

Evidence Tables

ANG 1 Are angiotensin II receptor antagonists (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	Sc of fu
ARB vs placebo									
Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev 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 <u>ARB studies</u> 1. Brenner et al 2001 (RENAAL) 2. Lewis et al 2001 (IDNT) 3. Parving et al 2001 (IRMA) 4. Tan et al 2002 5. Berl et al 2003 (CV data - IDNT)			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 ARB vs. placebo/no treatment NS reduction in the risk of all-cause mortality was found (5 studies, N=3409). *ESRD 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). *Doubling of serum creatinine 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). *Progression from micro to macroalbuminuria ARB vs. placebo/ no treatment ARB significantly reduced the risk of progression from micro to microalbuminuria (3 studies, N=761, RR 0.49, 0.32 to 0.75).	NA

								<p>*Regression from micro to normoalbuminuria 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>*Toxicity - cough ARB vs. placebo/no treatment There was NS difference (2 studies, N=194)</p> <p>Toxicity – hyperkalaemia 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>Toxicity – headache ARB vs. placebo/no treatment There was NS difference (1 study, N=91).</p>
<p>Appel GB, Radhakrishnan J, Avram MM, DeFronzo RA, EscobarJimenez F, Campos MM et al. Analysis of metabolic parameters as predictors of risk in the RENAAL study. Diabetes Care 2003; 26(5):1402-1407. Ref ID: 1488</p>	<p>Post-hoc analysis of RENAAL 1+</p>	<p>N= 1,513 with T2D</p>	<p>Baseline characteristics: At baseline, no differences were observed between the losartan and placebo groups for age, BMI, sex, or smoking. At baseline, similar % of patients in the losartan and placebo groups were receiving insulin (61.4 vs. 58.9%, $p=NS$), oral antidiabetic agents (48.1 vs. 50.0%, $p=NS$), and lipid-lowering agents (36.5 vs.36.1%, $p=NS$). Most patients in both treatment groups had</p>	<p>Losartan 50 to 100 mg OD</p>	<p>placebo</p>	<p>3.4 years</p>	<p>Glycemic control (HbA1c) and serum lipid, uric acid, and potassium levels were compared between the losartan and placebo groups over time, and baseline levels were correlated with the risk of reaching the primary composite end point (doubling of serum creatinine, ESRD, or death) or</p>	<p>Relationship between baseline metabolic profile and the primary composite end point Univariate analysis revealed that baseline total and LDL cholesterol and triglyceride levels were associated with increased risk of developing the primary composite end point.</p> <p>TC (risk increase 67% per 100 mg/dl, $p<0.001$) LDL (risk increase 32% per 50 mg/dl, $p<0.001$), and Tg (risk increase 47% per log-transformed mg/dl, $p<0.011$)</p> <p>Hazard ratios for the primary composite end point showed NS relationship with</p>

