

**Evidence Tables**

**ACE 1: Are ACE inhibitors (alone or in combination) effective in the lowering of blood pressure and or reduction of cardiovascular disease compared with other treatments in people with type 2 diabetes?**

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Strippoli GF, Bonifati C, Craig M et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. <i>Cochrane Database Syst Rev.</i> 2006;(4):CD006257. Ref ID: 3659	Systematic review – Cochrane  Search completed up to December 2005  1++	N=50 studies (N=13,215)  N=38 ACE vs. placebo  N=5 ARB vs. placebo  N=7 ACE vs. ARB	Inclusion: RCTs of at least 6 months duration in patients with diabetic kidney disease, independent of the stage of nephropathy.  Types of intervention: ACE or ARB vs. placebo, head-to-head comparisons of ACE vs. ARB			At least 6 mths	All-cause mortality, Progression to ESKD, Doubling of serum creatinine, progression from micro-macroalbuminuria, regression from micro-normoalbuminuria, toxicity	All CI 95% There was no significant study heterogeneity throughout the systematic review.  *All-cause mortality ACE VS. placebo/no treatment There was NS decrease in the risk of all-cause mortality with ACE compared with placebo/no treatment (21 studies, N=7295). A subgroup analysis of studies which used ACE at the maximum tolerable dose compared with placebo/no treatment, there was a significant decrease in the risk of all-cause mortality (5 studies, N=2034m RR 0.78, 0.61 to 0.98). This was not found in studies using half or less than half of the maximum tolerable dose of these agents (4 studies, N=5261).  ARB vs. placebo/no treatment NS reduction in the risk of all-cause mortality was found (5 studies, N=3409).  ACE vs. ARB NS reduction in all-cause mortality was found in comparing ACE vs. ARB (3	

								<p>studies, N=307).</p> <p><b>*ESRD</b>  ACE vs. placebo/no treatment  There was a significant reduction in the risk of ESKD with ACE compared with placebo/no treatment (10 studies, N=6819, RR 0.68, 0.39 to 0.93).</p> <p>ARB vs. placebo/no treatment  There was a significant reduction in the risk of ESRD with ARB vs. placebo/no treatment (3 studies, N=3251, RR 0.78, 0.67 to 0.91).</p> <p><b>*Doubling of serum creatinine</b>  There was a significant reduction in the risk of the doubling of serum creatinine with ARB compared with placebo/no treatment (3 studies, N=3251, RR 0.79, 0.67 to 0.93).</p> <p><b>*ACE vs. ARB</b>  This outcomes were not reported in these studies</p> <p><b>*Progression from micro to macroalbuminuria</b>  ACE vs. placebo/no treatment  ACE significantly reduced the risk of progression (17 studies, N=2036, RR 0.49, 0.29 to 0.69).</p> <p>ARB vs. placebo/ no treatment  ARB significantly reduced the risk of progression from micro to macroalbuminuria (3 studies, N=761, RR 0.49, 0.32 to 0.75).</p>	
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								<p>ACE vs. ARB This was reported in one study (N=41) and there was NS reduction in the progression of albuminuria.</p> <p>*Regression from micro to normoalbuminuria ACE vs. placebo/no treatment ACE significantly increased regression compared to placebo/no treatment (16 studies, N=1910, RR 3.06, 1.76 to 5.35).</p> <p>ARB vs. placebo/no treatment ARB significantly increased regression compared with placebo/no treatment (2 studies, N=670, RR 1.42, 1.05 to 1.93).</p> <p>ACE vs. ARB There was NS difference in the regression (2 studies, N=194).</p> <p>*Toxicity - cough ACE vs. placebo/no treatment ACE was associated with a significant increase in the risk of cough (10 studies, N=7087, RR 3.17, 2.29 to 4.38).</p> <p>ARB vs. placebo/no treatment There was NS difference (2 studies, N=194)</p> <p>ACE vs. ARB There was NS difference (2 studies, N=90)</p> <p>Toxicity – hyperkalaemia ACE vs. placebo/no treatment</p>	
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								<p>There was NS difference (2 studies, N=1219).</p> <p>ARB vs. placebo/no treatment There was a significant increase in the risk of hyperkalaemia with ARB compared with placebo/no treatment (2 studies, N=2287, RR 5.41, 1.87 to 15.65).</p> <p>ACE vs. ARB Not reported</p> <p>Toxicity – headache ACE vs. placebo/no treatment There was NS difference (4 studies, N=6196).</p> <p>ARB vs. placebo/no treatment There was NS difference (1 study, N=91).</p> <p>ACE vs. ARB Not reported.</p>
<p>Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. <i>Cochrane Database Syst Rev.</i> 2005;(4):CD004136.</p>	<p>Systematic review - Cochrane  1++</p>	<p>N=16 trials (N=7,603)  N=6 ACE vs. placebo N=6 ACE vs. CCB N=1 ACE vs. CCB or combined ACE+CCB</p>	<p>Inclusion: RCTs and quasi-RCTs<sup>1</sup> which had evaluated the effect of any antihypertensive agent administered to diabetic patients without kidney disease.  Types of intervention – any antihypertensive agents (compared to</p>					<p>All CI 95%</p> <p>ACE vs. placebo/no treatment *Risk of development of microalbuminuria ACE significantly reduced the risk of development of microalbuminuria compared with placebo/no treatment (6 trials, N=3480 participants; RR 0.60; 95%CI 0.43 to 0.84), with no significant heterogeneity in this analysis.</p>

