ACE Inhibitor Treatment in Diabetic Nephropathy

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GUIDELINES

a. **All patients with Type 1 or Type 2 diabetes mellitus complicated by microalbuminuria or overt nephropathy should be treated with an angiotensin converting enzyme inhibitor (ACEI), independent of blood pressure and GFR. (Level I evidence, greater for Type 1 than Type 2). There is no evidence that any specific ACEI offers any advantage over the class effect.**
b. **Hypertensive diabetics without albuminuria should be treated with ACEI as first-line antihypertensive therapy. (Level I evidence)**

c. **There is currently insufficient evidence to recommend universal ACEI treatment for all diabetic patients with normal blood pressure (BP) and albumin excretion rate (AER)**

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on level III and IV sources)

- **A strong association between acute increases (up to 30%) in serum creatinine on initiation of ACEI treatment, stabilizing within the first 2 months of therapy, and long-term preservation of renal function is shown in the meta-analysis of Bakris and Weir (2000). ACEI therapy should be withdrawn only if creatinine increases > 30% above baseline within the first 2 months of therapy.**
- **Use of ACE inhibitors may exacerbate hyperkalaemia in patients with kidney failure and/or hyporeninaemic hypoaldosteronism.**

Background

Type 2 diabetes with its increased vascular risks is expected to affect 370 million people by 2030 (http//www.who.int/diabetes/en/). The onset of nephropathy trebles the risks of fatal vascular events. Renin-angiotensin system blockade is known to be vasculoprotective in diabetes.

This section reviews the evidence that ACEI in diabetes protects against the onset and progression of diabetic nephropathy.

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials (RCT's) relating to the prevention of progression of kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A2 receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.

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What is the evidence?

ACEI in overt diabetic nephropathy

Type 1 diabetes
Lewis et al (1993) provided the first RCT evidence that ACEI delays progression of kidney failure in overt diabetic nephropathy. This RCT studied captopril vs placebo in 409 Type 1 diabetics with overt proteinuria (> 0.5 g/day) and BP < 140/90 mmHg. Endpoints were doubling of serum creatinine and end-stage kidney disease (ESKD)/death.

Further follow-up of the nephrotic subgroup (n = 108) of the total 409 patients randomised to captopril revealed long-term remission of nephrotic syndrome in 8 patients (Wilmer et al 1999).

Weidmann et al (1993, 1995) performed two meta-analyses, including 93 studies in the 1993 analysis, and added a further 11 studies for the updated analysis. Both Type 1 and Type 2 diabetic studies were included, and findings were similar for both groups. In overt nephropathy, GFR was better preserved in ACEI-treated patients than in those treated with beta-blockers, diuretics or nifedipine.

Type 2 diabetes
Evidence in Type 2 diabetic patients with overt nephropathy has taken longer to emerge.
Two studies (Neilsen et al 1997, Parving & Rossing 1994) in Type 2 diabetes with overt nephropathy concluded that ACEI may not affect GFR reduction rate beyond their antihypertensive effect. However, subsequent evidence (including the metaanalysis of Weidmann et al [1995]) documented that in overt nephropathy in both Type 1 and Type 2 diabetics, GFR was better preserved in ACEI-treated patients than in those treated with beta-blockers, diuretics or nifedipine.

Ferder et al (1992) randomised 30 Type 2 diabetics with overt nephropathy to either enalapril (40 mg/day) or nifedipine (40 mg/day) for 12 months. Mean arterial pressure (MAP) in the two groups was equivalent, but urine protein dropped significantly only in the ACEI group (4.4–0.56 g/day) and creatinine clearance decreased only in the nifedipine group

ACEI in microalbuminuria

Meta-analyses (predominantly Type 1)
Type 1 and Type 2 diabetes with microalbuminuria

The meta-analysis of Kasiske et al (1993), see CARI 'Antihypertensive therapy in diabetic nephropathy' guideline), showed ACEI to be better both at decreasing AER and in preserving GFR, in microalbuminuric diabetic patients, than were β-blockers and/or calcium channel blocker. Reducing blood pressure reduced proteinuria, but ACEI produced significant further reduction beyond their antihypertensive effect.

Analysis quantitated GFR preservation to be 3.7 ± .92 mL/min for each 10 mmHg reduction in MAP, plus a specific ACEI effect of 3.4 ± 1.7 mL/min.

