

# Clinical trials of anti hypertensive agents for diabetes type 2 in patients with or without hypertension

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## 1 angiotensin receptor blocker

Trial	Treatments	Patients	Trials design and methods
<b>candesartan vs control</b>			
SCOPE (diabetic subgroup) , 2003 n=313/284 follow-up: 3.7 years	candesartan versus control	sub group of diabetic patients aged 70-89 years, with systolic blood pressure 160-179 mmHg, and/or diastolic blood pressure 90-99 mmHg, and a Mini Mental State Examination (MMSE) test score $\geq 24$	Parallel groups double-blind 15 countries
<b>irbesartan vs placebo</b>			
IDNT (irbesartan vs pbo) , 2001 n=579/569 follow-up: 2.6 years	Irbesartan 300 mg daily versus placebo	hypertensive patients with nephropathy due to type 2 diabetes	Parallel groups double blind Worldwide
IPDM (150mg) , 2001 n=195/201 follow-up: 2 years	irbesartan 150 mg daily versus placebo	hypertensive patients with type 2 diabetes and microalbuminuria	Parallel groups double-blind Worldwide
<b>losartan vs placebo</b>			
RENAAL , 2001 n=751/762 follow-up: 3.4 y	losartan 50 to 100 mg once daily versus placebo	patients with type 2 diabetes and nephropathy	Parallel groups double-blind America, Europe, Asia
<b>olmesartan vs placebo</b>			
ROADMAP , 2010 [NCT00185159] n=2232/2215 follow-up: 3.2 y	olmesartan at 40 mg/day versus placebo	patients with diabetes and at least one additional cardiovascular risk factor, but no evidence of renal dysfunction	Parallel groups double-blind Europe (19 countries)
ORIENT [NCT00141453] n=282/284 follow-up:	olmesartan versus placebo	patients with diabetic Nephropathy and overt proteinuria secondary to type 2 diabetes mellitus	Parallel groups double-blind Japan, Hong Kong
<b>telmisartan vs placebo</b>			
PROFESS , 2008 n=2840/2903 follow-up: 2.4y	80 mg telmisartan once daily versus placebo	-	Parallel groups double-blind
<b>irbesartan vs amlodipine</b>			

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<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>IDNT (irbesartan vs amlodipine) , 2001</b> n=579/567 follow-up: 2.6 years	Irbesartan 300 mg daily versus amlodipine 10 mg daily	hypertensive patients with nephropathy due to type 2 diabetes	Parallel groups double blind Worldwide
<b>valsartan vs amlodipine</b>			
<b>NAGOYA HEART , 2011</b> <i>unpublished</i> [NCT00129233] n=575/575 follow-up: 3.2 y median	blood-pressure-lowering therapy based on valsartan; blood-pressure goal of <130/80 mm Hg versus blood-pressure-lowering therapy based on amlodipine; blood-pressure goal of <130/80 mm Hg	patients with hypertension with type 2 diabetes or impaired glucose tolerance	Parallel groups open Japan
<b>losartan vs atenolol</b>			
<b>LIFE (diabetic subgroup) , 2002</b> n=586/609 follow-up: 4.7 years	losartan 50mg daily at step 1 versus atenolol 50mg daily at step 1	patients with diabetes (subgroup) , hypertension, and signs of left-ventricular hypertrophy on electrocardiograms	Parallel groups double-blind USA, UK, Nordic countries
<b>temisartan vs enalapril</b>			
<b>DETAIL , 2004</b> n=120/130 follow-up: 5 years	telmisartan 80 mg daily versus enalapril 20 mg daily	subjects with type 2 diabetes and early nephropathy	Parallel groups double-blind northern Europe

2

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## 2 angiotensin-converting enzyme inhibitors

Trial	Treatments	Patients	Trials design and methods
<b><a href="#">captopril or atenolol vs control</a></b>			
<a href="#">UKPDS 38 , 1998</a> n=758/390 follow-up: 8.4y (median)	tight control of blood pressure aiming at a BP <150/85 (with the use of captopril or atenolol as main treatment, other treatment were added if the control criteria were not met) versus less tight control aiming at a blood pressure of <180/105 (avoiding treatment with ACE inhibitors or beta-blockers)	hypertensive patients with type 2 diabetes	Parallel groups open UK
<b><a href="#">ACE inhibitors vs placebo</a></b>			

continued...

