Chapter 6

Clinical Efficacy of a Combination of Bisoprolol and Amlodipine

Zbigniew Gaciong
Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw, Warsaw, Poland

Randomised and real-world evaluations of a bisoprolol/amlodipine combination tablet have shown this treatment to be more effective than monotherapy and to support good adherence to therapy in patients with hypertension. A consistent reduction in heart rate (HR) with this treatment is a further potential benefit likely to improve long-term clinical outcomes in this population.

Therapeutic efficacy of the bisoprolol/amlodipine combination tablet in patients with hypertension

Overview of studies that have evaluated the efficacy of bisoprolol/amlodipine combination tablets in patients with hypertension

A series of randomised and observational studies have evaluated single-tablet combinations of bisoprolol and amlodipine in patients with

hypertension with or without other comorbidities. These are summarised in Table 1 [1–12] and described below.

Table 1 Details of studies that evaluated the bisoprolol/amlodipine combination tablet in patients with hypertension.

Design (1st author)	N	Duration	Key details
Randomised (*Gottwald-Hostalek et al [1]*)	200	18 weeks	Study of the efficacy, tolerability and safety of the combination tablet in patients with BP previously sub-optimally controlled on bisoprolol 5 mg or amlodipine 5 mg monotherapy
Randomised (*Jędrusik et al [2]*)	367	8 weeks	Comparison of amlodipine 5 mg and bisoprolol/amlodipine 5/5 mg in patients uncontrolled on amlodipine 5 mg
Randomised (*Shirure et al [3]*)	60	1 month	Comparison of bisoprolol/amlodipine 5/5 mg with bisoprolol 5 mg and amlodipine 5 mg monotherapies in patients with WHO Stage 2 hypertension
Randomised (*Fendrikova et al [4] Tarlovskaya et al [5]*)	61	12 weeks	Study of effects of the bisoprolol/amlodipine combination tablet vs a free combination of bisoprolol and amlodipine (each added to enalapril) on BP and aortic pulse wave velocity in patients with sub-optimally controlled hypertension and coronary heart disease; a pharmacoeconomic evaluation was also conducted
Observational (modelled) (*Foch et al [6]*)	260	8 weeks	Anchored, simulated treatment comparison of effects on BP of the bisoprolol/amlodipine 5/5 mg combination with up titration of amlodipine monotherapy from 5 mg to 10 mg based on the results of two randomised trials
Observational (*Gottwald-Hostalek, et al [7]*)	12,424	6 months	Non-interventional cohort study of patients with hypertension switched from a co-administered combination of bisoprolol and amlodipine to the combination tablet ≥4 weeks in 6 countries in eastern Europe
Observational (*Mehta et al [8]*)	106	8 weeks	Observational, non-comparative study of the effects on BP of a bisoprolol/amlodipine 2.5/5 mg combination tablet in patients with moderate hypertension
Observational (*Rana et al [9]*)	801	4 weeks	Observational, non-comparative evaluation of the effects on BP of a bisoprolol/amlodipine 5/5 mg combination tablet in patients with Stage 2 hypertension

Observational (*Chesnikova et al [10]*)	100	4 weeks	Study of the effects of the bisoprolol/amlodipine combination tablet on BP and signs of cardiac ischaemia in patients with sub-optimally controlled hypertension and coronary heart disease
Observational (clin pharm) (*Bogomaz et al [11]*)	15	8 weeks	Study of peripheral (brachial) and central (aortic) haemodynamics in patients treated with bisoprolol/amlodipine 5/5 mg combination tablet (5/10 mg or 10/10 mg)
Observational (clin pharm) (*Zapesochnaya et al [12]*)	140	6 months	Study of the effects of a bisoprolol/amlodipine combination tablet on BP and on the structural and functional status of the myocardium in patients with hypertension

BP: blood pressure; Clin pharm: clinical pharmacy; WHO: World Health Organization.

Effects on blood pressure

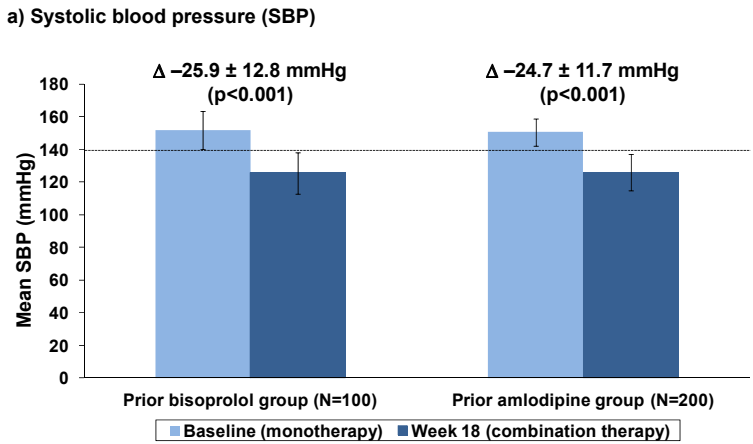
Randomised trials in patients with blood pressure (BP) uncontrolled on monotherapy with bisoprolol or amlodipine