In the meta-analyses of Weidmann et al (1993, 1995, discussed above) initially normotensive, microalbuminuric diabetics who received ACEI showed a fall in AER greater than that in non-ACE inhibitor- or placebo- treated patients. Type 2 diabetes with hypertension and microalbuminuria

Agardh et al (1996) studied 300 hypertensive Type 2 diabetics with microalbuminuria in a double-blind, parallel group, multicentre RCT of lisinopril (10–20 mg daily) vs. nifedipine (40–80 mg/day), with target diastolic blood pressure (DBP) < 90 mmHg at the time of trough drug level. Lisinopril but not equipotent-for-BP doses of nifedipine reduced AER over the 12–month study (AER fell from 65–39 mcg/min in the ACEI group, and from 63 58 mcg/min in the nifedipine group). Creatinine clearance did not change in either group.

Lebovitz et al (1994) studied renal function in 121 hypertensive Type 2 diabetics with microalbuminuria over 36 months following randomisation either to an antihypertensive regimen including enalapril or to "conventional" (non-ACEI) antihypertensives. ACEI specifically prevented progression to overt proteinuria (7% vs. 21% progressing) and prevented fall in GFR.

In a small, longitudinal, parallel group study of 13 hypertensive Type 2 diabetics with biopsy-proven nephropathy and mild-moderate hypertension, Mosconi et al (1996) randomised patients to either enalapril or nifedipine. Both antihypertensives produced comparable reduction in BP and in AER, and GFR increased in both groups at 15 and 27 months.

Retrospective analysis of annual serum creatinine levels from the diabetic subset within the HOPE study (Mann et al 2003, Microalbuminuria and Renal Outcomes in the Heart Outcomes and Prevention Evaluation study) compared ramipril with placebo over 4.5 years in 3577 diabetics, including 1139 with microalbuminuria and 333 with renal insufficiency. Participants with dipstick-positive proteinuria (> 1 +) or serum creatinine >0.2 mmol/L were excluded. Serum creatinine levels did not increase significantly during the study in the overall group, or in the microalbuminuric or renal insufficiency subgroups. There were no differences between serum creatinine in the placebo and ramipril-treated groups. However, ramipril decreased the risk of overt nephropathy by 24% (95% CI: 3–40, P = 0.027), even after adjustment for the small (2.4/1.0 mmHg) difference in BP (25%, 95% CI: 12–36, p =0.0004).

The smaller study of Chan et al (2000) confirmed the efficacy of ACEIs compared with other drugs in the hypertensive, microalbuminuric, Type 2 diabetic patient group (RRR 23%–68% for progression to overt proteinuria). In hypertensive microalbuminuric Type 2

diabetics ACE inhibitors diminish AER, or at least prevent an increase in AER. ACE inhibitors progressively lose their antiproteinuric advantage over other anti-hypertensives as blood pressure control increases. However, there remains a specific advantage for ACEI.

Type 1 diabetes with normotension and microalbuminuria

The studies of Marre et al (1988), Bilo et al (1993), Chase et al (1993), Hallab et al (1993), Mathieson et al (1991), Viberti et al (1994) and Parving et al (1989) are included in the Cochrane Group meta-analysis of Lovell (1995) asking the question "Are ACEI useful for normotensive diabetic patients with microalbuminuria?". This analysis concluded that ACEI decrease AER in both Type 1 and Type 2 diabetes, but that evidence for a direct link to postponement of End-stage Kidney Disease (ESKD) requires further evidence and longer follow-up.

Laffel et al (1995) reported on a double-blind placebo controlledRCT of captopril (50 mg b.d) in 26 North American centers, of 143 normotensive microalbuminuric patients with Type 1 diabetes. Within 24 months, 6% of captopril-treated subjects and 19% of placebo-treated subjects progressed to clinical proteinuria (RRR = 67.8%, P = 0.037). AER increased at an annual rate of 11.8% (95% CI: -3.3% to 29.1%) in the placebo group, while it declined by 17.9% (95% CI: -29.6% to -4.3%) in the captopril group (P = 0.004). Creatine clearance decreased by 4.9 mL/min per 1.73 m_2 per year in the placebo group, but remained stable in the captopril group (0.9mL/min per 1.73 m_2 per year, P = 0.039 between groups). Ten subjects required treatment for hypertension; 8 in the placebo group and 2 in the captopril group. There was little correlation between the 24-month changes in mean arterial blood pressure and AER in either group. Glycohemoglobin and urinary urea excretion did not differ between groups.