			<p>poor glycemic control, with ~81% of patients in both groups having HbA1c levels >7%. About one-third of patients had baseline TC levels within the recommended range of <200 mg/dl, whereas one-third of patients had baseline TC >240 mg/dl. Only 13.8% of patients taking losartan and 12.5% of patients on placebo had HDL cholesterol levels >60 mg/dl, as recommended by the Adult Treatment Panel III. Approximately half of the patients had high LDL cholesterol (>130 mg/dl; losartan 49.9% and placebo 50.7%) and one-third triglyceride levels >200 mg/dl (losartan 35.6% and placebo 38.7%)</p>			ESRD alone	<p>baseline serum potassium, HbA1c, and HDL.</p> <p>Relationship between baseline metabolic profile and ESRD Similarly, total and LDL cholesterol were also associated with increased risk of developing ESRD.</p> <p>TC (risk increase 96% per 100 mg/dl, p<0.001) and LDL(risk increase 47% per 50 mg/dl, p< 0.001</p> <p>NS relationship was observed for HbA1c or HDL, and Tg were borderline significant</p> <p>HbA1c and serum lipids Losartan did not adversely affect glycemic control or serum lipid levels.</p> <p>At study-end Losartan-treated patients had lower total and LDL cholesterol when compared with baseline. (TC 227.4 vs. 195.4 mg/dl) (LDL 142.2 vs. 111.7mg/dl). However, no significant differences between losartan and placebo were reported at the last follow-up</p> <p>Potassium levels Losartan was associated with increased serum potassium at all time points, the mean rise never exceeded 0.3 mEq/l. However, increased serum potassium levels led to similar discontinuation rates (losartan 1.1% vs. placebo 0.5%, p=NS).</p> <p>Losartan was associated with a mean increase of up to 0.3 mEq/l in serum potassium levels; however, the rate of</p>
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								hyperkalemia-related discontinuation was similar between the placebo and losartan groups.	
Andersen S B-M. Kidney function during and after withdrawal of long-term irbesartan treatment in patients with type 2 diabetes and microalbuminuria. Diabetes Care 2003; 26(12):3296-3302. Ref ID: 3474	Sub-study of IRMA ¹ 1+	N= 133	<p>The present substudy was prespecified in the main study protocol. A total of 11 centres capable of measuring GFR were invited to the substudy. All 133 patients from these 11 centres participated in the substudy</p> <p>Baseline characteristics did not differ between treatment groups. In the placebo, irbesartan 150-mg, and irbesartan 300-mg groups,</p>	<p>Irbesartan 150mg</p> <p>Placebo</p>	<p>Irbesartan 300mg</p>	25 months	<p>Mean arterial blood pressure (MABP), urinary albumin excretion rate, and GFR were measured at baseline, after a single-blind 3-week run-in period, at 3 months, at 24 months, and 1 month after withdrawal of all antihypertensive treatment²</p>	<p>MABP In the placebo, irbesartan 150-mg, and irbesartan 300-mg groups MABP was similarly lowered from 112 ±1 (mean ±SE) 111± 1, and 112 ± 2 mmHg to 105 ±2, 103 ± 2, and 102± 2 mmHg, respectively, after 24 months of treatment (P< 0.05 vs. baseline).</p> <p>UAE UAE decreased by 8% (95% CI -16 to 27) (NS), 34% (8 to 53), and 60% (46 to 70) in the placebo, irbesartan 150-mg, and irbesartan 300-mg groups, respectively (p<0.05).</p> <p>GFR Rates of decline in GFR were 1.3± 0.7, 1.2 ± 0.7, and 1.0 ±0.8 ml/min 1.73 m2 per month in the placebo, irbesartan 150-mg, and irbesartan 300-mg groups, respectively, during the initial 3 months of the study.</p> <p>The sustained decreases in GFR were 0.3 ±0.1, 0.3 ±0.1, and 0.4±0. ml/min 1.73 m2 per month in the three groups, respectively, during the remaining study period</p> <p><u>One month after withdrawal of all antihypertensive medication</u></p>	SA BI

¹ The original IRMA study was included in the Cochrane review, but in brief, 590 hypertensive type 2 diabetic patients with microalbuminuria were included in this multinational, randomized, double-masked, placebocontrolled study of irbesartan (150 and 300 mg o.d.) and were followed for 24 months. The primary outcome was time to onset of diabetic nephropathy, defined as persistent albuminuria in overnight specimens with a urinary albumin excretion rate >200 ug/min and ≥30% increase from baseline level. Target trough blood pressure was <135/85 mmHg 3 months after randomization. Additional antihypertensive treatment used included diuretics, B-blockers, calcium-channel blockers (except dihydropyridines), and alpha-blockers. These agents were added if target blood pressure was not reached 3 months after randomization.

² A total of 15 patients did not complete the 1-month withdrawal phase due to increasing blood pressure >165/95 mmHg or development of peripheral oedema

								<p>MABP MABP was unchanged in the placebo group, 105 ±2mmHg, but increased significantly in the irbesartan groups, to 109 ±2 and 108 ±2mmHg, respectively (P< 0.01)</p> <p>UAER UAER increased by 13% (-10 to 42) (NS) in the placebo group, 68% (21 to 133) (p< 0.05) in the irbesartan 150-mg group, and 26% (-14 to 87) (NS) in the irbesartan 300-mg group.</p> <p>Comparing data to baseline levels, urinary albumin excretion rate was insignificantly increased by 14% (-17 to 54) in the placebo group and by 11% (-26 to 65) in the irbesartan 150-mg group but remained persistently reduced by 47% (24 to 63) in the irbesartan 300-mg group (p<0.05 vs. baseline).</p> <p>The persistent reduction in the irbesartan 300-mg group, as compared with baseline, was highly significantly different from irbesartan 150 mg (p< 0.01).</p> <p>GFR GFR levels increased to baseline values, 109 ±5 8 ml/min 1.73 m2, in the placebo group but only approached initial levels in the irbesartan groups, 107 ±6 and 108 ±6 8 ml/min 1.73 m2, respectively.</p> <p>No significant differences in rate of decrease in GFR between treatment groups were found (data not shown)</p>
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								<p>Plasma renin levels At baseline, plasma renin levels were 22 ±2 (geometric mean ±SE), 21 ±2, and 20 ±2 mIU/l in the placebo, irbesartan 150-mg, and irbesartan 300-mg groups, respectively.</p> <p>At the end of the study, levels were unchanged in the placebo group, 27 ±3 mIU/l (NS), but dose-dependently increased in irbesartan 150- and 300-mg groups, to 45 ± 9 and 68 ±15 mIU/l, respectively (p< 0.05 vs. baseline).</p> <p>Plasma angiotensin levels Plasma angiotensin II levels were 8 ±1, 7 ±1, and 8 ± pmol/l, respectively, at baseline. At the end of study, angiotensin II levels were unchanged in the placebo group, 9 ± 1 pmol/l, but significantly increased in the irbesartan 150- and 300-mg groups, to 14 ±2 and 17 ±2 pmol/l, respectively (p< 0.05 vs. baseline).</p> <p>Of the 133 patients included in the present substudy, nephropathy developed in 10 patients: 4 patients randomized to placebo and 6 patients in the irbesartan 150-mg group</p> <p>Compliance Compliance to study medication was acceptable; by the end of the study, an average of 81% of the irbesartan was taken in the 150-mg group and 89% of the irbesartan was taken in the 300-mg group.</p> <p>Progression to ESRD³</p>
Remuzzi G, Ruggenti	Post-hoc	N= 1,513	Overall, 1513 patients	Losartan	placebo	3.4 years	Incidence of ESRD,	