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>HOPE (diabetic subgroup) , 2000</b> n=1808/1759 follow-up: 4.5 years	ramipril 10 mg once per day orally versus placebo	patients with diabetes (sub group), aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction	Factorial plan double-blind North, South america, Europe
<b>enalapril vs placebo</b>			
<b>SCAT (diabetic subgroup) , 2000</b> n=25/25 follow-up: Jun 1991 - Jul 1995	enalapril 2.5mg twice daily versus placebo	normocholesterolemic patients	Factorial plan double-blind Canada
<b>SOLVD (subgroup) , 1996</b> n=646/664 follow-up: 3.5y	enalapril versus placebo	patients with chronic heart failure	Parallel groups double-blind
<b>perindopril vs placebo</b>			
<b>EUROPA (PERSUADE substudy) , 2005</b> n=721/781 follow-up: 4.3y	perindopril 8mg once daily versus placebo	patients with known coronary artery disease and without heart failure, sub group of diabetic patients	Parallel groups double-blind
<b>PROGRESS (diabetic subgroup) , 2001</b> n=393/368 follow-up: 3.9 y	perindopril 4 mg daily versus placebo	hypertensive and non-hypertensive individuals with cerebrovascular disease, subgroup of diatebic patients	Parallel groups double-blind
<b>perindopril and indapamide vs placebo</b>			
<b>ADVANCE , 2007</b> [NCT00145925] n=NA follow-up:	fixed combination of perindopril and indapamide versus placebo	patients with type 2 diabetes irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs	
<b>ADVANCE , 2007</b> [NCT00145925] n=5569/5571 follow-up: 4.3 yrs	low-dose fixed combination of perindopril and indapamide versus placebo	individuals with type 2 diabetes	Factorial plan double-blind Asia, Australasia, Europe, and North America
<b>ramipril vs placebo</b>			
<b>DIABHYCAR , 2004</b> n=2443/2469 follow-up: median 4 years	ramipril 1.25 mg/day versus placebo	patients with type 2 diabetes who have microalbuminuria or proteinuria	Parallel groups double-blind Europe, North Africa
<b>DREAM , 2008</b> n=2623/2646 follow-up: 3 years	ramipril(up to 15 mg per day) versus placebo	people aged >=30 years, with Impaired glucose tolerance and/or impaired fasting glucose without known CVD or renal insufficiency	Factorial plan open
<b>captopril vs atenolol</b>			

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<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>UKPDS 39 , 1998</b> n=400/358 follow-up: ND	captopril 25 mg/d aiming at a BP <150/85 versus atenolol 50mg/d aiming at a BP <150/85	hypertensive patients with type 2 diabetes	Parallel groups open UK
<b>ACE inhibitor vs calcium-channel blocker</b>			
<b>STOP-2 (ACEI vs CCB) (diabetic subgroup) , 2000</b> n=235/231 follow-up: 5.03y	ACE inhibitor versus calcium antagonists	diabetic (subgroup) elderly patients aged 70-84 years	open with blind assessment Sweden
<b>lisinopril vs chlorthalidone</b>			
<b>ALLHAT (lisi vs chlor, diabetic subgroup) , 2002</b> n=2431/4498 follow-up: 4.9 y	lisinopril 10 to 40 mg/d versus chlorthalidone 12.5 to 25 mg/d	diabetic (subgroup) participants aged 55 years or older with hypertension	Parallel groups double-blind
<b>captopril vs diuretic and/or beta-blockers</b>			
<b>CAPP (diabetic subgroup) , 1999</b> n=309/263 follow-up: 6.1 year	Captopril initial dose of 50 mg daily given in one or two doses versus thiazide diuretic or beta-blocker	Patients aged 25-66 years with a measured diastolic blood pressure of 100 mm Hg or more on two occasions; subgroup of diabetic patients	Parallel groups open with blinded assessment Sweden, Finland
<b>ACE inhibitor vs diuretic or beta-blocker</b>			
<b>STOP-2 (ACEI, diabetic subgroup) , 2000</b> n=235/253 follow-up: 5.03y	ACE inhibitor versus conventional treatment (diuretic or beta-blocker)	diabetic (subgroup) elderly patients aged 70-84 years with hypertension	Parallel groups open with blind assessment Sweden