<sup>1</sup> RCTs in which allocation to treatment was obtained by alternation, use of alternative medical records, date of birth or other predictable methods

Ref ID: 3660		N=3 ACE vs. other agents	<p>placebo, no treatment or other antihypertensive agent) for preventing diabetic kidney disease, irrespective of class, administered at any dose and for a duration of at least six months.</p> <p>Exclusion: the major reasons for exclusion were a non-randomised design, non-antihypertensive interventions, non-diabetic study populations, diabetic patients with established kidney disease, and duplicate populations.</p>					<p>A test of interaction did not demonstrate any difference in the effect of ACE vs. placebo in hypertensive and non-hypertensive participants, type 1 and type 2 diabetes and normal and abnormal renal function.</p> <p>*Doubling of creatinine There was NS difference in the risk of doubling of creatinine with ACE compared with placebo (3 trials, N=2683).</p> <p>*All-cause mortality The risk of all-cause mortality was NS difference with ACE compared with placebo (3 trials, N=2683).</p> <p>*Cough The risk of cough was significantly increased with ACE compared with placebo/no treatment (4 trials, N=3725, RR 1.79, 1.19 to 2.69).</p> <p>ACE vs. CCB *Development of kidney disease (micro or macroalbuminuria) There was a significant decrease in the risk of developing kidney disease with ACE vs. CCB (4 trials, N=1210, RR 0.58, 0.40 to 0.84).</p> <p>*All-cause mortality There was NS difference in the risk of all-cause mortality with ACE vs. CCB (6 trials, N=1286) and no data given on other cardiovascular end points.</p> <p>ACE vs. other agents</p>	
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								One trial (N=229) was considered which showed NS difference in the risk of developing kidney disease with ACE compared with $\beta$ -blockers.	
Fernandez R, Puig JG, Rodriguez PJ et al. Effect of two antihypertensive combinations on metabolic control in type-2 diabetic hypertensive patients with albuminuria: a randomised, double-blind study. <i>Journal of Human Hypertension</i> . 2001; 15(12):849-856. Ref ID: 3473	RCT, double-blind  1++	N=120 for 4-week run-in  N=103 randomised to main study  N=97 ITT	Inclusion: T2D, taking antihypertensive therapy with one single drug, a sitting SBP $\geq 140$ mmHg and/or DBP $\geq 90$ mmHg and stable albuminuria within a non-nephrotic range (30-3000mg/d) <sup>2</sup> .  Exclusion: secondary hypertension without pharmacological treatment or taking a combination of two or more antihypertensive drugs, CHF, serum creatinine >3mg/dl, known hypersensitivity or intolerance to ACE inhibitors or calcium channel blockers.	N=51 verapamil 180mg + trandopril 2mg  Following a 4-week single blind, period	N=52 enalapril 20mg + hydrochlorotiazide 12.5mg	6 months	BP (casual and ambulatory), albuminuria, HbA1c	*Casual BP SBP and DBP were reduced with both treatments, this was NS between the treatments  *Ambulatory BP 24-h SBP and DBP were reduced with both treatments, NS difference between the groups.  *Albuminuria Both treatments reduced albuminuria (estimated mean with verapamil/trandopril 210.4(94.8 to 326.1, 95% CI), enalapril/hydrochlorothiazide 302.9 (183.6 to 422.2, 95% CI). NS between the groups.  *HbA1c Mean values did not change with verapamil/trandopril from baseline 5.91 $\pm$ 1.43% to end of treatment 5.94 $\pm$ 1.62%. With enalapril/hydrochlorothiazide HbA1c increased from baseline 5.96 $\pm$ 1.25% to final 6.41 $\pm$ 1.51%. Difference between groups was p=0.040  *Mean blood glucose Crude blood glucose changes were	Laboratories Knoll

<sup>2</sup> Before entering the study, the metabolic control recommendation was HbA1c

			-					<p>23±69mg/dl for verapamil/trandopril (16.8% reduction) and 1±32mg/dl (0.8%reduction) with enalapril/hydrochlorothiazide. The percentage of participants with glycaemic control (blood glucose &lt;126mg/dl) increased from 50% to 72% on week 24 with verapamil/trandopril, but did not change with enalapril/hydrochlorothiazide (47.7% to 50% at week 24).</p> <p>*Discontinuation N=10 participants did not complete the study</p> <p>*Adverse events Reported AEs were mild/moderate. N=2 (N=1 in each treatment group), had oedema</p>	
Holzgreve H, Nakov R, Beck K et al. Antihypertensive therapy with verapamil SR plus trandolapril versus atenolol plus chlorthalidone on glycemic control. <i>American Journal of Hypertension</i> . 2003;	RCT, double-blind  1++	N=463 (N=450 included in ITT analysis)  (94 GP offices, 5 European countries)	Inclusion: 40-80yrs, non-insulin dependent T2D, mild-to-moderate hypertension (seated BP of either ≥95 and ≤114mmHg diastolic and ≤200mmHg systolic, or ≤94mmHg diastolic and ≥160 and ≤200mmHg systolic), stable antidiabetic therapy for ≥3mths	N=243 verapamil SR 180mg + trandopril 1mg <sup>4</sup>  If after 4 weeks diastolic BP was	N=229 atenolol 50mg + chlorthalidone 12.5mg	20 weeks treatment after 2 week run-in	Primary end point HbA1c, secondary efficacy measures were the change in sitting systolic and diastolic BP after 4 and 20 weeks of	<p>*HbA1c The HbA1c in the verapamil SR + trandopril remains stable (7.9 (1.17) at baseline, 7.9 (1.42) at last visit). The HbA1c increases with atenolol + chlorthalidone (7.8 (1.26) at baseline, 8.6(1.77) at last visit). The treatment difference was (95%CI) -0.79 (-1.04 to -0.54), p=0.0001.</p> <p>*Glycaemic control Fasting glucose and fructosamine</p>	Not stated