³ As expected, the observed crude incidence of ESRD was significantly higher in the highest (40.5%) and middle (19.3%) tertiles as compared with the lowest (7.3%) tertile (trend test across tertiles, p<0.0001).

<p>P, Perna A, Dimitrov BD, de ZD, Hille DA et al. Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: a post hoc analysis of the RENAAL trial results. Journal of the American Society of Nephrology 2004; 15(12):3117-3125. Ref ID: 3462</p>	<p>analysis of RENAAL 1+</p>		<p>entered the study and were followed for a mean follow-up of 3.4y:</p> <p>511 patients were in the highest (Scr 2.1 to 3.6 mg/dl),</p> <p>508 were in the middle (Scr 1.6 to 2.0 mg/dl), and</p> <p>494 were in the lowest (Scr 0.9 to 1.6 mg/dl) tertile.</p> <p>Within each tertile, the main baseline demographic, clinical, and laboratory characteristics were comparable between the two treatment groups</p>	<p>50 to 100 mg OD</p>			<p>hospitalizations for heart failure, withdrawals for adverse events, and proteinuria during losartan or conventional treatment were compared within three tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl).</p>	<p>Losartan decreased the risk of ESRD by 24.6, 26.3, and 35.3% in highest, middle, and lowest tertiles, respectively.</p> <p>For every 100 patients with serum creatinine >2.0, 1.6 to 2.0, or <1.6 mg/dl, respectively, 4 yr of losartan therapy was estimated to save 18.9, 8.4, and 2.9 ESRD events and US\$1,502,855, US\$1,021,770, and US\$528,591 costs for renal replacement therapy</p> <p>Incidence of hospitalizations⁴ Losartan also decreased the hospitalizations for heart failure by 50.2 and 45.1, in the highest and middle tertile, respectively but was associated with a nonsignificant <u>increased risk</u> (42.5%) of hospitalizations in the lowest tertile</p> <p>Incidence of proteinuria Proteinuria decreased more on losartan than on placebo in all tertiles (highest, 24 <i>versus</i> -8%; middle, 16 <i>versus</i> -8%; lowest, 15 <i>versus</i> -10%)</p> <p>In proteinuric individuals T2D, losartan therapy reduced ESRD and hospitalizations for heart failure and was well tolerated at all levels of renal function.</p> <p>Adverse events Withdrawals for adverse events other than heart failure were comparable between tertiles and treatment groups.</p> <p>Overall, 16 (1.1%) patients (10 [1.3%] on losartan) were withdrawn because of hyperkalemia. As expected, serum</p>
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⁴ The crude incidence of first hospitalizations for heart failure was higher in the highest (16.4%) and middle (15.0%) tertiles than in the lowest (11.1%) tertile (trend test across tertiles, p= 0.02).

								<p>potassium levels tended to increase from the lowest to the highest tertile, and within each tertile, follow-up levels tended to be higher in patients who were taking losartan than in those who were taking placebo.</p> <p>However, average follow-up differences between treatment groups within each tertile never exceeded 0.2 mEq/L.</p> <p>Of interest, the overall incidence of cardiovascular events, including acute MI, stroke, and angina, was comparable between tertiles and between treatment groups within each tertile.</p>
ARB vs Calcium antagonist								
<p>Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345(12):851-860. <u>IDNT study</u> Ref ID: 3656</p>	<p>RCT double blind. 1++</p>	<p>N= 1,715</p>	<p>Inclusion criteria: The criteria for eligibility included an age b/w 30 and 70 years, a documented diagnosis of T2D, hypertension (SBP >135 mm Hg while sitting, DBP > 85 mm Hg while sitting, or documented treatment with antihypertensive agents), and proteinuria, with urinary protein excretion of at least 900 mg per 24 hours. The serum creatinine concentration was required to be between 1.0 and 3.0 mg per</p>	<p>Irbesartan⁵ 300 mg daily Placebo</p>	<p>Amlodipine 10 mg daily</p>	<p>2.6 years</p>	<p>Primary endpoint: A composite of a doubling of the baseline serum creatinine concentration, the development of ESRD, or death from any cause</p> <p>Secondary endpoint was the composite of death from CV causes, nonfatal MI, heart failure resulting in hospitalization, a permanent</p>	<p>Primary composite endpoint⁶ Treatment with irbesartan was associated with a risk of the primary composite end point that was 20% lower than that in the placebo group (p=0.02) and 23% lower than that in the amlodipine group (p=0.006). The relative risk of the primary end point in the placebo and amlodipine groups did not differ significantly.</p> <p><u>Individual endpoints</u> The risk of a doubling of the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group (p=0.003) and 37% lower in the irbesartan group than in the amlodipine group (p<0.001)</p>