Jerums et al (2001) prospectively randomised 42 normotensive microalbuminuric Type 1 diabetics to perindopril 2-8 mg/day, nifedipine 20–80 mg/day or placebo, and followed 33 patients for at least 24 (mean = 67) months. AER decreased, and GFR was stable in the perindopril group, while AER increased and GFR fell in the nifedipine group, despite no statistical difference in BP.

Type 2 diabetes with normotension and microalbuminuria

Ravid et al (1993) studied 94 normotensive microalbuminuric Type 2 diabetics, and followed them over 7 years. Enalapril at 10 mg/day protected against rise in AER (AER increased in the placebo group by 41% per year, but remained stable in the enalapril group), protected against an increase in serum creatinine (Cr increased by 3.3% per year in the placebo group but was stable in the enalapril group), and protected against progression to macroalbuminuria (seen in 18% of enalapril patients vs. 60% of placebo patients).

Ravid et al (1996) extended the above to show that ACEI slowed renal functional decline in Type 2 diabetes.

Trevison and Tiengo (1995) documented a decrease in AER with ACEI in normotensive Type 2 diabetes with microalbuminuria. Ahmad et al (1997) enrolled 103 normotensive Type 2 diabetics with microalbuminuria, treated them with enalapril or placebo, and followed them for 5 years. AER decreased in the enalapril group (55–20 microg/min), increased in the placebo group (53–85 microg/min), and progressed to overt proteinuria in 7.7% of enalapril- and 23.5% of placebo-treated patients.

Included in the meta-analysis of Lovell et al (1995) for the Cochrane Diabetes Group, as well as the Type 1 studies as discussed above, were the following studies in Type 2 diabetics – Marre et al (1988), Ravid et al (1994), Sano et al (1994), and Stornello et al (1989). Again, there is strong evidence that ACEIs decrease AER in Type 2 as well as Type 1 diabetes, but an extrapolation to postponement of ESKD requires further follow-up.

ACEI in normoalbuminuria

Recent evidence verifies earlier suggestions that ACE inhibition may prevent the onset of microalbuminuria. Some studies have included only hypertensive patients, some only normotensives, and some are mixed.

Type 1 diabetes with normotension and normoalbuminuria

The EUCLID Study (1997) followed 530 normotensive Type 1 diabetics with normal urine or microalbuminuria, and documented decrease of AER on lisinopril.

Type 2 diabetes with hypertension or normotension and normoalbuminuria

Lacourciere et al (1993) studied hypertensive Type 2 diabetics without albuminuria, documenting that captopril protected against development of microalbuminuria, but did not provide long-term renal functional data.

Ravid et al (1998) reported a RCT of 156 Type 2 diabetics with normal BP and albumin excretion, randomised to enalapril 10mg or placebo, and followed for a mean of 6 years. This study documented protection from microalbuminuria onset and minor GFR protection, although function was normal in both groups. Follow-up in this group needs to be longer.

The Benedict trial (Ruggenenti et al 2004) studied 1204 hypertensive (defined as BP > 130/80 mmHg or on antihypertensive therapy) Type 2 diabetics without albuminuria, to assess whether ACEIs and non-dihydropyridine calcium channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, Type 2 diabetes mellitus, and normal urinary albumin excretion. Patients were randomised to trandalopril 2mg (T), trandalopril 2mg plus verapamil 180 SR (T+V), Verapamil alone 240 SR (V) or placebo (P) for 3 years. The primary endpoint was the development of persistent microalbuminuria (≥ 20 mcg/min at 2 consecutive visits), and target BP was 120/80 mmHg, achieved if required via prescribed stepwise addition of drugs without RAS blockade action or nondihydropyridine calcium channel blockers. Progression to microalbuminuria occurred in 12% of Group V, and 10% of placebo patients (NS), and in 6% of each of the T alone and T+V groups (p = .01, T+V vs P). Serious adverse events were comparable in all groups. Comparable numbers of patients in each group were on statin therapy.

Summary of the evidence

A large body of Level 1 evidence, larger for Type 1 than Type 2 diabetes, supports the recommendations to treat all diabetic patients with microalbuminuria or overt nephropathy with ACEI. There is no evidence that any specific ACEI offers any advantage over the class effect.

Hypertensive diabetics without albuminuria should be treated with ACEI as first-line antihypertensive therapy (Level I evidence), and one RCT in Type 2 diabetes documents protection against development of microalbuminuria in this group.

There is currently insufficient evidence to recommend universal ACEI treatment for all diabetic patients with normal BP and AER.

