

Evidence Tables

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

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Bakris GL FV. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA : the journal of the American Medical Association 2004; 292(18):2227-2236. Ref ID: 3616 GEMINI study	RCT double blind 1++	N= 1,235 from 205 centres in US	Inclusion criteria: Participants were men and women aged 36 to 85 years with documented T2D and stage 1 or 2 hypertension. Antidiabetic treatment must have been stable for 3 months and antihypertensive treatment stable for 1 month, and include an ACE inhibitor or ARB. Exclusion criteria: included significant CV disease (uncontrolled or symptomatic	Carvedilol ^{1 2} 6.25- to 25- mg BID N= 498 The mean dose required to achieve target BP was 17.5 mg BID for carvedilol, with approx half of each group requiring the highest dose	Metoprolol 50- to 200- mg BID N= 737 The mean dose required to achieve target BP was 128 mg BID for metoprolol, with approx half of each group requiring the	5 months ³	HbA1c Difference between groups in mean change from baseline HbA1c <u>Additional prespecified comparisons</u> Included: change from baseline HbA1c in individual treatment groups,	HbA1c change between groups The mean difference between carvedilol and metoprolol with respect to the change in HbA1c from baseline was 0.12% (SD, 0.04%; 95% CI, -0.20% to -0.03%; p=006) for the ITT analysis using LOCF. HbA1c change within groups Carvedilol treatment had no effect on HbA1c (mean [SD] change from baseline to end point, 0.02% [0.04%]; 95% CI, -0.06% to 0.10%; p= 0.65), while metoprolol increased HbA1c (0.15% [0.04%]; 95% CI, 0.08%-0.22%; p<001) More participants withdrew due to worsening glycemic control in the	GSK

¹ Participants continued to receive their ACE inhibitor or ARB following screening. All other antihypertensive medications were discontinued over a 2- to 4-week period. Participants were eligible for randomization if they had mild to moderate hypertension after washout (systolic BP > 130≤179mmHg and diastolic BP >80≤109 mm Hg), and fasting HbA1c was 6.5% to 8.5% with 0.5% or less increase from screening

² Each patient's dose was titrated progressively from 6.25 mg of carvedilol twice daily and 50 mg of metoprolol twice daily to a maximum dose of 25 mg and 200 mg twice daily, respectively, at 1- to 2-week intervals toward target BP levels for a total of 2 to 7 weeks. Target systolic BP was 135 mm Hg or less for those participants with baseline of 140 to 179mmHg and 130mmHg or less for those with baseline of 130 to 140 mm Hg. Target diastolic BP was 85mmHg or less for those participants with baseline diastolic BP of 90 to 109 mm Hg and 80 mm Hg or less for those participants with baseline diastolic BP of 80 to 90 mm Hg. Open-label Hydrochlorothiazide and a dihydropyridine calcium antagonist were added, if needed, to achieve blood pressure target (in both groups).

³ On reaching target BP or the highest dose level, participants began 5 months of maintenance therapy. Maximum study length per participant was 35 weeks, including down-titration as necessary and safety follow-up. No longer was term follow- up planned.

		<p>arrhythmias, unstable angina, sick sinus syndrome, second or third degree heart block without a pacemaker, congestive heart failure, a MI or stroke within the previous 3 months, bradycardia), pulmonary disease, stage 3 or higher kidney disease, or use of a non-ocular B-blocker within the previous 3 months.</p> <p>Patient Characteristics: At screening, nearly all participants were receiving an ACE inhibitor or ARB; 718 (58%) of 1235 participants were receiving 2 or more antihypertensive agents and almost half were taking statins. A total of 674 participants were receiving multiple antidiabetic medications and 100 (8%) were taking insulin</p> <p>Following discontinuation of antihypertensive medications other than ACE inhibitor or ARB, baseline BPs remained well above the</p>	highest dose		<p>treatment effect on insulin sensitivity, and microalbuminuria.</p> <p>Adverse events</p>	<p>metoprolol group (16 [2.2%] of 737 participants in the metoprolol group vs 3 (0.6%) of 498 in the carvedilol group, p= 0.04).</p> <p>Other Metoprolol increased <u>triglycerides</u> (13%, p<0.001), whereas carvedilol had no effect; no treatment difference for LDL or HDL cholesterol was noted between groups</p> <p><u>Blood pressure</u> and heart rate were similarly controlled in both groups Approx 44% of each treatment group required hydrochlorothiazide and approximately 25% required a dihydropyridine calcium antagonist, or both to achieve goal BP.</p> <p><u>Microalbuminuria</u>, defined as a urinary albumin/creatinine excretion rate of approximately 30 to 300 mg/g, was present in 77 (20%) of 388 participants in the carvedilol group and 97 (18%) of 542 participants in the metoprolol group at baseline. At study end, carvedilol reduced the albumin/ creatinine ratio compared with metoprolol (16% relative reduction, p=0.003).</p> <p>Of those with albuminuria of 30 mg/g or less at baseline, fewer participants progressed to microalbuminuria in the carvedilol group (25 [6.4%] of 388 in the carvedilol group vs 56 [10.3%] of 542 in the metoprolol group; odds ratio [OR] for carvedilol vs metoprolol, 0.60; 95% CI, 0.36-0.97; p=0.04).</p>
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			recommended target of 130/80 mm Hg.					<p>Adverse events</p> <p>No differences were observed between groups in overall safety profile. Significant weight gain was observed in the metoprolol group (Mean [SD], 1.2 [0.2] kg for metoprolol, p<0.001 vs 0.2 [0.2] kg for carvedilol, p=0.36). No statistical analysis was reported between groups.</p> <p>A total of 19 participants (3.8%) taking carvedilol and 36 (4.9%) taking metoprolol had nonfatal serious adverse events. In the carvedilol group, 6 participants had 7 cardiac events recorded, of which 2 were acute MI; in the metoprolol group, 7 participants had events recorded, of whom 1 had acute MI.</p> <p>Metabolic events were recorded for 1 participant in the carvedilol group vs 3 in the metoprolol group. Two participants had 3 nervous system events reported in the carvedilol group vs 6 in the metoprolol group; 1 participant in each group had a stroke.</p> <p>No participant taking carvedilol had a respiratory event in contrast with 7 events in 6 participants taking metoprolol.</p> <p>One report of gangrene was made in the carvedilol group.</p>	
Dahlöf B. Prevention of cardiovascular events with an	RCT, double-blind	N=19,257 (N=5,145 diabetes)	Inclusion: 40-79yrs, either untreated hypertension	N=9,639 (N=2,567 diabetes)	N=9,618 (N=2,578 diabetes)	Stopped prematurely after 5.5yrs	Primary: non-fatal MI and fatal	*BP On average, in both treatment groups, BP dropped from a mean of 164.0/94.7	Pfizer

<p>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. <i>Lancet</i>. 2005; 366(9489):895-906. Ref ID: 3618</p>	<p>1++</p>	<p>ITT analysis</p>	<p>(SBP>160mmHg, DBP >100mmHg or both), or treated hypertension (SBP>140mmHg, DBP>90mmHg or both), at least 3 of the following CV risk factors; left ventricular hypertrophy, other specified abnormalities on ECG, T2D, PAD, previous stroke or TIA, male, age 55 or older, microalbuminuria or proteinuria, smoking, ratio of TC to HDL-C of 6 or higher, family history of premature CHD.</p> <p>Exclusion: previous MI, currently treated angina, a cerebrovascular event within the previous 3 mths, fasting triglycerides higher than 4.5mmol/l, heart failure, uncontrolled arrhythmias, any clinically important haematological or biochemical abnormality on routine screening</p> <p>Participants were well matched between groups; over 80% were on previous antihypertensive</p>	<p>amlodipine 5-10mg adding perindopril 4-8mg as required</p> <p>By the end of the trial most participants (78%, 14,974/19,452) were taking at least 2 antihypertensives, 15% (1,401/9,634) were taking amlodipine monotherapy and 9% (857/9,608) were taking atenolol monotherapy</p>	<p>atenolol 50-100mg adding bendroflumethiazide 1.25-2.5mg and potassium as required</p>	<p>CHD Secondary: all-cause mortality, total stroke, primary endpoints minus silent MI, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, non-fatal and fatal heart failure Tertiary: silent MI, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias, development of diabetes, development of renal impairment, the effects of the primary endpoint and on total</p>	<p>(SD18.0/10.4) to a mean of 136.9/78.3 (16.7/9.8) – ie an average reduction of 26.6/16.6 (21.7/15) mmHg. An trial close-out N=10,070 (53%) of participants had reached both SBP and DBP (32%, 1646/5109 of those with diabetes and 60% 8424/14034 of those without).</p> <p>*Primary Non-fatal MI plus fatal CHD was NS lowered by 10% in amlodipine based group vs. the atenolol based group.</p> <p>*Secondary There were significant reductions with the amlodipine based group vs. atenolol based for all secondary endpoints (except fatal and non-fatal heart failure).</p> <p>*Tertiary There were significant reductions associated with the amlodipine based group for unstable angina, PAD, development of diabetes and development of renal failure.</p> <p>*Diabetes subgroup For the effects of treatment on total cardiovascular events and procedures in relation to subgroups the diabetes subgroup showed significantly lower occurrence with the amlodipine based group vs. atenolol based group; HR (95% CI) 0.87 (0.76 to 0.99), p=0.0283. This significance was also identified in the non-diabetic group; HR 0.82 (0.75 to 0.90), p<0.0001.</p>
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			treatment				cardiovascular events and procedures among prespecified subgroups.	*Adverse events 25% (4,760/19,257) stopped therapy because of an adverse event. The most frequent were amlodipine based group (peripheral oedema 23%; cough 19%; joint swelling 14%; dizziness 12%; chest pain 8%; fatigue 8%) and atenolol based group (dizziness 16%; fatigue 16%; dyspnoea 9%; cough 8%; erectile dysfunction 7%).	
Black HR EWG. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA : the journal of the American Medical Association 2003; 289(16):2073-2082. Ref ID: 3475	Subpopulation analysis of CONVINCE trial. 1+	N= 3,239 T2D patients 19.6% Of total population 16,476	Inclusion criteria: patients were 55 years or older, diabetic, in addition to hypertension. Patient characteristics: The mean age was 66 years, 56% of participants were women. Most participants (84%) had previously been prescribed antihypertensive drugs	COER ⁴ verapamil <u>T2D</u> N= 1,616 (19.9%) <u>Total population</u> N= 8,179	Atenolol or Hydrochlorothiazide ⁵ <u>T2D</u> N= 1,623 (19.7%) <u>Total population</u> N = 8,297	3 years ⁶	Primary endpoint: A composite of acute MI, stroke or CV related death.	Primary composite endpoint <u>Diabetic subpopulation</u> NS differences were found for the T2D subpopulation in the incidence of the primary composite endpoint The incidence of any component of the primary composite endpoint was 101 (1.2%) in those diabetics taking COER verapamil and 116 (1.4%) for those receiving atenolol or hydrochlorothiazide. RR 0.86 95% CI (0.66 to 1.12) p=0.16 <u>Total population</u> NS differences were found in the total population in the incidence of the primary composite endpoint There were 364 first primary events in the group randomized to COER	Searle & Co. - Pharmacia

⁴ Control-Onset Extended Release (COER). It should be noted that in both groups any additional antihypertensive agent (except a non-dihydropyridine calcium antagonist, thiazide diuretic, or B-blocker) could be added as a step-3 medication (non-blinded) if needed.

⁵ The active-control group began with either hydrochlorothiazide or atenolol. This choice was made by the investigator prior randomization, based on which treatment the investigator thought would be more suitable for the individual participant, should the participant be randomized to the atenolol or hydrochlorothiazide group

⁶ The sponsor closed the study 2 years earlier than originally planned for commercial reasons.

								<p>verapamil compared with 365 among the atenolol of hydrochlorothiazide group. RR 1.02 95% CI (0.88 to 1.18) p=0.77</p> <p>Blood pressure <u>Total population</u> NS differences were found in terms of lowering blood pressure efficacy between the two groups. At the last follow-up visit attended, a SBP < 140mm Hg and a DPB <90 mm Hg was achieved in the 65.5% of the COER verapamil group and the 65.9% of the atenolol or hydrochlorothiazide group.</p> <p>Adverse events <u>Total population</u> Participants assigned COER verapamil withdrew more often due to adverse signs or symptoms compared with those assigned atenolol of hydrochlorothiazide (p = 0.02); the most common reason was constipation (216 in the COER verapamil compared with 28 in the atenolol of hydrochlorothiazide group).</p> <p>However, fewer participants assigned COER verapamil (n=115) atenolol of hydrochlorothiazide withdrew because of poor blood pressure control compared with those assigned atenolol of hydrochlorothiazide (N=207) (p<0.001 by log-rank)</p>	
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<p>Pepine CJ HEC-DRMRK. 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 : the journal of the American Medical Association 2003; 290(21):2805-2816. Ref ID: 3483</p>	<p>RCT open label 1+</p>	<p>N= 22,576 hypertensive with CAD</p> <p>T2D N= 6,400 (28.3%)</p>	<p>Inclusion criteria: patients were eligible if they were aged 50 years or older and had documented CAD⁷, with essential hypertension.</p> <p>Exclusion criteria: Patients taking B-blockers within 2 weeks of randomization or taking B-blockers for an MI that occurred in the previous 12 months were excluded to avoid withdrawal phenomena in patients randomized to the CAS group.</p>	<p><u>Calcium antagonist strategy:</u></p> <p>Verapamil SR 240mg/d</p> <p>N= 11,267</p> <p>T2D N= 3,169 (28.1%)</p>	<p><u>Non-calcium antagonist strategy:</u></p> <p>Atenolol 50mg/d</p> <p>N= 11,309</p> <p>T2D N= 3,231 (28.6%)</p>	<p>24 months</p>	<p>Primary endpoint: First occurrence of death (all cause), nonfatal MI, or nonfatal stroke.</p> <p>Secondary endpoint: individual components</p> <p>Other: CV death, angina, AEs, hospitalizations, and BP control at 24 months.</p>	<p>Primary endpoint: <u>NS differences non-diabetic population</u></p> <p>The number of patients without diabetes who experimented the primary endpoint was 656/8,098 (8.1%) in those receiving CAS and 700/8,078 (8.6%) in those receiving non-CAS. RR 0.93 (0.84 to 1.04)</p> <p><u>NS differences in diabetic population</u></p> <p>The number of patients with diabetes who experimented the primary endpoint was 463/3,169 (14.6%) in those receiving CAS and 450/3,231 (13.9%) in those receiving non-CAS. RR 1.05 (0.93 to 1.18)</p> <p>Adverse events General population: Both drug combinations were generally well tolerated in each treatment group. Patients in the CAS group reported constipation and cough more frequently than patients in the NCAS group, while NCAS patients had more dyspnea, lightheadness, symptomatic bradycardia, and wheezing.</p>	<p>Abbot – BASF Pharma</p>
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⁷ Defined as any of the following: remote (≥ 3 months prior to enrolment) confirmed MI, coronary angiogram with more than 50% narrowing of at least 1 major coronary artery, diagnosis of classic angina pectoris, or concordant abnormalities on 2 different types of signals (ECGs, echocardiograms, and/or radionuclide scans) from stress test provided that 2 different signals showed findings consistent for ischemia. Patients with heart failure classes I through III were included.