⁵ Antihypertensive agents other than ACE inhibitors, angiotensin-receptor blockers, and calcium-channel blockers were used as needed in each group, and the target blood pressure for all patients was the same (a systolic blood pressure of 135 mm Hg or less, or 10 mm Hg lower than the value at screening if that value was more than 145 mm Hg, and a diastolic blood pressure of 85 mm Hg or less). At the study end the distribution of classes of nonstudy drugs used to control blood pressure — primarily diuretics, beta-blockers, peripheral alpha-blockers, and central alpha2 agonists — was similar in all groups. The patients in the placebo group required an average of 3.3 nonstudy drugs for the control of blood pressure, as compared with an average of 3.0 nonstudy drugs among the patients in the irbesartan and amlodipine groups.

⁶ The better renal outcomes in the irbesartan group could not be explained by differences in the mean arterial blood pressure during follow-up. The mean arterial pressure in the irbesartan group was not significantly different from that in the amlodipine group

			<p>decilitre (88 and 265 μmol per litre) in women and 1.2 and 3.0 mg per decilitre (106 and 265 μmol per litre) in men.</p> <p>The baseline demographic, clinical, and laboratory characteristics of the three groups were similar, except that a slightly lower proportion of the patients in the placebo group were female ($p=0.02$).</p>			<p>neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle.</p>	<p>Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23% lower than that in both other groups ($p=0.07$ for both comparisons).</p> <p>The serum creatinine concentration increased 24% more slowly in the irbesartan group than in the placebo group ($p=0.008$) and 21% more slowly than in the amlodipine group ($p=0.02$).</p> <p>There were no significant differences in the rates of death from any cause.</p> <p>Secondary CV endpoint There were no significant differences in the CV composite end point.</p> <p>BP values The mean arterial pressure was significantly higher (by 3.3 mm Hg) in the placebo group than in the two active-treatment groups ($p=0.001$ for both comparisons), between which it did not differ significantly.</p> <p>Adverse events One episode of an early increase in the serum creatinine concentration suggestive of renal-artery stenosis necessitated the stopping of the study medication.</p> <p><u>Hyperkalemia necessitating a discontinuation of the study medication occurred in 11 of the patients in the irbesartan group (1.9%), as compared with 3 of those in the amlodipine group (0.5%) and 2 of those in the placebo group (0.4%, $p=0.01$ for both comparisons).</u></p>
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								The patients in the irbesartan group had a significantly lower rate of adverse events per 1000 days of treatment than those in the placebo and amlodipine groups (p=0.002).
Viberti G, Wheeldon NM, MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect.[see comment]. Circulation 2002; 106(6):672-678. Ref ID: 719	RCT multicenter, double-blind, parallel group, 1++	N= 332 from 31 centres in the UK	Inclusion criteria: Patients 35 to 75 years of age with T2D and evidence of persistent microalbuminuria (median UAER of 3 non-consecutive timed overnight urine collections in the range of 20 to 200 µg/min during a 5-week period before entry) Other inclusion criteria were normal serum creatinine and BP at baseline <180/105 mm Hg Exclusion criteria: Exclusion criteria were: T1D (onset <35 years and requiring insulin within the first year), use of ACE inhibitors, ARBs, and CCBs in the 5 weeks before random assignment; child-bearing potential for women; heart failure within the preceding 6 months requiring ACE inhibitor therapy; history of MI, PTCA or	Valsartan 80mg/day N= 169 mean daily doses at end of study 122 mg	amlodipine 5mg/day N= 163 mean daily doses at end of study 8 mg	24 weeks	Primary end point %change in UAER from baseline to 24 weeks. Secondary endpoint: % of patients returning to normoalbuminuria Blood pressure levels Adverse events	UAER The UAER at 24 weeks with valsartan was 56% (95% CI, 49.6 to 63.0) of baseline, equivalent to a 44% reduction. The UAER for amlodipine at week 24 was 92% (95% CI, 81.7 to 103.7) of baseline, a reduction of only 8%. The treatment effect was highly significant (p<0.001; 95% CI for ratio, 0.520 to 0.710). When baseline hypertensive status was entered into the model, there was no change to the outcome of the analysis. <u>Subgroup analyses</u> for patients who were hypertensive or normotensive at entry produced a similar pattern of results for change in UAER (hypertensive subgroup: p<0.001, 95% CI for ratio, 0.482 to 0.737; normotensive subgroup: p< 0.001, 95% CI for ratio, 0.486, 0.772). % of patients returning to normoalbuminuria The secondary end point analysis showed a significantly greater percentage of patients returning to normoalbuminuria status by week 24 with valsartan (29.9%; N=49) than with amlodipine (14.5%; N=23) (between-treatment difference,