There is a gap in the clinical trial evidence between decreasing AER and preventing progression to ESKD.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: Patients with diabetic kidney disease, with or without hypertension, should be treated with an ACE inhibitor or an ARB.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

JNCVII (2003): ACE inhibitors and ARBs have demonstrated favorable effects on the progression of diabetic kidney disease. An increase in serum creatinine ≤ 35% above is acceptable and not a reason to withhold treatment unless hyperkalemia develops. If glomerular filtration rate < 30 mL/min per 1.73 m_2, increasing doses of loop diuretics are usually needed in combination with other drug classes.

American Diabetic Association (2001): recommends ACEI as first-line antihypertensive agent in all hypertensive diabetic patients, and in normotensive diabetics with microalbuminuria.

American Diabetes Association (2004): In hypertensive Type 1 diabetic patients with any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. (A)
In hypertensive Type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)
If ACE inhibitors or ARBs are used, monitor serum potassium levels for the development of hyperkalemia. (B)

Canadian Diabetes Association (2003): In Type 1 diabetes and albuminuria, an ACE inhibitor should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1A).
In people with Type 2 diabetes, albuminuria, and Ccr > 60mL/min, an ACE inhibitor (Grade A, Level 1A).or an ARB (Grade A, Level 1A) should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1A).
In people with Type 2 diabetes, albuminuria, and Ccr < 60mL/min, an ARB (Grade A, Level 1A) should be given, to reduce urinary albumin and prevent progression of nephropathy (Grade A, Level 1A).
Patients placed on an ACE inhibitor or an ARB should have their Se, Sr and K levels

checked within 2 weeks of initiation of therapy and periodically thereafter (Grade D, consensus).

Suggestions for future research

Studies to determine optimal dosage of ACEI for protection against proteinuria progression and GFR reduction could be considered.

progression to macroalbuminuria (seen in 18% of enalapril patients vs. 60% of placebo patients).

Ravid et al (1996) extended the above to show that ACEI slowed renal functional decline in Type 2 diabetes.

Trevison and Tiengo (1995) documented decrease in AER with ACEI in normotensive Type 2 diabetes with microalbuminuria.

Ahmad et al (1997) 103 normotensive Type 2 diabetics with microalbuminuria treated with Enalapril or placebo, followed 5 years. AER decreased in Enalapril group (55–20), increased in placebo group (53–85), and progressed to overt proteinuria in 7.7% of Enalapril and 23.5% placebo.

Included in the meta-analysis of Lovell et al (1995) for the Cochrane Diabetes Group, as well as the Type 1 studies as discussed above, were the following studies in Type 2 diabetics – Marre et al (1988), Ravid (1994), Sano (1994), Stornello (1989). Again, there is strong evidence that ACEI decrease AER in Type 2 as well as Type 1 diabetes, but an extrapolation to postponement of ESKD requires further follow-up.

References

Agardh CD, Garcia PJ, Charbonnel B et al. Greater reduction of urinary alburmin excretion in hypertensive type 2 diabetic patients with incipient nephropathy by Lisinopril than by Nifedipine. J Hum Hypertens 1996; 10: 185–192.

Ahmad J, Siddiqui MA, Ahmad H. Effective postponement of diabetic nephropathy with enalapril in normotensive Type 2 diabetic patients with microalbuminuria. Diabetes Care 1997; 20: 1576–81.

American Diabetes Association: Standards of Medical Care in Diabetes -- Diabetes Care 2004; 27 (Supplement 1): S15–S35.

Bakris GL, Weir MR. Angiotensin –converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Int Med 2000; 160: 685–93.

Bilo H, Kluitman E, van Ballegooie E et al. Long term use of captopril or nifedipine in normotensive microalbuminuric patients with insulin-dependent diabetes mellitus. Diabetes Research 1993; 23: 115–122.

Canadian Diabetes Association. 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Available from: http://www.diabetes.ca/cpg2003/default.aspx.

Chan JC, Ko GT, Leung DH et al. Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. Kidney Int 2000; 57(2): 590-600.

Chase HP, Garg SK, Harris S et al. Angiotensin-converting enzyme inhibitor treatment for young normotensive diabetic subjects: a two-year trial. Ann Ophthamol 1993; 25: 284–9.

Chobanian AV, Bakris GL, Black HR et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report, JAMA 2003; 289: 2560–72.

Ferder L, Daccordi H, Martello M et al. Angiotensin converting enzyme inhibitors versus calcium antagonists in the treatment of diabetic hypertensive patients. Hypertension 1992; 19(Suppl 2):II237–II42.

Hallab M. Gallois Y. Chatellier G et al. Marre M. Comparison of reduction in microalbuminuria by enalapril and hydrochlorothiazide in normotensive patients with insulin dependent diabetes. BMJ 1993; 306(6871): 175–82.

Jerums G, Allen TJ, Campbell DJ et al. Long-term comparison between perindopril and nifedipine in normotensive patients with Type 1 diabetes and microalbuminuria. Am J Kidney Dis 2001; 37: 890–9.

National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002; 39(Suppl. 2): SI–S246.

Kasiske BL, Kalil RS, Ma JZ et al. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta regression analysis. Ann Intern Med 118: 129–38.

Lacourciere Y, Nadeau A, Poirier R et al. Captopril or conventional therapy in hypertensive Type 2 diabetics. Three year analysis. Hypertension 1993; 21: 786–94.

Lebovitz HE, Wiegmann TB, Cnaan A et al. Renal protective effects of enalapril in hypertensive NIDDM: Role of baseline albuminuria. Kidney Int 45(Suppl 45): S150–S55.

Lewis EJ, Hunsickeler LG, Bain RP, Rohde RD for the Collaborative Study Group:The effect of angiotension converting enzyme inhibition on diabetic nephropathy. The collaborative study group N Engl Med 1993; 329:1456–62.

Lovell HG for the Cochrane Diabetes Group. Are angioconverting enzyme inhibitors useful for normotensive diabetic patients with microalbuminuria? Cochrane Databse of Systematic Reviews 1995; Issue 2 Oxford Update Software.

Mann JF, Gerstein HC, Yi QL et al. HOPE Investigators. Progression of renal insufficiency in type 2 diabetes with and without microalbuminuria: results of the Heart Outcomes and Prevention Evaluation (HOPE) randomized study. Am J Kidney Dis 2003; 42: 936–42.

Marre M, Chatellier G, Leblanc H et al. Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. BMJ 1988; 297:1092–95.

Mathiesen ER, Hommel E, Giese J et al. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetics with microalbuminuria. BMJ 1991; 303: 81–7.

Molitch ME, De Fronzo RA, Franz MJ et al. Diabetic nephropathy. Diabetes Care. 2003 ; 26(Suppl 1): S94–S98.

Mosconi L, Ruggenenti P, Perna A et al. Nitrendipine and enalapril improve albuminuria and glomerular filtrate rate in non-insulin dependent diabetes. Kidney Int Suppl 1996; 49(Suppl 55): S91–S3.

Nielsen S Rossi Gaul Scott Schmitz A Parving. Longterm effect of lisinopril compared with atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy Diabetes 1997; 46: 1182–88.

Parving HH, Hommel E, Nielsen MD et al. Effect of captopril on blood pressure and kidney function in normotensive insulin dependent diabetics with nephropathy. BMJ 1989; 299: 533–6.

Parving HH, Rossing P. The use of anti-hypertensive agents in prevention and treatment of diabetic nephropathy. Curr Opin Nephrol Hypertens 1994; 3: 292–300.

Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1998; 128: 982–88.

Ravid M, Lang R, Rachmani R et al. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin dependent diabetes mellitus. A 7-year follow-up study. Arch Intern Med 1996; 156: 286–9.

Ravid M, Savin H, Jutrin I et al. Long term effect of ACE inhibition on development of nephropathy in diabetes mellitus type II. Kidney Int Suppl 1994; 45(Suppl 45): S161–S64.

Ravid M, Savin H, Jutrin I et al. Long-term stablizing effect of angiotensive-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive Type II diabetic patients. Ann Intern Med 1993; 118: 577–81.

Ruggenenti P; Fassi A, Ilieva AP et al. Preventing Microalbuminuria in Type 2 Diabetes The multicenter double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT). N Engl J Med 2004; 351: 1941–51.

Sano T, Hara T, Kawamura T et al. Effects of long-term enalapril treatment on persistent microalbuminuria in well-controlled hypertensive and normotensive NIDDM patients. Diabetes Care 1994; 17: 420–24.

Stornello M, Valvo EV, Scapellato L. Angiotensin converting enzyme inhibition in normotensive Type II diabetics with persistent mild proteinuria. J Hypertens 1989; 7(Suppl 6): S314–S15.

The Euclid Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. Lancet 1997; 349: 1787–92.