<sup>3</sup> Diet and antidiabetic medications were kept constant where possible through the study

<sup>4</sup> Participants had a 2 week placebo run-in period without any antihypertensive treatment

<p>16(5:Pt 1):381-386. Ref ID: 3469</p>			<p>before enrolment, HbA1c <math>\geq 6.5</math> and <math>\leq 10\%</math>.</p> <p>Exclusion: contraindications for the 4 study medications, T1D or insulin dependent T2D, concomitant medication with other antihypertensives, systolic BP <math>&gt; 200</math>mmHg, cerebrovascular ischaemia within the last 6 mths or MI within the last 3 mths, a history of hypersensitivity to the study medications.</p> <p>The groups were well balanced with regard to most demographic and other baseline values.<sup>3</sup></p>	<p><math>\geq 90</math>mmHg or systolic BP was <math>\geq 150</math>mmHg, participants were given verapamil 180mg + trandopril 2mg or atenolo 100mg + chlorthalidone 25mg</p>			<p>treatment, the proportions of patients achieving normal BP or responding to antihypertensive treatment</p>	<p>remained stable with verapamil SR + trandopril, whereas an increase was observed with atenolol + chlorthalidone. The treatment difference was (95%CI) -1.17 (-1.64 to -0.70), <math>p=0.0001</math>.</p> <p>*BP control BP was significantly reduced in both groups. Comparing the groups showed a difference of 4.85mmHg systolic (95% CI, 1.94 to 7.76, <math>p=0.0011</math>) and of 1.79mmHg diastolic (95% CI, 0.26 to 3.32, <math>p=0.0222</math>) favouring atenolol + chlorthalidone. Normal BP was achieved by 65% and 70% of participants, NS between the groups.</p> <p>*Discontinuation N=20 discontinued in the verapamil SR + trandopril N=25 discontinued in the atenolol + chlorthalidone For N=33 withdrawal was considered to be related to treatment adverse events: verapamil SR + trandopril (N=8 adverse events; N=3 progression of diabetes; N=3 unsatisfactory therapeutic response) and; atenolol + chlorthalidone (N=11 adverse events; N=4 progression of diabetes; N=4 unsatisfactory therapeutic response).</p> <p>21 adverse events (6%) in each group were judged to be severe.</p>	
<p>Barnett AH, Bain</p>	<p>RCT, double-</p>	<p>N=250, 39 centres</p>	<p>Inclusion: 35-80yrs, T2D, treated by diet,</p>	<p>N=120 telmisartan</p>	<p>N=130 enalapril</p>	<p>5 years</p>	<p>Primary: changes in</p>	<p>*GFR (after 5yrs) Mean changes in GFR -</p>	<p>Boehringer</p>