⁷ Patients could be withdrawn from the study because of intolerable adverse events (AEs), exclusion criteria, noncompliance, or protocol violations. Patients were not excluded if they failed to reach the target BP. Hypertension was defined as BP ≥140/90 mm Hg and/or antihypertensive therapy at baseline. All antihypertensive medications were withdrawn and replaced by study drug, before randomization. The target BP was 135/85 mm Hg, based on evidence at the time of study design that these BP values slow progression of renal disease in type 2 diabetes. If adequate BP control was not achieved with study drug by week 4, the valsartan or amlodipine dose was doubled. If necessary, 2.5 mg/d bendrofluazide could be added from week 8 and doxazosin from week 12.

		<p>cerebrovascular accident within the preceding 3 months; severe diabetic neuropathy; history of hypertensive or hepatic encephalopathy; and evidence of hepatic disease.⁷</p> <p>The demographic and clinical characteristics of the two treatment groups were comparable at baseline</p> <p><u>Age:</u> Valsartan 59 Amlodipine 57</p> <p><u>Ethnic origin</u> Valsartan White (88%) Asian (10%) Amlodipine White (85%) Asian (10%)</p> <p><u>SBP (mm/Hg)</u> Valsartan 147.3 Amlodipine 148.3</p> <p><u>DBP (mm/Hg)</u> Valsartan 85.4 Amlodipine 85.7</p> <p><u>UAER, µg/min</u> Valsartan 57.9 Amlodipine</p>				<p>15.4%; 95% CI, 5.6 to 25.8; p<0.001).</p> <p>Blood pressure levels The mean reductions in trough BP from baseline to week 24 were similar in both treatment groups (NS differences were reported). This was also true for both the normotensive as well as the hypertensive subgroup.</p> <p>Adverse events Treatment was well tolerated in both groups, but ankle edema occurred less frequently with valsartan (1.2% versus 7.4% difference, -6.2%; 95% CI, -12.9% to -0.4%, p<0.006).</p> <p>There were no deaths related to study medication. There were 9 serious AEs with valsartan and 10 with amlodipine, of which 2 were suspected to be study drug-related. Both events resolved within 6 days.</p> <p>Main reasons for withdrawal were AEs (valsartan 8, amlodipine 7), protocol violations (valsartan 7, amlodipine 5), withdrawn consent (valsartan 4, amlodipine 4), and others (valsartan 4, amlodipine 2).</p>
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<p>Derosa G, Cicero AF, Bertone G, Piccinni MN, Fogari E, Ciccarelli L et al. Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. Clinical Therapeutics 2004; 26(8):1228-1236. Ref ID: 378</p>	<p>RCT double blind 1+</p>	<p>N= 116</p>	<p>55.4</p> <p>Inclusion criteria: non-smoking patients diagnosed with T2D according to the ADA criteria, who had achieved adequate glycemic control (HbA1c <7.0%) were eligible for inclusion in the study. Patients were required to have been diagnosed with diabetes for ≥ 2 years and to have mild hypertension based on WHO (i.e. DBP 90-99 mm Hg on repeated measurements). Moreover, their antihyperglycemic treatment and any antihypercholesterolemic treatment must have been stable ≥ 2 months.</p> <p>Exclusion criteria: Patients with secondary hypertension, malignant hypertension, unstable angina, MI within the preceding 6 months, abnormalities of liver or renal function, or contraindications to or current use of ARBs or ACE inhibitors were excluded from participation.</p> <p>The baseline characteristics of the 2 treatment groups were</p>	<p>Telmisartan 40mg OD N= 58</p>	<p>Nifedipine GITS 20mg OD N= 58</p>	<p>12 months⁸</p>	<p>SBP DBP HbA1c FPG BMI Lipid profile Safety profile</p>	<p>Blood pressure</p> <p>At 12 months both telmisartan and nifedipine GITS had produced significant mean reductions from baseline of seated trough SBP of 7 and 10 mm Hg respectively (both p<0.01)</p> <p>Telmisartan produced a mean reduction in SBP from 139 mm Hg at baseline to 132 mm Hg at the end of the study, and nifedipine GITS produced a reduction from 140 to 130 mm Hg.</p> <p>Telmisartan and nifedipine GITS also produced significant mean reductions in DBP of 8 and 9 mm Hg from baseline, respectively (both p<0.01). the reductions in DBP with telmisartan (from 95 to 86 mm Hg) were not significantly different from those achieved with nifedipine GITS (from 94 to 84 mm Hg)</p> <p>Glucose metabolism</p> <p>At 12 months there were no significant changes from baseline in HbA1c, FPG, BMI and there were no significant differences in any of these parameters between treatments</p> <p>Lipid profile</p> <p>TC & LDL</p> <p>Telmisartan was associated with significant reductions from baseline in plasma concentrations of TC (-9%) and LDL (-11.5%) (Both p<0.01). In contrast there were no significant changes from baseline in the lipid profiles of patients who had received nifedipine GITS for 12 months (TC -2%; LDL -1.5%). The reductions in TC and LDL with</p>
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⁸ Preceded by an initial 4-week placebo washout period of previous antihypertensive therapy,