Trevison R, Tiengo A. Effect of low dose ramipril on microalbuminuria in normotensive or mild hypertensive non-insulin dependent diabetic patients. Am J Hypertens 1995; 8: 876–83.

Viberti G, Mogensen CE, Groop LC et al. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. JAMA 1994; 271: 275–79.

Weidmann P, Boehlen LM, De Courten M. Effects of different antihypertensive drugs on human diabetic proteinuria. Nephrol Dial Transplant 1993; 8: 582–84.

Weidmann P, Schneider M. Bohlen L. Effects of different antihypertensive drugs on human diabetic nephropathy an updated meta-analysis. Nephrol Dial Transpl 1995; 10(Suppl 9): 39–45.

Wilmer WA, Hebert LA, Lewis EJ et al. Remission of nephrotic syndrome in type 1 diabetes: long-term follow-up of patients in the Captopril Study. Am J Kidney Dis 1999; 34: 308–14.

Appendices

Table 1 Characteristics of included studies

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
Agardh et al, 1996	335	Randomised controlled clinical trial	Multicentre, multinational	314 Type 2 diabetic patients with microalbuminuria and early diabetic nephropathy	Lisinopril	Nifedipine	12 mo	
Ahmad et al, 1997	120	Randomised controlled clinical trial	Outpatient clinic	103 non-obese normotensive patients with Type 2 diabetes	Enalapril	Placebo	5 yrs	
Bilo et al, 1993	24	Randomised controlled clinical trial	5 hospitals	24 normotensive IDDM patients with albuminuria	Captopril 50 mg	Placebo	1 yr	Third arm intervention 20 mg nifedipine retard
Chan et al, 2000	102	Randomised controlled clinical trial	University hospital	102 hypertensive Type 2 diabetes patients	Enalapril	Nifedipine	5.5 yrs	
Chase et al, 1993		Randomised controlled clinical trial	University hospital	16 Type 1 diabetics with diabetic nephropathy and normal BP	Captopril BID	Placebo	2 yrs	
EUCLID 1997	530	Randomised controlled clinical trial	18 European centres	530 IDDM with normo- or microalbuminuria	Lisinopril	Placebo	2 yrs	
Ferder et al, 1992	30	Randomised controlled clinical trial	Hospital	30 Type 2 diabetic patients with proteinuria	Enalapril	Nifedipine	12 mo	
Hallab et al, 1993	25	Randomised controlled clinical trial	Diabetic clinic in a tertiary referral centre	21 diabetic patients with low/ high albuminuria	Enalapril 20 mg	Hydrochlorothiazaide	1 yr	
Jerums et al, 2001	42	Randomised controlled clinical trial	5 hospitals	42 normotensive patients with Type 1 diabetes and microalbuminuria	Perindopri	Placebo	2 yrs	Third arm intervention nifedipine
Laffel et al, 1995	143	Randomised controlled clinical trial	26 centres; US and Canada	143 normotensive patients with IDDM	Captopril 50 mg	Placebo	24 mo	
Lebovitz et al, 1994	165	Randomised controlled clinical trial	Multicentre	121 NIDDM patients with hypertension	Enalapril	Placebo	3 yrs	
Lewis et al, 1993	409	Randomised controlled clinical trial	30 clinical centres	409 IDDM patients with urinary protein excretion $\geq$ 55 mg/d;	Captopril	Placebo	3 yrs	

				serum Cr ≤ 2.5 mg/dl				
Mosconi et al, 1996	13	Randomised controlled clinical trial	Hospital, Italy	13 microalbuminuric NIDDM patients with mild hypertension and diabetic glomerulopathy	Nitrendipine	Enalapril	27 mo	
Mathiesen et al, 1991	44	Randomised controlled clinical trial	Outpatient clinic	44 normotensive IDDM patients with persistent microalbuminuria	Captopril	No treatment	4 yrs	
Nielson et al, 1997	43	Randomised controlled clinical trial	Hospital	36 hypertensive NIDDM patients with diabetic nephropathy	Lisinopril	Atenolol	42 mo	
Ravid et al, 1998	156	Randomised controlled clinical trial	8 outpatient clinics	94 normotensive Type 2 diabetics with microalbuminuria	Enalapril	Placebo	6 yrs	
Ruggenenti et al, 2004	1204	Randomised controlled clinical trial	Multicentre	1204 Type 2 diabetics, hypertension with normal urinary albumin excretion	Trandolapril and verapamil	Placebo	3 yrs	Third arm intervention = trandopril; Fourth arm intervention = verapami
Sano et al, 1994	52	Randomised controlled clinical trial	Hospital	52 normotensive non-IDDM with normal renal function, persistent microalbuminuria	Enalapril	No treatment	4 yrs	
Stornello et al, 1989	16	Randomised controlled clinical trial	Diabetic clinic	16 normotensive Type 2 diabetics with persistent proteinuria	Enalapril	Placebo	1 yr	
Viberti et al, 1994	92	Randomised controlled clinical trial	12 hospital based diabetes centres	92 normotensive IDDM patients with albuminuria	Captopril	Placebo	2 yrs	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
Agardh et al, 1996	Central	Yes	Yes	Unclear	No	Unclear
Ahmad et al, 1997	Not specified	Yes	No	No	Unclear	12.6
Bilo et al, 1993	Not specified	Yes	Yes	Unclear	No	25.0
Chan et al, 2000	Not specified	Yes	Yes	Unclear	Yes	0.0
Chase et al, 1993	Not specified	Yes	Yes	Unclear	Unclear	0.0
EUCLID 1997	Central	Yes	Yes	Yes	Yes	7.5
Ferder et al, 1992	Not specifed	Yes	Yes	Unclear	Unclear	0.0
Hallab et al, 1993	Computer-generated	Yes	Yes	Unclear	Yes	16.0
Jerums et al, 2001	Third party (pharmacy)	No	Yes	No	Yes	9.5
Laffel et al, 1995	Block randomisation	Yes	Yes	Unclear	Yes	13.3
Lebovitz et al, 1994	Not specified	Yes	Yes	Unclear	No	18.9
Lewis et al, 1993	Standard urn design	Yes	Yes	Yes	Yes	14.2
Mosconi et al, 1996	Not specified	Yes	Yes	Unclear	No	18.8
Mathiesen et al, 1991	Not specified	No	No	Unclear	Yes	0.0
Nielson et al, 1997	Not specified	Yes	Yes	Unclear	Yes	16.3
Ravid et al, 1998	Central	Yes	Yes	Unclear	No	19.6
Ruggenenti et	Not specified	Yes	Yes	Yes	Yes	Unclear

al, 2004						
Sano et al, 1994	Not specified	No	No	No	No	7.8
Stornello et al, 1989	Not specified	Yes	Yes	Unclear	Unclear	0.0
Viberti et al, 1994	Block randomisation	Yes	Yes	Unclear	Yes	7.6

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Agardh et al, 1996	Abdominal Complaints	19/156	19/158	1.01 (95%CI: 0.56, 1.84)	0.00 (95%CI: -0.07, 0.07)
	Dizziness	14/156	12/158	1.18 (95%CI: 0.56, 2.47)	0.01 (95%CI: -0.05, 0.07)
Ahmad et al, 1997	Albuminuria	4/52	12/51	0.33 (95%CI: 0.11, 0.95)	-0.16 (95%CI: -0.30, -0.02)
Chan et al, 2000	Renal events	6/50	5/52	1.25 (95%CI: 0.41, 3.83)	0.00 (95%CI: -0.11, 3.83)
	Reversion to normoalbuminuria	12/50	8/52	1.56 (95%CI: 0.70, 3.49)	0.09 (95%CI: -0.07, 0.24)
	Development of microalbuminuria	10/50	16/52	0.65 (95%CI: 0.33, 1.29)	-0.11 (95%CI: -0.28, 0.06)
Chase et al, 1993	Decrease in Hb > 10%	4/7	3/9	1.71 (95%CI: 0.56, 5.28)	0.24 (95%CI: -0.24, 0.72)
	Worsened retinal grade	1/7	4/9	0.32 (95%CI: -0.72, 0.11)	-0.30 (95%CI: -0.72, 0.11)
	Improved retinal grade	2/7	0/9	6.25 (95%CI: 0.35, 112.52)	0.29 (95%CI: -0.06, 0.63)
EUCLID 1997	AER greater or equal to 20 µg/mL	13/213	18/227	0.77 (95%CI: 0.39, 1.53)	-0.02 (95%CI: -0.07, 0.03)
	Hypoglycaemia	12/265	8/265	1.50 (95%CI: 0.62, 3.61)	0.02 (95%CI: -0.02, 0.05)
Jerums et al, 2001	**Perindopril group:**				
	Regression to normoalbuminuria	7/13	0/10	11.79 (95%CI: 0.75, 184.66)	0.54 (95%CI: 0.25, 0.83)