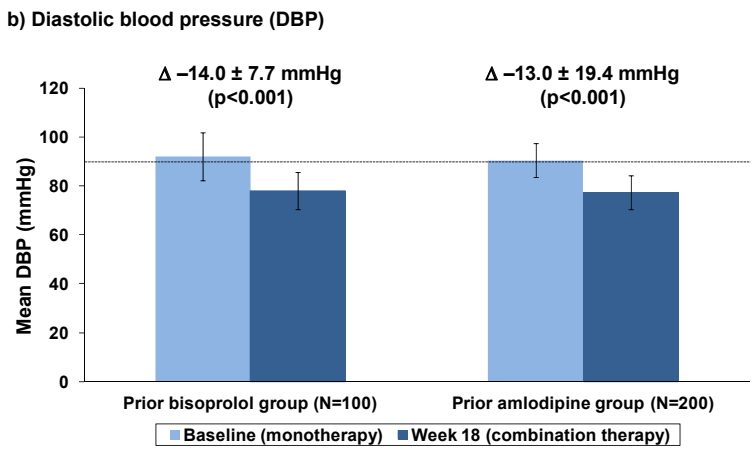
A randomised clinical trial evaluated the single-tablet combination of bisoprolol/amlodipine in 200 patients with hypertension sub-optimally controlled by monotherapy with either amlodipine 5 mg or bisoprolol 5 mg [1]. Initially patients were randomised into two groups ("A" and "B") and all received bisoprolol/amlodipine 5/5 mg for 6 weeks. Patients with sub-optimally controlled BP (≥140/≥90 mmHg) at week 6 in group A were up-titrated to bisoprolol/amlodipine 5/10 mg, while sub-optimally controlled patients in group B were up-titrated to the 10/5 mg dosage strength. BP control was evaluated again at week 12, when patients with sub-optimal control of BP received the 10/10 mg combination tablet for another 6 weeks. Patients with well-controlled BP (<140/<90 mmHg) continued on their previous treatment at each stage.

The primary outcome of the trial was the mean change in systolic BP (SBP) from baseline (when patients were receiving antihypertensive monotherapy) to week 18. Mean changes in SBP were substantial, clinically and statistically ($p<0.001$) significant, and essentially identical

in patients from both the prior bisoprolol and prior amlodipine groups (–26 mmHg and –25 mmHg, respectively; Figure 1a). Substantial reductions in diastolic BP (DBP) were also seen (–14 mmHg and –13 mmHg, respectively; Figure 1b). The majority of patients (74%) had achieved

Figure 1 Effect of treatment with a bisoprolol/amlodipine combination tablet on blood pressure in patients with hypertension sub-optimally controlled by monotherapy with bisoprolol 5 mg or amlodipine 5 mg.



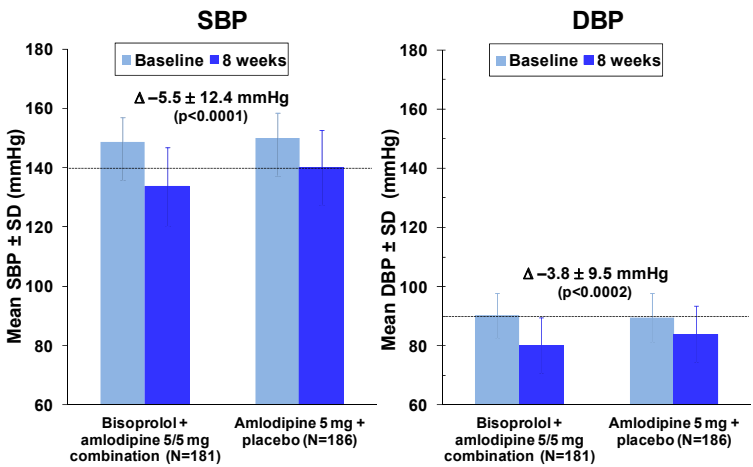


Δ: mean change. The mean change in SBP from baseline to week 18 was the primary endpoint of the trial; mean change in DBP was a pre-specified secondary endpoint.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented in reference [1].

control of BP on the 5/5 mg combination tablet at study end. Up titration of therapy, where required, increased the proportion of patients with well-controlled BP to 88% by the end of the study. Control rates were similar for patients in each prior therapy group.

The AMCOR trial involved randomisation of 367 patients with BP sub-optimally controlled by amlodipine 5 mg to the same treatment with additional placebo or to treatment with a combination of bisoprolol and amlodipine 5/5 mg, for 8 weeks [2]. Mean SBP and DBP were reduced in both groups (Figure 2). There was a statistically and clinically significant treatment difference in favour of the combination of –5.5 ± 12.4 mmHg for SBP ($p<0.0001$) and of –3.8 ± 9.5 mmHg for DBP ($p<0.0002$).

Figure 2 Effects of bisoprolol/amlodipine 5/5 mg combination treatment vs. amlodipine 5 mg and placebo on BP in patients uncontrolled on amlodipine 5 mg monotherapy: data from the AMCOR trial.



BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented in reference [2].

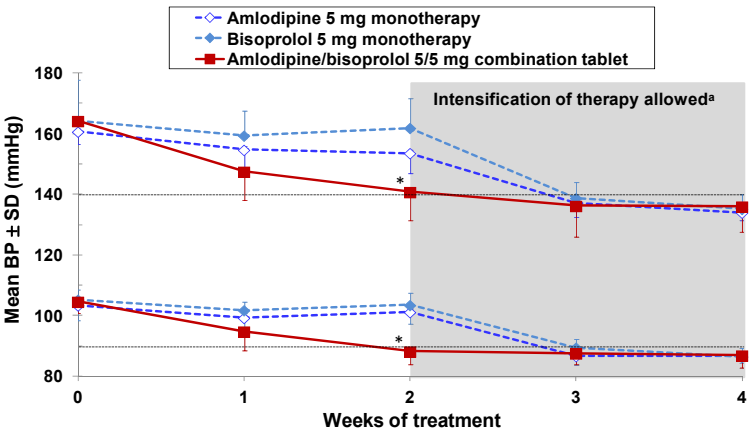
Other randomised evaluations of bisoprolol/amlodipine combination tablets

Sixty patients with Stage 2 hypertension (SBP ≥160 mmHg or DBP ≥100 mmHg[a]) were randomised to receive bisoprolol 5 mg, amlodipine 5 mg, or the bisoprolol/amlodipine 5/5 mg combination tablet for 1 month [3]. After 2 weeks of treatment, patients with sub-optimal BP (target <140/<90 mmHg) on monotherapy were switched to the bisoprolol/amlodipine 5/5 mg combination tablet; enalapril was added at 2 weeks for patients uncontrolled on the combination tablet. The combination tablet was significantly more effective than either monotherapy over the first 2 weeks of treatment (Figure 3). Thereafter, mean SBP and DBP became similar as antihypertensive therapy was intensified where required; 80% of the amlodipine monotherapy group and 90% of the bisoprolol monotherapy group required a switch to the combination tablet due to sub-optimal BP control, compared with only 5% of the combination tablet group requiring additional enalapril.

Another randomised trial conducted in Russia employed ambulatory BP recording to study the effects of the bisoprolol/amlodipine combination tablet versus a free combination of bisoprolol and amlodipine (each added to enalapril) in 61 patients with sub-optimally controlled hypertension and pre-existing coronary heart disease [4]. Daytime and nighttime BP was reduced in both groups, becoming well controlled in 97% of the combination tablet group and in 87% of the free combination group. Aortic pulse wave velocity, aortic augmentation index and aortic DBP improved significantly only in the combination therapy group. A pharmacoeconomic evaluation derived from these data (from the Russian healthcare system perspective) found lower costs per unit of reduction of SBP, DBP and HR for the combination tablet versus the free combination approach [5].

a. See Chapter 1 of this book for details of classifications of hypertension.

Figure 3 Changes in blood pressure in a randomised comparison of the bisoprolol 5 mg/amlodipine 5 mg combination tablet with bisoprolol 5 mg or amlodipine 5 mg monotherapy in patients with Stage 2 hypertension.



BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation.
[a]If BP was >140/90 mmHg, patients randomised to either monotherapy could be switched to the combination tablet and enalapril could be added to the regimen of patients randomised to the combination tablet.
Some SD bars have been omitted for clarity.
*p<0.001 vs. either monotherapy at week 2.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented in reference [3].

Model-derived analysis based on data from randomised clinical trials

No randomised clinical trial to date has compared the effects of up titration of amlodipine with a switch to bisoprolol/amlodipine combination therapy in patients sub-optimally controlled on monotherapy with amlodipine 5 mg. A modelling approach was used to simulate this treatment comparison, based on data from two randomised clinical trials in patients with hypertension sub-optimally controlled on amlodipine 5 mg monotherapy [6]:

Study 1: randomised comparison of bisoprolol/amlodipine 5/5 mg combination versus amlodipine 5 mg plus placebo [2];

Study 2: the amlodipine monotherapy arms of a randomised comparison of amlodipine 5 mg, amlodipine 10 mg, and two strengths of a telmisartan/amlodipine tablet [13].

This was an anchored, simulated treatment comparison; the term "anchored" refers to the amlodipine 5 mg arm, which was present in both studies. Briefly, the analysis used individual patient data from Study 1 to construct a model that adjusted its study population to resemble that of Study 2, based on the baseline characteristics of each trial. This enabled the model to make predictions of average changes in BP that would be expected to occur had the two studies had the same patient populations. In this way, the model enabled a comparison of the predicted effect on BP of a switch from amlodipine 5 mg monotherapy to an amlodipine/bisoprolol 5 mg/5 mg combination (evaluated in Study 1) with the observed effect of up titrating amlodipine 5 mg to amlodipine 10 mg (evaluated in Study 2).