			comparable. There was no between-group difference in the previous use of specific antihypertensive medications.					<p>telmisartan were significantly greater than those with nifedipine GITS ($p<0.05$)</p> <p>Tg Telmisartan and nifedipine GITS were associated with respective mean 8% and 6.5% decreases from baseline in Tg levels, but these decreases were not statistically significant.</p> <p>HDL No significant changes in HDL were observed with either treatment.</p> <p>Safety issues No severe or serious adverse events resulting in withdrawal from the study occurred in either group. No clinically relevant negative changes in laboratory parameters were observed in either group during the observation period.</p> <p>Compliance was similar in both treatment groups. The telmisartan group took 97% of the assigned pills, and the nifedipine GITS group took 95%.</p>									
Zanchetti A, Julius S, Kjeldsen S, McInnes GT, Hua T, Weber M et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: An analysis of findings from the VALUE trial. Journal of Hypertension 2006; 24(11):2163-2168. Ref ID: 5104	T2D subanalysis of the VALUE RCT ⁹ 1+	N=15,245 T2D= 4,823	<p>Inclusion criteria: patients 50 years or older, with treated or untreated hypertension at baseline and predefined combinations of CV risk factors and CV disease. Additional inclusion criteria were: men or women of any racial background,</p> <p>Exclusion criteria: renal artery stenosis, pregnancy, acute MI,</p>	Valsartan	Amlodipine	4.2 years	<p>Primary endpoint: time to first cardiac event (a composite of sudden cardiac death, fatal MI, death during or after PCI or coronary artery bypass graft, death as a result of heart failure, and death associated with recent MI at autopsy, heart failure requiring</p>	<p>Primary endpoint: The presence or absence of T2D had no influence on the relative risk of cardiac events in valsartan compared with amlodipine-treated patients</p> <table border="0"> <tr> <td></td> <td style="text-align: center;">Valsartan</td> <td style="text-align: center;">Amlodipine</td> </tr> <tr> <td>Primary endpoint</td> <td style="text-align: center;">14.7%</td> <td style="text-align: center;">14.6%</td> </tr> <tr> <td>ΔSBP/DBP mmHg</td> <td style="text-align: center;">2.16</td> <td style="text-align: center;">1.70</td> </tr> </table> <p>Secondary endpoints: NS differences were seen between in the T2D population receiving amlodipine or valsartan in terms of the secondary</p>		Valsartan	Amlodipine	Primary endpoint	14.7%	14.6%	Δ SBP/DBP mmHg	2.16	1.70
	Valsartan	Amlodipine															
Primary endpoint	14.7%	14.6%															
Δ SBP/DBP mmHg	2.16	1.70															

⁹ This subgroup analysis focuses on the primary endpoint and the three key secondary endpoints of myocardial infarction, heart failure and stroke.

