

# 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unpublished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

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## References

### SCOPE (diabetic subgroup), 2003:

Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003;21:875-86 [[12714861](#)] [10.1097/01.hjh.0000059028.82022.89](#)

Trenkwalder P, Elmfeldt D, Hofman A, Lithell H, Olofsson B, Papademetriou V, Skoog I, Zanchetti A The Study on COgnition and Prognosis in the Elderly (SCOPE) - major CV events and stroke in subgroups of patients. *Blood Press* 2005;14:31-7 [[15823945](#)] [10.1080/08037050510008823](#)

### IDNT (irbesartan vs pbo), 2001:

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60 [[11565517](#)]

### IPDM (150mg), 2001:

Parving HH, Lehnert H, Brchner-Mortensen J, Gomis R, Andersen S, Arner P The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870-8 [[11565519](#)]

### RENAAL, 2001:

Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9 [[11565518](#)]

### ROADMAP, 2010:

Ritz E, Viberti GC, Ruilope LM, Rabelink AJ, Izzo JL Jr, Katayama S, Ito S, Mimran A, Menne J, Rump LC, Januszewicz A, Haller H Determinants of urinary albumin excretion within the normal range in patients with type 2 diabetes: the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study. *Diabetologia* 2010;53:49-57 [[19876613](#)] [10.1007/s00125-009-1577-3](#)

Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, Mimran A, Rabelink TJ, Ritz E, Ruilope LM, Rump LC, Viberti G Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011 Mar 10;364:907-17 [[21388309](#)]

**ORIENT, :**

**PROFESS, 2008:**

Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol* 2008;7:875-84 [[18757238](#)] [10.1016/S1474-4422\(08\)70198-4](#)

**IDNT (irbesartan vs amlodipine), 2001:**

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60 [[11565517](#)]

**NAGOYA HEART, 2011:**

Matsushita K, Muramatsu T, Kondo T, Maeda K, Shintani S, Murohara T Rationale and design of the NAGOYA HEART Study: comparison between valsartan and amlodipine regarding morbidity and mortality in patients with hypertension and glucose intolerance. *J Cardiol* 2010;56:111-7 [[20409690](#)] [10.1016/j.jjcc.2010.03.004](#)

**LIFE (diabetic subgroup), 2002:**

Lindholm LH, Ibsen H, Dahlf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H, Aurup P, Edelman J, Snapinn S Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:1004-10 [[11937179](#)] [10.1016/S0140-6736\(02\)08090-X](#)

Dahlf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995-1003 [[11937178](#)] [10.1016/S0140-6736\(02\)08089-3](#)

**DETAIL, 2004:**

Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004;351:1952-61 [[15516696](#)] [10.1056/NEJMoa042274](#)

## 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

## References

### UKPDS 38, 1998:

Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ* 1998;317:713-20 [[9732338](#)]

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-13 [[9732337](#)]

### HOPE (diabetic subgroup), 2000:

Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;355:253-9 [[10675071](#)]

Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:145-53 [[10639539](#)]

### SCAT (diabetic subgroup), 2000:

Teo KK, Burton JR, Buller CE, Plante S, Catellier D, Tymchak W, Dzavik V, Taylor D, Yokoyama S, Montague TJ Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation* 2000;102:1748-54 [[11023927](#)]

Burton JR, Teo KK, Buller CE, Plante S, Catellier D, Tymchak W, Taylor D, Dzavik V, Montague TJ Effects of long term cholesterol lowering on coronary atherosclerosis in patient risk factor subgroups: the Simvastatin/enalapril Coronary Atherosclerosis Trial (SCAT). *Can J Cardiol* 2003 Apr;19:487-91 [[12717482](#)]

### SOLVD (subgroup), 1996:

Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, Pinkett T, Ghali JK, Wilson AC Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol* 1996;77:1017-20 [[8644628](#)]

Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet* 2003;361:1077-83 [[12672310](#)] [10.1016/S0140-6736\(03\)12892-9](#)

#### **EUROPA (PERSUADE substudy), 2005:**

Daly CA, Fox KM, Remme WJ, Bertrand ME, Ferrari R, Simoons ML The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy. *Eur Heart J* 2005;26:1369-78 [[15860521](#)] [10.1093/eurheartj/ehi225](#)

#### **PROGRESS (diabetic subgroup), 2001:**

Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033-41 [[11589932](#)] [10.1016/S0140-6736\(01\)06178-5](#)

Berthet K, Neal BC, Chalmers JP, MacMahon SW, Bousser MG, Colman SA, Woodward M Reductions in the risks of recurrent stroke in patients with and without diabetes: the PROGRESS Trial. *Blood Press* 2004;13:7-13 [[15083634](#)]

Chapman N, Huxley R, Anderson C, Bousser MG, Chalmers J, Colman S, Davis S, Donnan G, MacMahon S, Neal B, Warlow C, Woodward M Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. *Stroke* 2004 Jan;35:116-21 [[14671247](#)] [10.1161/01.STR.0000106480.76217.6F](#)

Ratnasabapathy Y, Lawes CM, Anderson CS The Perindopril Protection Against Recurrent Stroke Study (PROGRESS): clinical implications for older patients with cerebrovascular disease. *Drugs Aging* 2003;20:241-51 [[12641480](#)]

#### **ADVANCE, 2007:**

Rationale and design of the ADVANCE study: a randomised trial of blood pressure lowering and intensive glucose control in high-risk individuals with type 2 diabetes mellitus. Action in Diabetes and Vascular Disease: PreterAx and DiamicroN Modified-Release Controlled Evaluation. *J Hypertens Suppl* 2001 Nov;19:S21-8 [[11848259](#)]

Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007 Sep 8;370:829-40 [[17765963](#)]

#### **ADVANCE, 2007:**

Chalmers J, Kengne AP, Joshi R, Perkovic V, Patel A New insights from ADVANCE. *J Hypertens Suppl* 2007;25:S23-30 [[17579315](#)] [10.1097/01.hjh.0000271506.69949.46](#)

Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829-40 [[17765963](#)] [10.1016/S0140-6736\(07\)61303-8](#)

#### **DIABHYCAR, 2004:**

Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Mnard J Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 2004;328:495 [[14960504](#)] [10.1136/bmj.37970.629537.0D](#)

#### **DREAM, 2008:**

Dagenais GR, Gerstein HC, Holman R, Budaj A, Escalante A, Hedner T, Keltai M, Lonn E, McFarlane S, McQueen M, Teo K, Sheridan P, Bosch J, Pogue J, Yusuf S Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care* 2008;31:1007-14 [[18268075](#)] [10.2337/dc07-1868](#)

Bosch J, Yusuf S, Gerstein HC, Pogue J, Sheridan P, Dagenais G, Diaz R, Avezum A, Lanans F, Probstfield J, Fodor G, Holman RR Effect of ramipril on the incidence of diabetes. *N Engl J Med* 2006;355:1551-62 [[16980380](#)] [10.1056/NEJMoa065061](#)

#### **UKPDS 39, 1998:**

Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;317:703-13 [[9732337](#)]

Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ* 1998;317:713-20 [[9732338](#)]

**STOP-2 (ACEI vs CCB) (diabetic subgroup), 2000:**

Lindholm LH, Hansson L, Ekblom T, Dahlf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens* 2000 Nov;18:1671-5 [[11081782](#)]

Hansson L, Lindholm LH, Ekblom T, Dahlf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354:1751-6 [[10577635](#)]

**ALLHAT (lisi vs chlor, diabetic subgroup), 2002:**

Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97 [[12479763](#)]

Whelton PK, Barzilay J, Cushman WC, Davis BR, Iamathi E, Kostis JB, Leenen FH, Louis GT, Margolis KL, Mathis DE, Moloo J, Nwachuku C, Panebianco D, Parish DC, Pressel S, Simmons DL, Thadani U Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005;165:1401-9 [[15983290](#)] [10.1001/archinte.165.12.1401](#)

**CAPP (diabetic subgroup), 1999:**

Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmki K, Dahlf B, de Faire U, Mrlin C, Karlberg BE, Wester PO, Bjrcck JE Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611-6 [[10030325](#)]

Niklason A, Hedner T, Niskanen L, Lanke J Development of diabetes is retarded by ACE inhibition in hypertensive patients—a subanalysis of the Captopril Prevention Project (CAPPP). *J Hypertens* 2004;22:645-52 [[15076172](#)]

Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. *Diabetes Care* 2001;24:2091-6 [[11723089](#)]

**STOP-2 (ACEI, diabetic subgroup), 2000:**

Lindholm LH, Hansson L, Ekblom T, Dahlf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens* 2000;18:1671-5 [[11081782](#)]

Hansson L, Lindholm LH, Ekblom T, Dahlf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354:1751-6 [[10577635](#)]

Hansson L, Hedner T, Dahlf B Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. *Blood Press* 1992;1:113-9 [[1366259](#)]

### 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

## References

### MERIT-HF, 2005:

Deedwania PC, Giles TD, Klibaner M, Ghali JK, Herlitz J, Hildebrandt P, Kjekshus J, Spinar J, Vitovec J, Stanbrook H, Wikstrand J Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. Am Heart J 2005;149:159-67 [[15660048](#)] [10.1016/j.ahj.2004.05.056](#)

### GEMINI, 2004:

Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JT Jr, Oakes R, Lukas MA, Anderson KM, Bell DS Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA 2004;292:2227-36 [[15536109](#)] [10.1001/jama.292.18.2227](#)

## 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

## References

INVEST (subgroup), 2003:

Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancina G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003;290:2805-16 [[14657064](#)] [10.1001/jama.290.21.2805](#)

Sharma SK, Ruggenenti P, Remuzzi G Managing hypertension in diabetic patients—focus on trandolapril/verapamil combination. *Vasc Health Risk Manag* 2007;3:453-65 [[17969376](#)]

#### **IDNT (amlodipine vs PBO), 2001:**

Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60 [[11565517](#)]

Hunsicker LG, Atkins RC, Lewis JB, Braden G, de Zeeuw DJ, DeZeeuw G, Drury P, Locatelli F, Wiegmann TB, Lewis EJ Impact of irbesartan, blood pressure control, and proteinuria on renal outcomes in the Irbesartan Diabetic Nephropathy Trial. *Kidney Int Suppl* 2004;:S99-101 [[15485429](#)] [10.1111/j.1523-1755.2004.09223.x](#)

POHL, MA, CORDONNIER, DJ, SPITALOWITZ, S, et al, FOR THE COLLABORATIVE STUDY GROUP Impact of angiotensin receptor blockade with irbesartan on renal function at different systolic blood pressure (SBP) levels in type 2 diabetic nephropathy. *J Am Soc Nephrol* 2002 13: 650A,

Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, Esmatjes E, Gilbert RE, Hunsicker LG, de Faria JB, Mangili R, Moore J Jr, Reisin E, Ritz E, Scherthaner G, Spitalowitz S, Tindall H, Rodby RA, Lewis EJ Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. *J Am Soc Nephrol* 2005;16:3027-37 [[16120823](#)] [10.1681/ASN.2004110919](#)

#### **ACTION, 1998:**

Danchin N, Wagener G, Kirwan B, De Brouwer S, Lubsen J, Poole-Wilson P. Efficacy and safety of long-acting nifedipine in patients with symptomatic stable angina pectoris with and without diabetes: the action trial. Doctoral thesis <http://publishing.eur.nl/ir/repub/asset/10627/>

Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA, Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarson A, Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J, We Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004;364:849-57 [[15351192](#)] [10.1016/S0140-6736\(04\)16980-8](#)

#### **Syst-Eur (diabetic subgroup), 1999:**

Tuomilehto J, Rastenyte D, Birkenhger WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 1999;340:677-84 [[10053176](#)]

#### **JMIC-B (diabetic subgroup), 2004:**

Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K, Origasa H, Iimura O, Ishii M, Saruta T, Arakawa K, Hosoda S, Kawai C Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. *Hypertens Res* 2004;27:181-91 [[15080377](#)]

Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K, Origasa H, Iimura O, Ishii M, Saruta T, Arakawa K, Hosoda S, Kawai C Nifedipine retard was as effective as angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive patients with diabetes and coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) subgroup analysis. *Hypertens Res* 2004;27:449-56 [[15302980](#)]

#### **ASCOT (subgroup), 2008:**

Ostergren J, Poulter NR, Sever PS, Dahlf B, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients with type II diabetes. *J Hypertens* 2008;26:2103-11 [[18854748](#)] [10.1097/HJH.0b013e328310e0d9](#)

Dahlf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895-906 [[16154016](#)] [10.1016/S0140-6736\(05\)67185-1](#)

#### **ACCOMPLISH (diabetic subgroup), 2010:**

Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB, Velazquez EJ, Dahlf B, Kelly RY, Hua TA, Hester A, Pitt B Cardiovascular events during differing hypertension therapies in patients with diabetes. *J Am Coll Cardiol* 2010;56:77-85 [[20620720](#)] [10.1016/j.jacc.2010.02.046](#)

Jamerson K, Weber MA, Bakris GL, Dahlf B, Pitt B, Shi V, Hester A, Gupta J, Gatlin M, Velazquez EJ Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417-28 [[19052124](#)] [10.1056/NEJMoa0806182](#)

### **ALLHAT (amlodipine vs chlor, diabetic subgroup), 2002:**

Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97 [[12479763](#)]

Berecek KH, Farag A, Bahtiyar G, Rothman J, McFarlane SI The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) Trial: focus on the diabetic patient. *Curr Hypertens Rep* 2004;6:212-4 [[15128474](#)]

Whelton PK, Barzilay J, Cushman WC, Davis BR, Iamathi E, Kostis JB, Leenen FH, Louis GT, Margolis KL, Mathis DE, Moloo J, Nwachuku C, Panebianco D, Parish DC, Pressel S, Simmons DL, Thadani U Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med* 2005;165:1401-9 [[15983290](#)] [10.1001/archinte.165.12.1401](#)

### **INSIGHT (diabetic subgroup), 2000:**

Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, Ruilope LM Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000;356:366-72 [[10972368](#)] [10.1016/S0140-6736\(00\)02527-7](#)

Mancia G, Brown M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, Wagener G, Ruilope LM Outcomes with nifedipine GITS or Co-amilozone in hypertensive diabetics and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension* 2003;41:431-6 [[12623939](#)] [10.1161/01.HYP.0000057420.27692.AD](#)

### **NORDIL (diabetic subgroup), 2000:**

Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J, de Faire U, Dahlf B, Karlberg BE Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000;356:359-65 [[10972367](#)]

Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L, Lanke J, Lindholm LH, De Faire U, Dahlf B, Karlberg BE Influence of age, sex and blood pressure on the principal endpoints of the Nordic Diltiazem (NORDIL) Study. *J Hypertens* 2002 Jun;20:1231-7 [[12023696](#)] [10.1097/00004872-200206000-00038](#)

Kjeldsen SE, Hedner T, Syvertsen JO, Lund-Johansen P, Hansson L Comparison of home and office blood pressure in treated hypertensives in the Nordic Diltiazem (NORDIL) Study. *Blood Press* 2002;11:371-6 [[12523681](#)]

Thijs L, Staessen JA, Wang J, Fagard R Subgroup analysis of the NORDIL trial. *J Hypertens* 2002;20:1085-7 [[12023676](#)]

### **STOP-2 (CCB, diabetic subgroup), 2000:**

Lindholm LH, Hansson L, Ekblom T, Dahlf B, Lanke J, Linjer E, Scherstn B, Wester PO, Hedner T, de Faire U Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens* 2000;18:1671-5 [[11081782](#)]

Hansson L, Lindholm LH, Ekblom T, Dahlf B, Lanke J, Scherstn B, Wester PO, Hedner T, de Faire U Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999;354:1751-6 [[10577635](#)]

### **ABCD (hypertension), 1998:**

Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998;338:645-52 [[9486993](#)] [10.1056/NEJM199803053381003](#)

Schrier RW, Estacio RO, Esler A, Mehler P Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;61:1086-97 [[11849464](#)] [10.1046/j.1523-1755.2002.00213.x](#)

### **FACET, 1997:**

Tatti et al. *Circulation* 1997; 96:I-764 (abstr) [0]

Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998 Apr;21:597-603 [[9571349](#)]

## **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

## References

### SHEP (diabetic subgroup), 1996:

Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR, Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. JAMA 1996;276:1886-92 [[8968014](#)]

## 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

## References

### ABCD normotensives, 1993:

Savage S, Johnson Nagel N, Estacio RO, Feig PU, MacCarthy EP, Lukken NJ, Ziegler R, Schrier RW The ABCD (Appropriate Blood Pressure Control in Diabetes) trial. Rationale and design of a trial of hypertension control (moderate or intensive) in type II diabetes. Online J Curr Clin Trials 1993;Doc No 104:[6250 words; 128 paragraphs] [[8305994](#)]

Schrier RW, Estacio RO, Esler A, Mehler P Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-97 [[11849464](#)] [10.1046/j.1523-1755.2002.00213.x](#)

### ACCORD (blood pressure), 2010:

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes. N Engl J Med 2010 Jun 29;: [[20587587](#)] [10.1056/NEJMoa1001288](#)

Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH Jr, Hamilton BP, Hoogwerf B, Karl D, Katz L, Krikorian

A, O'Connor P, Pop-Busui R, Schubart U, Simmons D, Taylor H, Thomas A, Weiss D, Hramiak I Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010 Jun 29;: [20594588] [10.1016/S0140-6736\(10\)60576-4](#)

Chew EY, Ambrosius WT, Howard LT, Greven CM, Johnson S, Danis RP, Davis MD, Genuth S, Domanski M Rationale, design, and methods of the Action to Control Cardiovascular Risk in Diabetes Eye Study (ACCORD-EYE). *Am J Cardiol* 2007;99:103i-111i [17599420] [10.1016/j.amjcard.2007.03.028](#)

Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59 [18539917] [10.1056/NEJMoa0802743](#)

Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85 [20228401] [10.1056/NEJMoa1001286](#)

### **HOT $\leq 80$ (diabetic subgroup), 1998:**

Hansson L, Zanchetti A, Carruthers SG, Dahlf B, Elmfeldt D, Julius S, Mnard J, Rahn KH, Wedel H, Westerling S Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *HOT Study Group. Lancet* 1998;351:1755-62 [9635947]

Wesseling H [Lowering of diastolic blood pressure  $\leq 90$  mmHg should not be attempted, except in type 2 diabetics; the 'Hypertension optimal treatment' (HOT) trial] *Ned Tijdschr Geneesk* 1999 Jun 5;143:1188-91 [10389531]

Hansson L The Hypertension Optimal Treatment study and the importance of lowering blood pressure. *J Hypertens Suppl* 1999 Feb;17:S9-13 [10340838]

Lopes AA, Andrade J, Noblat AC, Silveira MA Reduction in diastolic blood pressure and cardiovascular mortality in nondiabetic hypertensive patients. A reanalysis of the HOT study. *Arq Bras Cardiol* 2001;77:132-7 [11514824]

Zanchetti A; Hansson L Intensive blood pressure lowering: Contrast between benefits in diabetics and other groups of hypertensive patients and increased risk in smokers: Further analysis of the hypertension optimal treatment (HOT) study *Abstract JOURNAL OF HYPERTENSION* 2000;18(Supp: 2):S92-S92

Hansson L, Zanchetti A The Hypertension Optimal Treatment (HOT) Study—patient characteristics: randomization, risk profiles, and early blood pressure results. *Blood Press* 1994;3:322-7 [7866597]

Hansson L, Zanchetti A The Hypertension Optimal Treatment (HOT) Study: 24-month data on blood pressure and tolerability. *Blood Press* 1997;6:313-7 [9360003]

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