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### 3 beta-blockers

Trial	Treatments	Patients	Trials design and methods
<b>metoprolol vs placebo</b>			
<a href="#">MERIT-HF</a> , 2005 n=495/490 follow-up: 1y	metoprolol CR/XL versus placebo	patients with CHF NYHA classe 2 to 4 and EF<=40% sub group of diabetic patients	Parallel groups double-blind USA and Europe
<b>carvedilol vs metoprolol</b>			

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Trial	Treatments	Patients	Trials design and methods
<b>GEMINI , 2004</b> n=498/737 follow-up: 5 months	6.25- to 25-mg dose of carvedilol twice daily versus 50- to 200-mg dose of metoprolol tartrate twice daily	patients with hypertension and type 2 diabetes mellitus receiving renin-angiotensin system blockade	Parallel groups double-blind

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## 4 calcium-channel blockers

Trial	Treatments	Patients	Trials design and methods
<b>verapamil vs control</b>			
<b>INVEST (subgroup) , 2003</b> n=3169/3231 follow-up: 24 months	calcium antagonist strategy (verapamil sustained release) versus non-calcium antagonist strategy (atenolol)	hypertensive CAD patients aged 50 years or older	Parallel groups open 14 countries
<b>amlodipine vs placebo</b>			
<b>IDNT (amlodipine vs PBO) , 2001</b> n=567/569 follow-up: 2.6 years	Amlodipine 10 mg daily versus placebo	hypertensive patients with nephropathy due to type 2 diabetes	Parallel groups double-blind Worldwide
<b>nifedipine vs placebo</b>			
<b>ACTION , 1998</b> n=565/545 follow-up: 4.9y	Nifedipine GITS versus placebo	patients aged at least 35 years with stable angina pectoris and proven coronary artery disease; subgroup of diabetic patients	Parallel groups double-blind 19 countries
<b>nitrendipine vs placebo</b>			
<b>Syst-Eur (diabetic subgroup) , 1999</b> n=252/240 follow-up: 2 years	Calcium-channel blocker versus placebo	subgroup of diabetic patients, age, >=60 years) with systolic blood pressure of 160 to 219 mm Hg and diastolic pressure below 95 mm Hg	Parallel groups double blind
<b>nifedipine vs ACE inhibitor</b>			
<b>JMIC-B (diabetic subgroup) , 2004</b> n=199/173 follow-up: 3 years	nifedipine retard versus angiotensin converting enzyme inhibitors	outpatients aged under 75 years who had diagnoses of both hypertension and coronary artery disease	Parallel groups open Japan

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Trial	Treatments	Patients	Trials design and methods
<b>amlodipine vs atenolol</b>			
ASCOT (subgroup) , 2008 n=2565/2572 follow-up: 5.7y	amlodipine with addition of perindopril as required versus atenolol with addition of thiazide as required	Patients with untreated hypertension or treated hypertension; diabetic subgroup with two additional risk factors	Parallel groups double-blind
<b>benazepril + amlodipine vs benazepril + hydrochlorothiazide</b>			
ACCOMPLISH (diabetic subgroup) , 2010 [NCT00170950] n=1432/1410 follow-up: 36 months	benazepril, combined with amlodipine versus benazepril, combined with hydrochlorothiazide	patients with diabetes (subgroup) and hypertension at high risk of cardiovascular and related events	Parallel groups double-blind US, Norway, Denmark, Finland
<b>amlodipine vs chlorthalidone</b>			
ALLHAT (amlodipine vs chlor, diabetic subgroup) , 2002 n=2664/4498 follow-up: 4.9 y	amlodipine versus chlorthalidone	diabetic (subgroup) participants aged 55 years or older with hypertension	Parallel groups double-blind
<b>nifedipine vs coamilofide</b>			
INSIGHT (diabetic subgroup) , 2000 n=649/653 follow-up: 4 y	Nifedipine GITS 30 mg daily versus co-amilofide hydrochlorothiazide 25 mg plus amiloride 2.5 mg	diabetic (subgroup) patients aged 55-80 years with hypertension (blood pressure $\geq$ 150/95 mm Hg, or $\geq$ 160 mmHg systolic)	Parallel groups double-blind Europe, Israel
<b>diltiazem vs diuretic and/or beta-blocker</b>			
NORDIL (diabetic subgroup) , 2000 n=351/376 follow-up: 4.5 y	Diltiazem 180/360 mg diltiazem daily at step one versus thiazide diuretic or a beta-blocker at step one	diabetic patients (subgroup), aged 50-74 years who had diastolic blood pressure of 100 mm Hg or more	Parallel groups open Norway, Sweden
<b>calcium-channel blocker vs diuretic or beta-blocker</b>			
STOP-2 (CCB, diabetic subgroup) , 2000 n=231/253 follow-up: 5.03y	Calcium-channel blocker versus diuretic or beta-blocker	diabetic (subgroup) elderly patients aged 70-84 years	Parallel groups open with blind assessment Sweden
<b>nisoldipine vs enalapril</b>			
ABCD (hypertension) , 1998 n=235/235 follow-up: 5 y	nisoldipine (long acting) versus enalapril	patients with non-insulin-dependent diabetes and hypertension	Factorial plan Double blind USA
<b>amlodipine vs fosinopril</b>			
FACET , 1997 n=191/189 follow-up: 3.5 y	amlodipine (long acting) 10 mg daily versus fosinopril 20 mg daily	hypertensive patients with NIDDM	Parallel groups open Italy

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## **5 diuretics**

Trial	Treatments	Patients	Trials design and methods
<b>chlorthalidone vs placebo</b>			
<b>SHEP (diabetic subgroup) , 1996</b> n=283/300 follow-up: 5 year	low dose of chlorthalidone (12.5-25.0 mg/d) with a step-up to atenolol (25.0-50.0 mg/d) or reserpine (0.05-0.10 mg/d) if needed versus placebo	men and women aged 60 years and older , non-insulin-treated diabetic (sub group) patients with isolated systolic hypertension (systolic BP $\geq$ 160 mm Hg; diastolic BP, $<$ 90 mm Hg)	Parallel groups double-blind

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## 6 intensive treatment

Trial	Treatments	Patients	Trials design and methods
<b>intensive vs usual</b>			
<b>ABCD normotensives , 1993</b> n=237/243 follow-up: 5.3 y	intensive (10 mm Hg below the baseline DBP) DBP control versus moderate (80 to 89 mm Hg) DBP control	normotensive type 2 diabetic patients	Parallel groups open
<b>ACCORD (blood pressure) , 2010</b> [NCT00000620] n=2363/2371 follow-up: 4.7 y	intensive blood-pressure control, targeting a systolic pressure of less than 120 mm Hg versus standard blood-pressure control	high-risk patients with type 2 diabetes, high HbA1c concentrations ( $>$ 7.5% ), and cardiovascular disease (or $\geq$ 2 cardiovascular risk factors)	Factorial plan open United States, Canada
<b>HOT <math>\leq</math>80 (diabetic subgroup) , 1998</b> n=499 follow-up: 3.8y	target diastolic blood pressure $\leq$ 80 mmHg versus target diastolic blood pressure $\leq$ 90 mmHg	patients aged 50-80 years with hypertension and diastolic blood pressure between 100 mm Hg and 115 mm Hg; diabetics subgroup	Parallel groups open 26 countries

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