			OCI or CABG within the past 3 months, clinically relevant valvular disease, cerebrovascular accident in the past 3 months, severe hepatic disease, severe chronic renal failure, congestive heart failure requiring ACE inhibitor therapy, patients on monotherapy with B blockers for both coronary artery disease and hypertension				hospital management, non-fatal MI, or emergency procedures to prevent MI) Secondary endpoint: - MI - Heart Failure - Stroke	endpoints.	
Fogari R, Derosa G, Zoppi A, Preti P, Lazzari P, Destro M et al. Effect of telmisartan-amlodipine combination at different doses on urinary albumin excretion in hypertensive diabetic patients with microalbuminuria. American Journal of Hypertension 2007; 20(4):417-422. Ref ID: 4966	RCT 1-	N= 210	Inclusion criteria: outpatients of both gender, aged 35 to 70, with essential hypertension, T2D well controlled by diet or by oral antidiabetic drugs, and microalbuminuria (UAER> 30 and < 300 mg/24h in tow distinct 24-h urine collections during 7 days before enrolment) were considered for screening. Exclusion criteria: patients were excluded if they had secondary hypertension, history of MI or stroke within 6 months before the start of the study, CHF, cancer or any severe disease likely to interfere with the conduct	High-dose telmisartan /low-dose amlodipine ¹⁰ Group T N= 105	High-dose amlodipine /low-dose telmisartan Group A N= 105	48 weeks	UAER Blood pressure Body weight Creatinine clearance Other paramenters	Blood Pressure Both groups produced similar reductions in SBP and DBP values, with no significant difference between the two regimens at any time of the study. UAER The UAER was significantly decreased from baseline by both combination regimes, but such a decrease was significantly more marked in the T group. Reductions of UAER were 47.5% ($p < .01$), 65.3% ($Pp < .001$), and 77% ($p < .0001$) for telmisartan 80, 120, and 160 mg/amlodipine 2.5 mg daily, respectively, whereas reductions of UAER were 34% ($p < .03$), 37% ($p < .03$), and 33% ($p < .03$) for amlodipine 5, 7.5, and 10 mg/telmisartan 40 mg daily, respectively,. The difference between the two regimens was statistically significant ($p < .05$, $p < .01$, and $p < .001$, respectively).	Ne

¹⁰ One group, increasing dose of telmisartan (40mg every 4 weeks until 160 mg) and fixed 2.5mg dose of amlodipine (group T), the other based on increasing dose of amlodipine (2.5mg every 4 weeks until 10mg) and fixed 40mg dose of telmisartan (group A)

			<p>of the study, smoking habits and BMI>30 KG/M2</p> <p>There were no statistical differences between the two regime groups for the analyzed parameters.</p>					<p>Body weight Body weight remained substantially unchanged in all patients.</p> <p>Creatinine clearance Creatinine clearance did not significantly change from baseline during the 48-week study period with both treatment regimens.</p> <p>Other parameters Neither combination therapy significantly affected levels of plasma potassium and fasting glycemia. The HbA1c levels were not significantly influenced by any treatment.</p> <p>Adverse events Both treatment regimens were well tolerated. The %r of patients who reported one or more adverse events were 10% in the T group and 14% in the A group, with no statistical difference between the two treatments.</p> <p>The reported side effects were dizziness (N=5), nausea (N=3), asthenia (N=2), and headache (N=1) in the T group; leg oedema (N=7), headache (N=3), hot flushes (N=3), and palpitations (N=2) in the A group.</p>
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ARB vs B-blockers									
Lindholm LH IH. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in	RCT double blind, parallel group. 1++	1,195 diabetic (13%) of 9,193 LIFE participants ¹¹	Inclusion criteria: patients aged 55-80 years with hypertension (either treated or untreated) ¹² and signs of LVH on ECGs.	Losartan ¹³ (N= 586)	Atenolol (N= 609)	4.7 years	primary composite endpoint of cardiovascular morbidity and mortality (CV death, stroke, or MI).	Primary endpoint The primary endpoint occurred in 103 patients assigned losartan and 139 assigned atenolol; relative risk 0.76 (95% CI 0.58 to 0.98), p=0.031	M

¹¹ Compared with the remaining LIFE participants without diabetes, patients with the disease had higher body-mass index, higher Framingham risk score, a higher prevalence of cardiovascular disease at baseline, higher systolic blood pressure (difference 3 mm Hg), lower diastolic pressure (2 mm Hg), higher pulse pressure (5 mm Hg), and higher serum glucose concentration (9.6 [SD 3.8] vs 5.5 [1.0] mmol/L). Fewer patients with diabetes smoked than other LIFE participants

¹² Before the start of the study, 958 patients had been treated with antihypertensive drugs, 472 (81%) in the losartan group and 486 (80%) in the atenolol group.