<p>SC, Bouter P et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy.[see comment][erratum appears in N Engl J Med. 2005 Apr 21;352(16)1731]. <i>New England Journal of Medicine</i>. 2004; 351(19):1952-1961. Ref ID: 368</p>	<p>blind 1+</p>	<p>N.Europe</p>	<p>diet or oral hypoglycaemic drugs (for at least 1yr), or insulin preceded by treatment with oral agents (for at least 1yr), among those taking insulin onset had to have occurred after the age of 40, BMI&gt;25, mild-to-moderate hypertension, resting BP&lt;180/95 after at least 3mths of ACE therapy, normal renal morphology, UAE (mean of 3 consecutive O/Nvalues) between 11-999µg/min with 2 values &gt;10µg/min, HbA1c &lt;12%, serum creatinine level below 1.6mg/dl, GFR&gt;70ml/min/1.73m2 body surface area</p> <p>Exclusion: any condition that could restrict long-term survival and known allergy to study drugs.</p> <p>The baseline characteristics of the N=250 were similar in the two treatment groups.</p>	<p>80mg (following 1mth of 40mg)</p> <p>Additional hypertensive medication (not an ACE or ARB) was allowed after 2mths if the resting SBP&gt;160 or restign DBP&gt;100m mHg. The target BP was initially less than 160/90 but lower targets were subsequentl y allowed as local or national guidelines changes during the study.</p>	<p>20mg (following 1mth of 10mg)</p>		<p>GFR after 5yrs Secondary: annual changes in GFR, UAE, serum creatinine level, BP, rates of clinical events, rate of death, adverse events</p>	<p>17.9ml/min/1.73m2 (telmisartan) compared with -14.9ml/min/1.73m2 (enalapril), treatment difference -3.0 (95%CI). The lower boundary of -7.6 in favour of enalapril was greater than the pre-deined level of -10.0 indicating that telmisartan was not inferior to enalapril.</p> <p>*Annual changes in GFR The rates of decrease in GFR (yrs 1,2,3 was -7.6, -5.6 and -3.6ml/min/1.73m2, changes were negible in yrs 4 and 5) were similar in the 2 groups.</p> <p>*Annual changes in UAE Annual changes in UAE in both groups were small, with large CIs</p> <p>*Serum creatinine Changes were NS between the groups</p> <p>*% changes in UAE Changes were NS between the groups</p> <p>*BP Reduction in BP between the groups was NS</p> <p>*Discontinuation N=20 (telmisartan) and N=30 (enalapril) had AEs which resulted in withdrawal from the study. A further N=32 (N=18 telmisartan; N=14 enalapril) withdrew for other reasons</p> <p>*Adverse events In each group there were N=6 strokes, and N=2 cases of raised serum creatinine. There were N=6 deaths in</p>	<p>Ingelheim</p>
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								each group. Telmisartan group (N=9 CHF, N=9 nonfatal MIs). Enalapril group (N=7 CHF, N=6 nonfatal MIs).	
Bosch J. Long-term effects of ramipril on cardiovascular events and on diabetes: results of the HOPE study extension. Circulation 2005; 112(9):1339-1346. Ref ID: 3617	Extension of HOPE  1+	N=4,528 (from original study N=9,297)  174 centres (from original 267 centres)	As for the HOPE trial	N=2317 originally randomised to ramipril	N=2211 originally randomised to placebo	2.6yrs study extension (median duration of follow-up total 7.2yrs)		<p>*BP At the end of the extended follow-up the mean BP in the two groups was similar</p> <p>*Major CV events There was a NS trend towards a further reduction in major CV events and reduction in risk of MI which is similar to that found in the first 4.5yrs of HOPE. There was no difference in stroke or CV death.</p> <p>During the entire 7.2yrs of follow-up (since original randomisation) there was a significant risk reduction with ramipril for the outcomes of MI, stroke, and CV death. There were also fewer participants with MIs in the ramipril group, fewer strokes and fewer CV deaths.</p> <p>*Other cardiac outcomes There were significantly fewer revascularisations with ramipril vs. placebo in the 2.6yrs extension; 235 (9.1%) vs. 259 (10.5%), RR 0.84 (95% CI, 0.70 to 0.99). Results were NS for MI, stroke or CV death; MI; stroke; CV death.</p> <p>*New diabetes In the extension phase there was a significant further reduction in risk for</p>	

								diabetes for the ramipril group N=48(2.7%) vs. placebo N=70 (4.0%); RR 0.66 (CI 95%), 0.46 to 0.95.	
Casas JP, Chua W, Loukogeorgakis S et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis.[see comment]. [Review] [34 refs]. <i>Lancet</i> . 2005; 366(9502):2026-2033. Ref ID: 3628	Systematic review and meta-analysis  Search from 1960 to January 2005  1+	N=127 studies corresponding to 150 group comparisons (99 used trials including participants only with diabetes, 36 participants without diabetes, 10 included both types of participants, 5 did not report presence or absence of diabetes).	Inclusion: studies had to be randomised, controlled, parallel-design in adults, and examine the effect of drug treatment with a blood-pressure-lowering action on progression of renal disease. Progression of renal disease was assessed by use of incident renal endpoints as primary outcomes (doubling of serum creatinine and end-stage renal disease, defined as the need for kidney transplantation or haemodialysis) and secondary continuous markers (GFR, serum creatinine, and urine albumin excretion). Studies had to have a minimum follow-up of 1 year.	The effect of drug treatment with a blood-pressure lowering action on progression of renal disease		Weighted mean follow-up of 4.2 years, minimum of 1yr		All CI 95%  *End stage renal disease (ESKD) <sup>5</sup> There was a reduction in the occurrence of ESKD compared with other antihypertensives (13 trials (N=37,089, RR 0.87, 0.75 to 0.99, p=0.04). For studies including participants with diabetes (4 trials, N=14,437) there was NS difference between ACE or ARB compared with other antihypertensives.  * Doubling of creatinine <sup>6</sup> There was NS reduction in the risk of doubling serum creatinine with ACE or ARBs compared other active interventions (11 trials, N=3376). This was NS difference also found for the studies including participants with diabetes (6 trials, N=3044).  *Serum creatinine ACE or ARB showed a small reduction in creatinine concentration compared with other agents (38 trials, N=5711, RR -7.07, -13.26 to 0.88, p=0.01). <sup>7</sup>	

<sup>5</sup> There was no significant study heterogeneity

<sup>6</sup> There was no significant study heterogeneity

<sup>7</sup> Some small study bias (p=0.07) and interstudy heterogeneity (p<0.0001) was indicated

<sup>8</sup> Small-study bias (p=0.001) and significant study heterogeneity (p,0.0001)

<sup>9</sup> No significant heterogeneity or small-study bias

								<p>There was NS difference between ACE or ARBs and other treatments in the studies with diabetic participants (18 trials, N=4315).</p> <p>*Urine albumin excretion ACE or ARBs showed a small reduction in urine albumin excretion compared with other treatments (44 trials, N=5266, RR -15.73, -24.72 to -6.74, p=0.001).<sup>8</sup> In participants with diabetes a small reduction in urine albumin excretion was noted for ACE or ARBs compared with other treatments (34 trials, N=4772, RR -12.68, -21.68 to -2.74).</p> <p>*GFR ACE or ARBs had NS difference on GFR than other antihypertensive treatments for both all studies (61 trials, N=39,485)<sup>9</sup> and also for participants with diabetes (37 studies, N=15,742).</p>	
Dalla VM, Pozza G, Mosca A et al. Effect of lercanidipine compared with ramipril on albumin excretion rate in hypertensive Type 2 diabetic patients with microalbuminuria: DIAL study (diabete, ipertensione,	RCT, double-blind  1+	N=226, 97 excluded during the run-in, N=180 randomised  19 centres in Italy	Inclusion: 40-70yrs, T2D, mild-to-moderate hypertension (mena DBP bwtween 85-109mmHg abd SBP<180mmHg), persistent microalbuminuria (AER 20-200µg/min during the last 3 mths)  Exclusion: arterial hypertension outside	N=91 lercanidipine 10mg/d  After 6 wks the dose of both treatments was doubled in subjects who did not reach the	N=89 ramipril 5mg/d	36-52 weeks	Primary outcome – change in AER Secondary endpoints – restoration of normoalbuminuria (AER<20µg/min), reduction or	*Change in AER Baseline AER differed significantly (p<0.05) between the two treatment groups (86.5±54.5µg/min for lercanidipine group and 66.9±42.4µg/min for ramipril group), at endpoint AER values were similar (69.0±73.9µg/min, reduction of -17.4±65µg/min lercanidipine and 47.2±65.2µg/min, reduction of -19.7±52.5µg/min ramipril), there was not differences between the groups. Using 90%CI the difference between	Not stated

<p>albuminuria, lercanidipina).  <i>Diabetes, Nutrition &amp; Metabolism - Clinical &amp; Experimental.</i>  2004; 17(5):259-266.  Ref ID: 3610</p>			<p>the range in the inclusion criteria, secondary arterial hypertension, orthostatic hypotension (SBP decrease &gt;20mmHg after standing for 2 min), AER &lt;20µg/min, ≥200µg/min not persistent, &gt;200µg/min, HbA1c &gt;10%, cardiac insufficiencies, other cardiac conditions, acute MI or CVA 3 mths prior to recruitment, transaminases &gt;2 times the normal limit, serum creatinine &gt;141.4µmol/l, anaemia, hypertensive retinopathy, obesity, known hypersensitivity to study drugs.</p> <p>Characteristics were similar at baseline</p>	<p>target for DBP (DBP &lt;85mm Hg).</p> <p>After 10 wks hydrochlorothiazide 25mg was added for those with DBP ≥85mmHg.</p> <p>After 14 wks atenolol 50mg was added in the not-normalised participants.</p>			<p>increase in AER ≥50% compared with baseline values, and the progression to macroalbuminuria (AER &gt;200µg/min), reduction in DBP and SBP</p>	<p>the reduction in AER observed was -14.9 (lercanidipine) and -19.4, thus the upper limit (19.4µg/min) does not exceed 21µg/min that was considered clinically significant.</p> <p>*Secondary outcomes  The percentage of participants who progressed from microalbuminuria to proteinuria and who reverted to normoalbuminuria showed no difference between the groups.  N=21(32.8%) lercanidipine and N=28 (42.4%) ramipril reverted to normoalbuminuria.  N=5(7.8%) lercanidipine and N=2 (3%) ramipril progressed to macroalbuminuria.</p> <p>The proportion of participants who had a reduction in AER &gt;50% was 34.2% in the lercanidipine and 22.2% in the ramipril group.</p> <p>BP levels at baseline were similar in the two groups. Significant reductions in SBP and DBP were observed in both groups.  N=45 (70.3%) lercanidipine and N=51 (77.3%) were considered normalised (DBP &lt;85mmHg) at end point, NS between the groups.</p> <p>*Supplementary medication  Of the lercanidipine group 35 participants required 20mg/d lercanidipine, 21 hydrochlorothiazide and 3 atenolol.  Of the ramipril group 31 participants</p>	
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								<p>required 10mg/d ramipril, 19 hydrochlorothiazide and 7 atenolol.</p> <p>*Discontinuation N=33 discontinued (N=11 for adverse events)</p> <p>*Adverse events 28.6% in the lercanidipine and 22.5% in the ramipril group experienced AEs. N=8 (8.8%) lercanidipine and N=5 (5.6%) ramipril had AEs considered to be study related. Lercanidipine (N=2 hypotension; N=1 ankle oedema and LVF; N=2 tachycardia; N=2 headache; N=1 epigastralgia and asthenia) Ramipril (N=3 cough; N=1 hypotension; N=1 worsened peptic ulcer)</p>
<p>Fogari R, Preti P, Zoppi A et al. Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. <i>American Journal of Hypertension</i>. 2002; 15(12):1042-1049. Ref ID: 3472</p>	<p>RCT, open-label, multicentre  1+</p>	<p>N=453 titrating phase  N=309 full trial</p>	<p>Inclusion: essential hypertension, T2D (well controlled by diet or metformin or metformin and sulfonylurea), sitting DBP&gt;90mmHg and &lt;110mmHg, UAE ≥30 and ≤300mg/24hin two distinct 24h urine collections, BMI &lt;30kg/m2, serum creatinine &lt;1.5mg/dl.  Exclusion: history of</p>	<p><sup>10</sup> N=103 amlodipine  N=102 fosinopril  Treatment was continued at the dose being taken</p>	<p>N=104 amlodipine+f osinopril</p>	<p>4 years following 3mth titration phase and 4-week placebo wash-out</p>	<p>BP, UAE, creatinine clearance, body weight, HbA1c</p>	<p>*Sitting BP Fosinopril and amlodipine had similar reductions in SBP and DBP, at 48mths mean decrease in BP 17.2/11.8 (fosinopril) and 19.9/12.8 (amlodipine)(p&lt;0.001 vs. placebo). Combination therapy had a reduction in BP of 28.7/17.1 (p&lt;0.001 vs. placebo, p&lt;0.01 vs. fosinopril and amlodipine).</p> <p>*UAE Fosinopril showed a significant reduction in UAE after 3 mths (from 98.2±67.3 to 63.8±38.4mg/24h, p&lt;0.01</p>

<sup>10</sup> Titration phase: Amlodipine 5-15mg/d or fosinopril 10-30mg/d or amlodipine+f osinopril 5/10 to 15/30mg/d. The aim of the titrating phase was to achieve a DBP<90mmHg with the monotherapies and <85mmHg with the combination therapy during a 3-mth period. Non-responders or those with AEs were discontinued at 3 mths. The remaining N=309 entered the main trial. The N=144 non-responders were equally distributed in the three treatment groups.

			<p>previous coronary heart disease, stroke, congestive heart failure, cancer, smoking habits, left ventricular hypertrophy, total cholesterol values exceeding 240mg/dl, use of diuretics or <math>\beta</math>-blockers.</p>	<p>at the end of the titration phase (CHECK)</p>			<p>vs. placebo). The decrease continued after 6 and 12 mths and then remained stable (45.5mg/24h at 48mths). Amlodipine showed a significant reduction in UAE only after 18mths of treatment (from 95.51<math>\pm</math>64.1 to 70.9<math>\pm</math>41.2mg/24h, p&lt;0.05 vs. placebo). This was unchanged at 48mths (62.3<math>\pm</math>32.3). Combination showed a significant reduction at 3mths (from 97.7<math>\pm</math>60.4 to 61.1<math>\pm</math>29.9mg/24h) vs. placebo (p not stated) this continued at 12mths and 36mths, at 48mths was 34.3<math>\pm</math>16.4mg/24h. The UAE reduction shown with combination therapy was significantly greater as compared to that produced by amlodipine monotherapy at any time of the study and than fosinopril monotherapy from 18mths onwards.</p> <p>*Nonmicroalbuminuric status After 48 mths 46% (fosinopril), 33% (amoldipine) and 67% (combination) of participants ahd moved into the nonmicroalbuminuric status (UAE &lt;30mg/24h).</p> <p>*Creatinine clearance Creatinine clearance was unaffected by fosinopril, with amlodipine significantly increased at 12mths (vs. baseline), returning to baseline levels with ongoing treatment. The combination therapy significantly decreased creatinine clearance at 3mths, but increased it with ongoing treatment.</p>
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								<p>*Body weight Body weight remained unchanged in all treatments.</p> <p>*HbA1c HbA1c were not significantly changed by any treatment and no participants required substantial changes in hypoglycaemic therapy.</p> <p>*Discontinuation and adverse events N=71 discontinued (N=27 amlodipine; N=26 fosinopril; N=18 combination). Withdrawal due to AEs (N=4 (3.8%) amlodipine; N=3 (2.9%) fosinopril; N=2 (1.9%) combination. Approximately 4% of the amlodipine, 7% fosinopril and 2% combination groups discontinued the study due to insufficient BP control.</p>	
<p>Mann JF GHYQLEHBR. Development of renal disease in people at high cardiovascular risk: results of the HOPE randomized study. Journal of the American Society of Nephrology : JASN 2003; 14(3):641-647. Ref ID: 3480</p>	<p>RCT, double-blind  1+</p>	<p>Subgroup analysis from the HOPE<sup>11</sup> study using the N=7,674 with complete albuminuria data  (HOPE study total N=10,576 in the run-in</p>	<p>Inclusion: ≥55 years, objective evidence of vascular disease or diabetes plus at least one other cardiovascular risk factor (hypertension, dyslipidaemia, smoking, microalbuminuria) or evidence of vascular disease. Exclusion: heart failure, uncontrolled hypertension, intolerance to ACE</p>	<p>N=4,645 ramipril 10mg  Ramipril analysis ITT  All participants were randomly assigned to receive</p>	<p>N=4,652 placebo</p>	<p>3.5 to 5.5 years (median 4.5yrs)</p>	<p>Progression of proteinuria (development of new microalbuminuria and new clinical proteinuria</p>	<p>*Progression of proteinuria Any progression of proteinuria<sup>12</sup> occurred in N=1859 (24%) of participants. The rate of progression was higher in diabetic than in nondiabetic participants (34% vs. 17%, p&lt;0.001).  *New microalbuminuria New microalbuminuria developed in 1542/6055 (25.5%) participants (38.2% diabetic and 18.1% nondiabetic participants).  Multivariate analysis indicated that</p>	<p>Medical Research Council of Canada, the Ontario Heart Foundation, Aventis, Astra-Zeneca, NEGMA</p>

<sup>11</sup> Heart Outcomes and Prevention Evaluation study

<sup>12</sup> from normal urine albumin excretion to either microalbuminuria or to clinical proteinuria or the progression from microalbuminuria to clinical proteinuria

		N=9297 participants; N=3,577 with diabetes)  267 centres	inhibitors or to vitamin E, a serum creatinine level above 200µmol (2.3mg/dl), and dipstick positive proteinuria	400IU of vitamin E or matching placebo				diabetes was most strongly associated with the progression of proteinuria; OR 2.45 (95% CI, 2.18 to 2.75), p<0.05. the association with current smoking, hypertension, male gender, and PVD was less strong.  Ramipril reduced the risk of progression of proteinuria by 13% (p=0.146), the risk of new microalbuminuria by 10% (p=0.046) and the risk of new proteinuria by 22% after adjustment for baseline characteristics (p=0.0495)	, Natural Source Vitamin E Producers Association, King Pharmaceuticals
Mann JF, Gerstein HC, Yi QL et al. Progression of renal insufficiency in type 2 diabetes with and without microalbuminuria: results of the Heart Outcomes and Prevention Evaluation (HOPE) randomized study. <i>American Journal of Kidney Diseases</i> . 2003; 42(5):936-942. Ref ID: 522	RCT, double-blind, 2x2 factorial design  1+	Subgroup analysis from the HOPE <sup>13</sup> study  HOPE study total N=9,297; N=3,577 with diabetes (including N=1,139 with microalbuminuria and N=333 with renal insufficiency)  267 centres	Major baseline characteristics did not differ between the entire group and those with serum creatinine measurements at 4 yrs.	N= ramipril 10mg  Ramipril analysis ITT	N= placebo	3.5 to 5.5 years (median 4.5yrs)		*Serum creatinine Serum creatinine levels did not significantly increase during the study for all participants with diabetes or for those in the subgroups with renal insufficiency and/or microalbuminuria.  There was no evidence of an effect of ramipril on serum creatinine levels.  *Slopes of yearly increase in serum creatinine There were slight increases over time in all subgroups except those with renal insufficiency. Changes were NS between ramipril and placebo groups.  *GFR Mean changes in GFR were -4.4±18.3 (placebo) vs. -4.5±19.0ml/min (ramipril)	Medical Research Council of Canada, the Ontario Heart Foundation, Aventis, Astra-Zeneca, NEGMA, Natural Source Vitamin E Producers Association,

<sup>13</sup> Heart Outcomes and Prevention Evaluation study

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Ruggenti P, Perna A, Ganeva M et al. Impact of blood pressure control and angiotensin-converting enzyme inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: a post hoc analysis of the BENEDICT trial. <i>Journal of the American Society of Nephrology</i> . 2006; 17(12):3472-3481. Ref ID: 3595	RCT, double-blind  Post-hoc analysis of the BENEDICT study  1+	N=1204	Inclusion: T2D, urinary albumin excretion rate (UAE <20mg/min)	N= verapamil 240mg/d  N= trandopril 2mg/d  Other antihypertensive drugs could be used to achieve and maintain the target BP according to predefined guidelines <sup>14</sup>	N= combination of verapamil SR 240mg/d + trandopril 2mg/d  N= placebo		Evaluation of whether the extent of BP reduction predicted the time to onset of persistent microalbuminuria in hypertensive participants with T2D.  Time to onset of persistent microalbuminuria (UAE ≥20mg/min in at least 2 of 3 consecutive overnight urine collections), trough SBP and DBP	*Baseline BP Baseline SBP, DBP, MAP and pulse pressure failed to predict the onset of microalbuminuria  *Follow-up BP (3 mths after randomisation to study end) Patients who developed microalbuminuria had significantly higher SBP (143.3±9.9 vs. 140.2±11.3), DBP (82.7±6.0 vs. 81.5±5.7) and MAP (102.9±6.3 vs. 101.1±6.5) than those who did not develop microalbuminuria (p≤0.01 for all). Pulse pressure NS.  *BP reduction Patients who developed microalbuminuria had significantly lower reductions in SBP than those who did not develop microalbuminuria (7.9±11.5 vs. 10.6±11.9, p<0.05)  *Achieved follow-up BP Patients with follow-up BP below the medians or with BP reduction above the medians, were more frequently on ACE therapy, in particular trandopril plus verapamil combination, and less frequently on concomitant treatment with diuretics, β blockers, dCCB. Those with follow-up BP above the	

<sup>14</sup> The target BP after randomisation and throughout the study period for all treatment groups was <130/80

								medians or with BP reduction below the medians were more frequently on verapamil or placebo, and more frequently required concomitant medication.	
Sengul AM, Altuntas Y, Kurklu A et al. Beneficial effect of lisinopril plus telmisartan in patients with type 2 diabetes, microalbuminuria and hypertension. <i>Diabetes Research &amp; Clinical Practice</i> . 2006; 71(2):210-219. Ref ID: 3599	RCT, open-label, cross-over  1+	N=219	Inclusion: T2D, 40-65years, previously diagnosed hypertension (SBP ≥140mmHg or DBP ≥90mmHg) despite receiving ACE inhibitor monotherapy for ≥6 mths, microalbuminuria (AER 30-300mg/24h for a minimum of 3 occasions)  Exclusion: T1D, BMI ≥40kg/m <sup>2</sup> , secondary diabetes, alcoholism, thyroid disease, SBP>200mmHg, any non-diabetic cause of secondary hypertension, UTI, persistent haematuria, chronic liver disease, overt carcinoma, any cardiovascular event in the previous 6mths, serum creatinine ≥150mmol/l, serum potassium ≥5.5mmol/l	N=110 lisinoprol 20mg/d  After 24 wks half of this group were randomised to additionally take telmisartan 80mg/d  Additionally 12.5mg/d of hydrochlorot hiazide was used to treat N=21 in the lisinopril group	N=109 telmisartan 80mg/d  After 24 wks half of this group were randomised to additionally take lisinopril 20mg/d  Additionally 12.5mg/d of hydrochlorot hiazide was used to treat N=19 in the telmisartan group	52 weeks  (2-week wash-out)  24 weeks monotherapy  28 weeks monotherapy or combination therapy	SBP, DBP, AER, development of macroalbuminuria	At 24 weeks *SBP and DBP SBP and DBP fell significantly from baseline for both monotherapies (p<0.001), this was NS between the groups.  *AER AER decreased by 31.3% with telmisartan and by 37.1% with lisinopril, the difference between the groups was NS.  At 52 weeks (those who discontinued not included in analysis) *SBP and DBP All treatments reduced both SBP and DBP significantly compared with baseline. The combination therapy groups had significantly greater reductions than the immunotherapies (p=0.003 for both SBP and DBP).  *AER All treatments reduced AER significantly compared with baseline: Telmisartan: baseline 256 (140 to 300), 52 wks 164 (36 to 190) Lisinopril: baseline 264 (150 to 300), 52	Not stated

<sup>15</sup> Lifestyle and diabetes treatment remained unchanged throughout the study. Participants were instructed to follow a normocaloric diet.

			<p>There were no statistically significant differences between the groups for age, BMI, lipid profiles, duration of DM, serum creatinine, BP and smoking.</p> <p>15</p>					<p>wks 157 (34 to 182)  Telmisartan+lisinopril: baseline 258 (132 to 294), 52 wks 122 (23 to 172)  Lisinopril+telmisartan: baseline 259 (141 to 292), 52 wks 120 (22 to 151).  At both 36 and 52 weeks the combination was more effective than either monotherapy (p&lt;0.001).</p> <p>Reductions for baseline to week 52 were 36.0% (telmisartan), 40.5% (lisinopril), 52.7% (telmisartan+lisinopril) and 53.6% (lisinopril+telmisartan).</p> <p>AER was reduced to within normal range (&lt;30mg/24h) in N=8 in the lisinopril+telmisartan group and N=7 in the telmisartan+lisinopril group. AER did not reach normal range in either monotherapy group.</p> <p>*Development of macroalbuminuria  None of the participants developed macroalbuminuria (AER&gt;300mg/24h)</p> <p>*Discontinuation  Total N=27 discontinued  N=15 lisinopril due to nausea, stomach upset, respiratory infection, cough, headache, dizziness or feeling weak  N=12 telmisartan due to nausea, headache, dizziness, stomach upset, cough, GI problems)</p>	
Whelton PK, Barzilay J, Cushman WC et al. Clinical outcomes in antihypertensive	RCT, double-blind  1+	N=42,418 randomised N=31,512 (after exclusions)	Inclusion: men or women ≥55 years, stage 1 or 2 hypertension and at least 1 additional risk factor for CHD.	Titration doses in step 1 – step 2 involved the introduction	N=9054 lisinopril  N=9048 amlodipine besylate	Mean duration of follow-up 4.9years	Primary: fatal CHD and nonfatal MI  Secondary:	<p>Primary Outcome  *Fatal and nonfatal MI  There was NS difference in the incidence of fatal CHD and nonfatal MI for chlorthalidone cf. lisinopril in any of the 3 glycaemic strata or for</p>	

<p>treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[see comment]. <i>Archives of Internal Medicine</i>. 2005; 165(12):1401-1409. Ref ID: 246</p>		<p>N=13,101 diabetes (T2D N=12,063)</p>	<p>Baseline characteristics were well balanced across the 3 treatment groups within each glycaemic stratum</p>	<p>of open-label atenolol, clonidine hydrochloride or reserpine), step 3 adding hydrochloride, or adding other drugs when necessary.</p>	<p>N=15255 chlorthalidone</p>		<p>total mortality, ESRD, cancer</p>	<p>chlorthalidone vs. amlodipine within the DM or NG strata. Within the IFG the primary outcome was significantly more frequent (p=0.02) in the amlodipine group vs. chlorthalidone (RR1.73 (95%CI, 1.10 to 2.72) after 2yrs follow-up. (p=0.01 for treatment x glycaemic stratum interaction)</p> <p>Secondary Outcomes Within the 3 glycaemic strata there was NS difference in the incidence of total mortality, ESRD, or cancer for those taking chlorthalidone vs. amlodipine or lisinopril.</p> <p>*Combined CHD Combined CHD was higher (p=0.05) in the IFG group (NS for DM or NG) taking amlodipine vs. chlorthalidone (RR 1.37 (95% CI, 1.00 to 1.87); p=0.03 for treatment x glycaemic strata.</p> <p>*Stroke and combined CVD The incidence of stroke (RR 1.30 (95% CI, 1.10 to 1.57) and combined CVD (RR 1.13 (95% CI, 1.05 to 1.22) was significantly higher for the NG taking lisinopril vs. chlorthalidone (NS for treatment x glycaemic stratum for both stroke and combined CVD).</p> <p>*Heart failure There was a significantly higher incidence of heart failure (p=0.001) for the DM group taking amlodipine vs. chlorthalidone (RR 1.39 (95% CI, 1.22 to 1.59) and also for NG (RR 1.30 (95%</p>	
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