	Microalbuminura	5/13	7/10	0.55 (95%CI: 0.25, 1.22)	-0.32 (95%CI: -0.70, 0.07)
	Progression to macroalbuminuria	1/13	3/10	0.26 (95%CI: 0.03, 2.11)	-0.22 (95%CI: -0.54, 0.10)
	Nifedipine group:				
	Regression to normoalbuminuria	0/10	0/10	Not estimable	0.00 (95%CI: -0.17, 0.17)
	Microalbuminura	6/10	7/10	0.86 (95%CI: 0.45, 1.64)	-0.10 (95%CI: -0.52, 0.32)
	Progression to macroalbuminuria	4/10	3/10	1.33 (95%CI: 0.40, 4.49)	0.10 (95%CI: -0.32, 0.52)
	Laffel et al, 1995 Progression to clinical proteinuria	4/67	13/70	0.32 (95%CI: 0.11, 0.94)	-0.13 (95%CI: -0.23, -0.02)
	Progression to hypertension	2/70	8/73	0.26 (95%CI: 0.06, 1.19)	-0.08 (95%CI: -0.16, 0.00)
	Neutropaenia	1/70	0/73	3.13 (95%CI: 0.13, 75.49)	0.01 (95%CI: -0.02, 0.05)
Lebovitz et al, 1994	Progression to clinical albuminuria	2/30	8/38	0.32 (95%CI: 0.07, 1.38)	-0.14 (95%CI: -0.30, 0.01)
Lewis et al, 1993	Death	8/207	14/202	0.56 (95%CI: 0.24, 1.30)	-0.03 (95%CI: -0.07, 0.01)
	Doubling of serum creatinine	25/207	43/202	0.57 (95%CI: 0.36, 0.89)	-0.09 (95%CI: -0.16, -0.02)
	Neutropaenia	1/207	1/202	0.98 (95%CI: 0.06, 15.50)	0.00 (95%CI: -0.01, 0.01)
	Hyperkalaemia	3/207	0/202	6.83 (95%CI: 0.36, 131.43)	0.01 (95%CI: 0.00, 0.03)
Mosconi et al, 1996	Normoalbuminuria	4/7	4/6	0.86 (95%CI: 0.36, 2.02)	-0.10 (95%CI: -0.62, 0.43)
Nielsen et al, 1997	Headache	4/17	4/19	1.12 (95%CI: 0.33, 3.79)	0.02 (95%CI: -0.25, 0.30)
	Dizziness	4/17	4/19	1.12 (95%CI: 0.33, 3.79)	0.02 (95%CI: -0.25, 0.30)
	Depression	2/17	5/19	0.45 (95%CI: 0.10, 2.01)	-0.15 (95%CI: -0.40, 0.10)
	Impotency	10/17	19/19	0.59 (95%CI: 0.40, 0.88)	-0.41 (95%CI: -0.65, -0.17)
Ravid et al,	Retinopathy at	12/77	20/79	0.62 (95%CI: 0.32, 1.17)	-0.10 (95%CI: -0.22, 0.03)

1998	6 yrs				
	Microalbuminuria	5/77	15/79	0.34 (95%CI: 0.13, 0.90)	-0.12 (95%CI: -0.23, -0.02)
Ruggenenti et al, 2004	**Trandolapril + verapamil group:**				
	Persistent microalbuminuria	17/300	30/300	0.57 (95%CI: 0.32, 1.01)	-0.04 (95%CI: -0.09, 0.00)
	CV death	0/300	3/300	0.14 (95%CI: 0.01, 2.75)	-0.01 (95%CI: -0.02, 0.00)
	Trandolapril alone:				
	Persistent microalbuminuria	18/301	30/300	0.60 (95%CI: 0.34, 1.05)	-0.04 (95%CI: -0.08, 0.00)
	CV death	1/301	3/300	0.33 (95%CI: 0.03, 3.18)	-0.01 (95%CI: -0.02, 0.01)
	Verapamil alone:				
	Persistent microalbuminuria	36/303	30/300	1.19 (95%CI: 0.75, 1.88)	0.02 (95%CI: -0.03, 0.07)
	CV death	1/303	3/300	0.33 (95%CI: 0.03, 3.15)	-0.01 (95%CI: -0.02, 0.01)
Viberti et al, 1994	Clinical proteinuria	4/46	12/46	0.33 (95%CI: 0.12, 0.96)	-0.17 (95%CI: -0.32, -0.02)