<p>hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359(9311):1004-1010. Ref ID: 3479</p>			<p>Baseline characteristics: Groups were closely matched in demographic characteristics, severity of hypertension, prevalence of coexisting CV conditions, Framingham risk score, and ECG-based LVH criteria</p> <p><u>Age:</u> Losartan 67.4 Atenolol 67.4</p> <p><u>Ethnic origin</u> Losartan White (86%) Black (11%) Hispanic (2%) Asian (0.9%) Other (0.2%)</p> <p>Atenolol White (85%) Black (12%) Hispanic (2%) Asian (0.8%) Other (0.2%)</p> <p><u>Blood pressure (mm/Hg)</u> Losartan 176/97 Atenolol 177/96</p> <p><u>BMI</u> Losartan 30.0</p>				<p>All cause mortality</p> <p>CV death</p> <p>Stroke</p> <p>MI</p> <p>Blood pressure levels</p> <p>Adverse events</p>	<p>All-cause mortality Mortality from all causes was 63 and 104 in losartan and atenolol groups, respectively; 0.61 (0.45 to 0.84), p=0.002.</p> <p>CV death 38 and 61 patients in the losartan and atenolol groups, respectively, died from cardiovascular disease; 0.63 (0.42 to 0.95), p=0.028.</p> <p>Stroke NS differences were reported. Stroke occurred in 51 losartan and 65 atenolol patients (p=0.205),</p> <p>MI NS differences were reported. MI occurred in 41 and 50 patients, respectively (p=0.373).</p> <p>Blood pressure levels NS differences were reported. Mean blood pressure fell to 146/79 mm Hg in losartan patients and 148/79 mm Hg in atenolol patients.</p> <p>Adverse events Albuminuria was reported less frequently (p=0.002) as an adverse event in the losartan than in the atenolol group. Losartan 43 (7%) Atenolol 79 (13%) 0.002</p> <p>Chest pain was reported more frequently in the losartan arm p=0.036 Losartan 71 (12%) Atenolol 51 (8%)</p>
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¹³ Patients received placebo drugs for 1–2 weeks after which they were assigned to treatment groups if they had a sitting systolic blood pressure of 160–200 mm Hg, a diastolic pressure of 95–115 mm Hg, or both. In both groups, hydrochlorothiazide and other agents were added (but not B-blockers, ACEs, or ARBs) if blood pressure remained high during follow-up.

			Atenolol 30.0						
ARB vs alpha-blockers									
Derosa G, Cicero AF, Gaddi A, Mugellini A, Ciccarelli L, Fogari R. Effects of doxazosin and irbesartan on blood pressure and metabolic control in patients with type 2 diabetes and hypertension. Journal of Cardiovascular Pharmacology 2005; 45(6):599-604. Ref ID: 271	RCT double blind 1+	N=96	<p>Inclusion criteria: patients with T2D, according to the ADA criteria, and mild hypertension, according to the WHO criteria (DPC>90 and <105 mm Hg) on repeated measurements in the absence of any antihypertensive treatment, were enrolled in this trial.</p> <p>In addition, all patients were in good general health, were non-smokers, were not taking hypocholesterolemic drugs, and did not have evidence of macroangiopathy (by ECG and Doppler examination), nephropathy (by microalbuminuria, defined as AER <30mg/24 hours, performed on overnight urine collections), or neuropathy (by vibration perception threshold).</p> <p>Exclusion criteria: Patients with secondary hypertension, malignant hypertension, unstable angina, MI within the preceding 6 months, and/or liver/renal function</p>	Irbesartan 300mg OD	Doxazosin 4mg OD	12 months ¹⁴	SBP DBP HbA1c FPG BMI Lipid profile Safety profile	<p>Blood Pressure At the end of the study, reductions in SBP and DBP from baseline were 12± 4 and 10 ± 3 mm Hg, respectively, in the doxazosin group and 16 ± 5 and 11 ± 4 mm Hg, respectively, in the irbesartan group.</p> <p>Decrease in both SBP and DBP were significantly greater with irbesartan therapy compared with doxazosin (p<0.05)</p> <p>HbA1c HbA1c was reduced by 1.2 ±0.2 and 1.0 ±0.1% (p<0.05) following 12 months of doxazosin and irbesartan, respectively, with a significantly greater decrease in the doxazosin group (p<0.05)</p> <p>FPG FPG was significantly reduced from baseline with doxazosin (-13 ± 5 mg/dl p<0.05) but not with irbesartan (-4 ± 1 mg/dl)</p> <p>Lipid profile TC, LDL and Tg were all significantly reduced from baseline at the end of the study in patients receiving doxazosin (13.3 ±3, 15.5 ± 5, and 23 ± 9 mg/dl, respectively; p<0.05). Irbesartan did not elicit significant changes in any of these parameters.</p> <p>Increases in HDL were 5 ± 1 and 1 ± 0.08 mg/dl for the doxazosin and irbesartan treatment groups,</p>	Ne

¹⁴ Preceded by an initial 4-week placebo run-in/washout period

			<p>abnormalities were excluded from the study.</p> <p>Clinical characteristics, hemodynamic parameters or laboratory measurements at baseline did not differ significantly between the two groups.</p>					<p>respectively ($p < 0.05$ for the between-group difference).</p> <p>Safety issues Although no subject experienced adverse effects serious enough to warrant discontinuing either drug, six patients receiving doxazosin reported postural hypotension, fainting, and dizziness and four in the irbesartan group reported nausea, headache, and dizziness.</p>
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