Baseline and follow-up measures of BP were available from 261 patients in the combination therapy arm and 255 patients in the amlodipine 10 mg monotherapy arm, and these patients were included in the analysis population. The analysis was based on 8 weeks of treatment. The predicted reduction in BP with the bisoprolol/amlodipine 5/5 mg combination (modelled to the population of Study 2) was larger than the effect of amlodipine 5 mg monotherapy (mean treatment difference [standard deviation (SD)] –6.5 [1.8]/–5.5 [1.2] mmHg), as was the observed effect of up titration of amlodipine from 5 mg to 10 mg in Study 2 (mean treatment difference [SD] –4.9 [1.0]/–2.2 [0.7] mmHg). The estimated mean difference for effects on BP between the combination tablet and amlodipine 10 mg was –1.6 [1.9]/–3.3 [1.3] mmHg.

The combination tablet, therefore, induced larger reductions in BP than either amlodipine 5 mg or amlodipine 10 mg in this analysis, though the magnitude of the difference between treatments was clinically meaningful only for DBP. It should be noted that 27% of patients in Study 2 reported peripheral oedema as a side-effect of amlodipine 10 mg, compared with 4–9% of patients in study arms that included amlodipine 5 mg [2]. Only 1–2% of patients in Study 1 reported peripheral oedema with regimens that included amlodipine 5 mg. Thus, in this analysis, the bisoprolol/amlodipine 5/5 mg combination tablet was more effective than amlodipine 5 mg, and at least as effective as amlodipine 10 mg, with less potential for oedema-related side-effects.

Real-world study that involved switching from a free combination of bisoprolol and amlodipine to the bisoprolol/amlodipine combination tablet

This study enrolled a population of 12,242 patients with hypertension who had been switched from a free combination of bisoprolol and amlodipine to bisoprolol/amlodipine combination tablets at least 4 weeks previously [7]. Patients were followed up for 6 months. Substantial reductions were observed for:

SBP – reduced from 147.6 ± 16 mmHg at baseline to 131.2 ± 10 mmHg at 6 months (mean difference ± SD: –16.5 ± 15 mmHg);

DBP – reduced from 88.3 ± 10 mmHg at baseline to 78.9 ± 7 mmHg at 6 months (mean difference: –9.5 ± 11 mmHg);

Pulse pressure – reduced from 59.3 ± 13 mmHg at baseline to 52.3 ± 10 mmHg at 6 months (mean difference: –7.1 ± 14 mmHg).

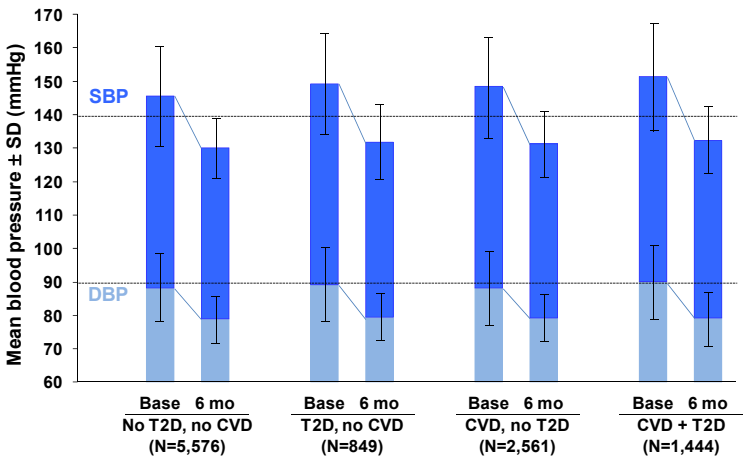
Effects on BP were studied after stratification of patients at baseline for normal body mass index (BMI; 19–25 kg/m^2), overweight (>25–30 kg/m^2) or obesity (>30 kg/m^2). Mean BP values at 6 months differed slightly across these BMI categories (130.3 ± 10/78.5 ± 7 mmHg, 131.1 ± 10/78.9 mmHg, and 131.8 ± 10/79.3 ± 7 mmHg, respectively), and were consistent with achievement of good BP control for most patients.

These BP reductions were achieved despite patients receiving similar average doses of bisoprolol and amlodipine before the switch (5.5 mg and 6.1 mg, respectively) and after the switch (5.8 mg and 6.3 mg, respectively); about 80% of patients received the same dose of the therapies before and after the switch. The improvement in BP was likely associated, at least in part, with good adherence to the combination therapy regimen. Adherence (measured as proportion of prescribed medication received in this study) was “good” or “excellent” in 99% of patients.

This real-world population contained patients with a range of comorbidities, and a subsequent analysis from the same patient population focussed on the impact of cardiovascular comorbidities in more detail [14]. Patients were stratified for the presence of cardiovascular disease without type 2 diabetes (N=2,561 [25% of the population]); type 2 diabetes without cardiovascular disease (N=849 [8%]); both cardiovascular

disease and type 2 diabetes (N=1,444 [14%]); or none of these (N=5,576 [53%]). Higher mean values of SBP were observed in patients with cardiovascular disease (148.5 mmHg), diabetes (149.3 mmHg), or both (151.5 mmHg) at baseline, compared with 145.5 mmHg for patients without these comorbidities (DBP was similar between these groups). BP was >140/90 mmHg in 28% of patients with no comorbidities, compared with 31% (cardiovascular disease), 33% (type 2 diabetes), and 38% (both comorbidities), consistent with this observation. These differences were no longer evident at study end, as mean SBP ranged between 130.0 mmHg and 132.2 mmHg across the four groups (Figure 4).

Figure 4 Changes in blood pressure according to the presence or absence at baseline of predefined comorbidities in a large cohort of patients with hypertension previously treated with a free combination of bisoprolol and amlodipine who received 6 months' treatment with bisoprolol/amlodipine combination tablets.



Base: baseline; CVD: cardiovascular disease; DBP: diastolic blood pressure; mo: months; SBP: systolic blood pressure; SD: standard deviation; T2D: type 2 diabetes.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented in reference [14].

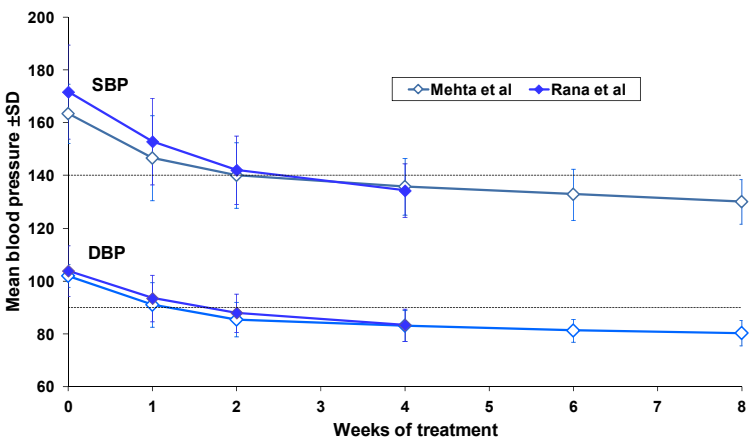
Other real-world analyses

Two real-world analyses evaluated the effects of bisoprolol/amlodipine 2.5/5 mg [8] or 5/5 mg [9] combination tablets in patients with Stage 2 hypertension in India, over 8 weeks (N=106) and 4 weeks (N=801) of treatment, respectively. Marked reductions in BP occurred in both studies (Figure 5), from 163/102 mmHg to 130/80 mmHg (8-week study) and from 172/104 mmHg to 134/83 mmHg (4-week study). The majority of patients in the 8-week study (89%) achieved BP <140/90 mmHg with the bisoprolol/amlodipine 2.5/5 mg tablet.

Three other real-world analyses (from Russia) are briefly summarised below:

- Mean BP was reduced from 163/93 mmHg to 128/77 mmHg during 4 weeks of treatment with bisoprolol/amlodipine combination tablets in an observational study in 100 patients with uncontrolled hypertension and coronary heart disease [10]. SBP and DBP goals were achieved by 90% and 97%, respectively.

Figure 5 Changes in mean blood pressure during treatment with bisoprolol/amlodipine 5/5 mg combination tablets in patents with Stage 2 hypertension in India.



DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation.
Dotted lines show targets for BP control of 140 mmHg (SBP) and 90 mmHg (DBP).
Drawn from data presented by Mehta et al [8] and Rana et al [9].

- The second study was conducted in 15 previously antihypertensive-drug naïve patients with BP not adequately controlled by a 4-week trial of bisoprolol 5–10 mg monotherapy [11]. Mean peripheral (brachial) BP decreased from 157/98 mmHg at baseline to 148/95 mmHg after 4 weeks of bisoprolol 10 mg, and to 133/81 mmHg after a further 4 weeks of treatment with bisoprolol/amlodipine. During treatment with bisoprolol monotherapy, central BP decreased slightly (from 145 mmHg to 140 mmHg), with little change in pulse pressure (from 48.2 to 47.1 mmHg) and a slight increase in Augmentation Index (from 32.8% to 34.7%). Treatment with the bisoprolol/amlodipine 5/5 mg combination tablet markedly reduced central SBP (to 121 mmHg), pulse pressure (to 41.2 mmHg) and Augmentation Index (to 22.5%). Thus, bisoprolol alone was less effective on central versus brachial BP, while addition of amlodipine overcame this limitation.
- A study in two groups of 72 and 68 patients with hypertension (stratified according to shift work patterns) used echocardiography to explore changes in left ventricular structure during 6 months of treatment with bisoprolol/amlodipine tablets [12]. A reduction in mean BP (93% and 88% of the two groups achieved goal BP) was accompanied by increases in the proportions of patients with normal left ventricular geometry (from 38% to 45% in one group and from 24% to 33% in the other) and a decrease in the proportions of patients with concentric left ventricular hypertrophy (from 31% to 24% in one group and from 46% to 38% in the other).

Effects on HR

Table 2 shows the effects of bisoprolol/amlodipine 5/5 mg combination tablets on HR, where reported. Variable, but substantial, reductions in HR occurred in all randomised or real-world studies, with average reductions in HR ranging from about –6 bpm to about –19 bpm in populations receiving bisoprolol/amlodipine combination tablets.

Table 2 Effects of bisoprolol/amlodipine combination tablets on heart rate in randomised and real-world studies.

Ref	Heart rate (bpm) + SD at		Δ	P-value
	Baseline	Study end		
Randomised trials				
[1]	71.7 ± 9.7	62.7 ± 9.5	–9.0 ± 9.5	<0.001
[2]	66.7 ± 9.78	74.2 ± 9.38	–6.3 ± 9.3	<0.0001
Real-world studies				
[7]	75.8 ± 10	68.4 ± 7	–7.7 ± 10	NR
[8]	87.3 ± 11.0	68.4 ± 8.1	–18.9[a]	NR
[9]	83.3 ± 9.6	74.6 ± 6.8	–8.7[a]	NR
[10]	80.1 ± 9.6	63.0 ± 5.4	–17.1[a]	NR
[11]	74.3 ± 5.8	62.4 ± 4.2	–11.9[a]	<0.05

bpm: beats per minute; NR: not reported; Ref: reference.
Δ: mean difference in heart rate between baseline and study end ([a]or difference in mean values where this was not reported).

Other clinical evidence

Studies with combinations of β-blockers and calcium channel blockers (CCBs)

Studies with other β_1-selective β-blockers in combination with amlodipine will be described briefly here, in the absence of randomised trials that specifically evaluated co-administered (free) combinations of bisoprolol and amlodipine. Trials for inclusion here were identified using a PubMed search for "*(atenolol OR metoprolol OR acebutolol OR nebivolol OR bisoprolol OR Xamoterol OR Acebutolol OR Celiprolol) AND amlodipine*", limited to "*Randomised controlled trial*". Relevant articles were identified by inspection of abstracts of the resulting 187 search hits.

Low-dose atenolol 25 mg/amlodipine 2.5 mg combination therapy was superior for effects on BP compared with atenolol 25 mg or amlodipine 2.5 mg alone in patients with hypertension [15]. A similar benefit for the combination was seen in patients who needed higher doses of combination therapy (atenolol 50 mg/amlodipine 5 mg) versus these doses of monotherapy in this study. Addition of amlodipine to atenolol reduced 24-hour BP significantly in patients with BP uncontrolled

by atenolol alone [16]. The highest dose of a single-tablet combination of metoprolol and amlodipine induced a numerically larger fall in BP than a lower-dose combination of these agents or the constituent monotherapies, although the difference did not achieve statistical significance [17]. The efficacy of a metoprolol extended release/amlodipine combination was similar to that of a losartan/amlodipine combination in another study [18]. A thiazide diuretic induced a larger reduction in BP than atenolol in patients with hypertension already receiving amlodipine and lisinopril [19].

A combination of atenolol and amlodipine reduced BP and arterial stiffness (measured using pulse wave velocity [PWV]) to a similar extent compared with a valsartan/amlodipine combination in patients with hypertension [20]. Reductions in BP and HR accounted largely for the reduced PWV in the β-blocker-amlodipine group. Another study showed that a valsartan/amlodipine combination induced comparable reductions in brachial BP versus an atenolol/amlodipine combination, although the valsartan/amlodipine combination reduced central BP more effectively [21]. Addition of valsartan, but not amlodipine, to atenolol suppressed indices of intracardiac conduction, consistent with the mechanisms of these drugs (see Chapter 4) [22].

Both cardioselective β-blockers and amlodipine are indicated for the management of angina pectoris, and studies evaluating combinations of these mechanisms in these patients are included briefly here for completeness. Results of trials that evaluated β_1-blockers in combination with amlodipine in patients with angina have been conflicting. Bisoprolol plus amlodipine was not more effective than bisoprolol alone in two studies that used treadmill exercise tolerance as its main outcome [23, 24], but reduced the occurrence of chest pain on exercise in two other studies [25, 26], and during exercise testing and in the ambulatory setting in a fifth [27]. Elsewhere, addition of atenolol to amlodipine was more effective in suppressing ischaemic episodes in ambulatory patients, compared with amlodipine alone [28]. Amlodipine was more effective than diltiazem added to atenolol in suppressing ischaemic symptoms in patients sub-optimally controlled by atenolol alone, and was better tolerated [29]. Finally, addition of amlodipine to

atenolol was haemodynamically safe 15 days after an acute myocardial infarction for normotensive patients without severe left ventricular dysfunction [30].

Comparisons of bisoprolol or amlodipine with other monotherapies

Large meta-analyses have confirmed that the BP-lowering efficacy of β-blockers and CCBs are comparable to that provided by other antihypertensive classes [31, 32]. A number of randomised, head-to-head trials have demonstrated that bisoprolol and amlodipine each have similar antihypertensive efficacy to other antihypertensive agents within their class, and to agents from the four other classes (Table 3).

Conclusions

Numerous randomised clinical trials have shown that bisoprolol and amlodipine monotherapies are as effective as members of other antihypertensive classes (Table 3). The effects on BP of combining two antihypertensive agents is essentially additive [32]. The results of the randomised and real-world studies that evaluated single-tablet combinations of these agents, summarised in this chapter, have confirmed the greater efficacy of this treatment for controlling BP compared with monotherapies. The consistent reductions in HR observed with the bisoprolol/amlodipine tablet is another potential source of clinical benefit, as higher versus lower HR has been identified as a predictor of adverse cardiac outcomes, especially (but not only) in people with coronary heart disease or heart failure [33–35].

The principle of applying combination antihypertensive therapy in the management of hypertension is well established in current European guidelines (see also Chapter 2 of this book) [36, 37]. Moreover, these guidelines recognise the valuable role of single-tablet combinations in simplifying the antihypertensive regimen and supporting good adherence to therapy [38, 39], which in turn helps to optimise long-term patient outcomes [40]. The large, real-world studies summarised here

Table 3 Overview of head-to-head randomised trials of bisoprolol and amlodipine vs antihypertensive agents from other classes.

	Effects of bisoprolol on BP vs other antihypertensive agents	Effects of amlodipine on BP vs other antihypertensive agents
β-blockers		
Acebutolol	Comparable [41]	Comparable [42]
Atenolol	Comparable [43–47] or larger effect [48–51] Lower effect on central BP [43]	Comparable [52–56]
Celiprolol	Less effective on central BP [57]	–
Metoprolol	Comparable [58] More effective during exercise [59]	Comparable (obstructive sleep apnoea) [60]
Nebivolol	Comparable [61]	Comparable [62]
Renin-angiotensin-aldosterone system blockers		
Captopril	Comparable [63]	Comparable [64] or more effective [65]
Enalapril	Comparable (office- [66, 67] and 24-hour [66] BP)	Comparable [42, 68–72] Larger effect on trough BP [73]
Zofenopril	–	Comparable [74]
Lisinopril	Comparable (ambulatory [75] or office [76] BP)	Comparable [77–82] or larger effect [83]
Benazepril	–	Comparable [84] or larger [85] effect
Quinapril	–	Comparable [86, 87]
Ramipril	–	Larger effect (ambulatory) [88, 89]
Irbesartan	–	Comparable [90]
Losartan	Comparable (office BP) [91, 92] Less effective on central BP [91]	Larger [93] or comparable [71, 82, 94–100] incl. post-renal transplant [101] and in NASH [102]
Valsartan	–	Comparable [103–105] or larger [106]
Telmisartan	–	Comparable (ambulatory) [89]
Candesartan	–	Comparable [107–109]
Calcium channel blockers		
Amlodipine	Comparable (haemodialysis) [110]	–
Manidipine	–	Comparable [111]
SR nifedipine	Comparable [67, 112, 113]	–
Diuretics		
Thiazides	Comparable [114]	Comparable [42, 68, 71, 77, 78, 115–117]
Spironolactone	Larger effect of spironolactone (drug-resistant hypertension) [118]	–

BP: blood pressure; incl.: including; NASH: non-alcoholic steatohepatitis; SR: sustained release.
Randomised head-to-head trials designed to measure efficacy of monotherapies in people with hypertension were included from a PubMed search for "*amlodipine AND ([list of drugs of interest]) AND hypertension*".
Comparisons are from the perspective of bisoprolol or amlodipine: for example, a "larger effect" means a larger effect of those drugs vs. the stated comparator.

confirmed that adherence rates to regimens based on the bisoprolol/amlodipine tablet were high.

In conclusion, these studies have shown that the bisoprolol/amlodipine tablet is an effective option for the management of hypertension that supports good adherence to therapy. This tablet has a place in the management of hypertension, particularly for people with a compelling indication for β-blockade (such as coronary heart disease, post-myocardial infarction or atrial fibrillation), or in younger women planning a family [37].

References

1 Gottwald-Hostalek U, Li L, Montenegro P. Bisoprolol/amlodipine combination therapy improves blood pressure control in patients with essential hypertension following monotherapy failure. Curr Med Res Opin. 2016;32:1735–43. https://doi.org/10.1080/03007995.2016.1205573

2 Jędrusik P, Placha G, Gaciong Z, AMCOR trial investigators. Efficacy and safety of bisoprol 5 mg plus amlodipine 5 mg in patients with hypertension uncontrolled on monotherapy with 5 mg of amlodipine, a phase III multicentre, randomized, double-blind, placebo-controlled clinical trial – the AMCOR study. Curr Med Res Opin 2022;Submitted.

3 Shirure PA, Tadvi NA, Bajait CS, Baig MS, Gade PR. Comparative effect of fixed dose combination of amlodipine + bisoprolol versus amlodipine and bisoprolol alone on blood pressure in stage-2 essential hypertensive patients. Int J Med Res Health Sci 2012;1:13–9.

4 Fendrikova A, Skibitsky V. Effectiveness of fixed-dose combination of bisoprolol and amlodipine in patients with arterial hypertension and coronary heart disease. J Hypertens 2015;(eSuppl):e322.

5 Tarlovskaya E, Malchikova S, Skibitskyi V, Fendrikova A, Skibitskyi A, Sirotenko D. Economy of antianginal and antihypertensive efficacy of the fixed combination of bisoprolol/amlodipine in patients with arterial hypertension and coronary heart disease. J Hypertens. 2015;(eSuppl):e328–e9.

6 Foch C, Feifel J, Gottwald-Hostalek U. An anchored simulated treatment comparison of uptitration of amlodipine compared with a low-dose combination treatment with amlodipine 5 mg/bisoprolol 5 mg for patients with hypertension suboptimally controlled by amlodipine 5 mg monotherapy. Curr Med Res Opin. 2022;38:587–93. https://doi.org/10.1080/03007995.2022.2030112.

7 Hostalek U, EMW K. Treatment of hypertension with a fixed-dose combination of bisoprolol and amlodipine in daily practice: results of a multinational non-investigational study. Cardiovasc Disord Med 2016;1:10. https://doi.org/10.15761/CDM.1000118.

8 Mehta S, Shah M, Shah A. Efficacy and tolerability of a fixed dose combination of amlodipine and bisoprolol in essential hypertension. Indian Pract. 2005;58:751–9.

9 Rana R, Patil A. Efficacy and safety of bisoprolol plus amlodipine fixed dose combination in essential hypertension. Indian Pract. 2008;61:225–34.

10 Chesnikova AI, Safronenko VA, Kolomatskaia OE. Evaluating the effectiveness of a fixed combination of amlodipine and bisoprolol in ambulatory patients with arterial hypertension and ischemic heart disease. Kardiologiia. 2014;54:17–23. https://doi.org/10.18565/cardio.2014.9.17–23.

11 Bogomaz A, Kotovskaya Y, Kobalava Z. Combination with amlodipine eliminates adverse effect of a beta-blocker on aortic pulse pressure augmentation. J Hypertens. 2015;33:e326. https://doi.org/10.1097/01.hjh.0000468379.55561.95.

12 Zapesochnaya IL, Avtandilov AG. Dynamics of structural and functional status of myocardium due to combination therapy with amlodipine and bisoprolol in patients with arterial hypertension. Rational Pharmacother Cardiol 2014;10:606–11. https://doi.org/10.20996/1819-6446-2014-10-6-606-611.

13 Neldam S, Lang M, Jones R. Telmisartan and amlodipine single-pill combinations vs amlodipine monotherapy for superior blood pressure lowering and improved tolerability in patients with uncontrolled hypertension: results of the TEAMSTA-5 study. J Clin Hypertens (Greenwich). 2011;13:459–66. https://doi.org/10.1111/j.1751-7176.2011.00468.x.

14 Hostalek U, Czarnecka D, Kurzeja A, Koch E. Efficacy of and adherence to a fixed-dose combination of bisoprolol and amlodipine in hypertensive patients with and without type 2 diabetes mellitus or coronary artery disease. J Heart Health 2015b. 2015. https://doi.org/10.16966/2379-769X.114.

15 Pareek A, Salkar H, Mulay P, Desai S, Chandurkar N, Redkar N. A randomized, comparative, multicentric evaluation of atenolol/amlodipine combination with atenolol alone in essential hypertensive patients. Am J Ther. 2010;17:46–52. https://doi.org/10.1097/MJT.0b013e3181a9db74.

16 Mettimano M, Pichetti F, Fazzari L, Migneco A, Specchia L, Romano Spica V, et al. Combination therapy with beta-adrenergic blockade and amlodipine as second line treatment in essential hypertension. Int J Clin Pract. 2000;54:424–8.

17 Devi P, Xavier D, Sigamani A, Pandey S, Thomas T, Murthy S, et al. Effect of fixed dose combinations of metoprolol and amlodipine in essential hypertension: MARS--a randomized controlled trial. Blood Press Suppl. 2011;2:5–12. https://doi.org/10.3109/08037051.2011.617040.

18 Pareek A, Chandurkar NB, Sharma R, Tiwari D, Gupta BS. Efficacy and tolerability of a fixed-dose combination of metoprolol extended release/amlodipine in patients with mild-to-moderate hypertension: a randomized, parallel-group, multicentre comparison with losartan plus amlodipine. Clin Drug Investig. 2010;30:123–31. https://doi.org/10.2165/11531770-000000000-00000.

19 Antonios TF, Cappuccio FP, Markandu ND, Sagnella GA, MacGregor GA. A diuretic is more effective than a beta-blocker in hypertensive patients not controlled on amlodipine and lisinopril. Hypertension. 1996;27:1325–8. https://doi.org/10.1161/01.hyp.27.6.1325.

20 Boutouyrie P, Beaussier H, Achouba A, Laurent S. Destiffening effect of valsartan and atenolol: influence of heart rate and blood pressure. J Hypertens. 2014;32:108–14. https://doi.org/10.1097/hjh.0000000000000014.

21 Boutouyrie P, Achouba A, Trunet P, Laurent S. Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: the EXPLOR study. