table 3 demonstrates, many large-scale trials have been done in hypertensive patients, with patients with diabetes making up a significant proportion. Unfortunately for clinicians and patients who want to know the comparative effects of these agents with kidney disease as an outcome, these trials are largely uninformative, because this outcome (onset of micro- or macroalbuminuria) was not reported. In our review, we sought to extract data for patients with and without diabetes to determine whether the diabetic state is an effect modifier for all-cause mortality and cardiovascular and renal outcomes, but this was possible only for the first two outcomes. No evidence of effect modification (significant variation in the estimates of treatment effect in patients with diabetes compared with patients without diabetes) was demonstrated for drug classes, but tighter control was found to be more effective for patients with diabetes than for patients without diabetes in the HOT trial (38). In short, from the large-scale antihypertensive trials, it is unclear whether any class of antihypertensive agent is more effective in preventing nephropathy control than any other, but
Table 3. Effect of antihypertensive agents in randomized, controlled trials that enrolled hypertensive patients (n > 4000, planned minimum of 1000 patient-years) and included patients who had diabetes with or without nephropathy (estimates of treatment effect where calculated from raw data of the trials)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>% with Diabetes</th>
<th>All-Cause Mortality (RR and 95% CI)</th>
<th>Major Cardiovascular Events (RR and 95% CI)</th>
<th>Follow-Up (mo)</th>
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<tr>
<td></td>
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<td>All Patients</td>
<td>Diabetes</td>
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<tr>
<td>ALLHAT 2002 (36)</td>
<td>Lisinopril versus chlorthalidone</td>
<td>24309</td>
<td>35.9</td>
<td>1.00 (0.94 to 1.08)</td>
<td>1.02 (0.91 to 1.13)</td>
<td>NA</td>
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<tr>
<td>HOT 1998 (38)</td>
<td>DIB* 90 versus 85</td>
<td>12528</td>
<td>8.0</td>
<td>0.97 (0.79 to 1.19)</td>
<td>1.03 (0.62 to 1.71)</td>
<td>0.78</td>
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<td>Wired versus 80</td>
<td></td>
<td>12526</td>
<td>8.0</td>
<td>0.93 (0.73 to 1.11)</td>
<td>1.09 (0.54 to 2.20)</td>
<td>0.02</td>
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<tr>
<td>INCIGHT 2000 (39)</td>
<td>Nifedipine versus co-amilozide</td>
<td>621</td>
<td>206</td>
<td>1.01 (0.81 to 1.26)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Syst-EUR 1999 (43)</td>
<td>Nitrendipine, possible enalapril</td>
<td>4695</td>
<td>105</td>
<td>0.86 (0.68 to 1.09)</td>
<td>0.59 (0.32 to 1.00)</td>
<td>0.92 (0.71 to 1.22)</td>
</tr>
</tbody>
</table>

aX2 test with 1 degree of freedom for interaction between cohort of patients with diabetes *versus* cohort of patients without diabetes.
bFatal coronary heart disease and nonfatal myocardial infarction.
cDiuretic, β-blocker, or both.
dData adjusted for age, gender, systolic BP, and previous treatment.
eFatty and nonfatal myocardial infarction, stroke, and other cardiovascular deaths.
fDiastolic BP in mmHg.
gMajor cardiovascular events, including all fatal and nonfatal myocardial infarctions, all fatal and nonfatal strokes, and all other cardiovascular deaths.
hMyocardial infarction, stroke, heart failure and cardiovascular death, noncardiovascular death, renal failure, angina, and transient ischemic attack.
iFatty and nonfatal stroke, fatal and nonfatal myocardial infarction, and other cardiovascular death.
jCardiovascular disease including nonfatal or fatal myocardial infarction, sudden cardiac death, rapid cardiac death, coronary artery bypass graft, angioplasty, nonfatal or fatal stroke, transient ischemic attack, aneurysm, and endarterectomy.
kFatty and nonfatal myocardial infarction.
1Fatty and nonfatal heart failure, fatal and nonfatal myocardial infarction, and sudden death
mRaw data not available to evaluate interaction; however, trialists reported no interaction.

Patients with diabetes required more treatment and were the group in which nifedipine and co-amilozide were most effective for all outcomes.
any additional downstream effect on all-cause mortality and cardiovascular events is very unlikely.

The strength of this study is that it represents the first comprehensive systematic review in this area, on the basis of previous publication of a detailed protocol (44); rigid inclusion criteria for randomized, controlled trials only; and a comprehensive MEDLINE, EMBASE, and Cochrane Controlled Trial Registry search. Data extraction, data analysis, and method quality assessment were performed by two independent investigators, and consistency was checked with an additional investigator. This method contrasts with strategies adopted in previous nonsystematic reviews, reports, and guidelines (11–16,45,46). We presented an explicit comparison of trial data with current guidelines and of data from trials that were conducted in patients with diabetes with those of large-scale trials that were conducted in hypertensive individuals and that included a proportion of patients with diabetes to check for consistency of findings. We also obtained previously unpublished data from trialists.

Our study shares the limitations of most systematic reviews, being susceptible to publication bias and outcomes reporting bias. These biases tend to favor the intervention being considered. We have attempted to reduce these biases by an extensive search for relevant papers and contacting authors for additional information. The reduction in microalbuminuria with ACEi is only a surrogate for the clinically important outcome of ESRD. We were unable to demonstrate any concomitant reduction in ESRD, but given the low-risk population for this outcome in these trials, this is not surprising. Evidence that microalbuminuria is a good surrogate for ESRD can be found in other trials, in patients with microalbuminuria, in whom ACEi have been shown to prevent macroalbuminuria, reverse microalbuminuria (to normoalbuminuria), and prevent ESRD (or doubling of serum creatinine) (10).

How do the results of our study compare with published guidelines on the treatment of patients with diabetes? Most guidelines recommend any agent in patients with diabetes and hypertension and without nephropathy, and only ACEi or ARB once nephropathy occurs. The use of any class of antihypertensive agents in patients with diabetes targeting tight BP control is justified by significant reduction in mortality and cardiovascular outcomes from the primarily nondiabetic trials of hypertension, but only ACEi have been proved to reduce the onset of microalbuminuria in this population compared with placebo, and the results of ACEi look more favorable than the only other class of drug evaluated, the calcium channel blockers. Our data therefore suggest that ACEi have an incremental effect on renal outcomes in patients with diabetes, compared with other agents, and so should be the treatment of choice unless other antihypertensive agents are evaluated against ACEi in the setting of a randomized, controlled trial. Future trials of antihypertensive agents in patients with diabetes and no renal disease should report microalbuminuria and other renal outcomes as well as the usually reported outcomes: all-cause mortality and cardiovascular end points.

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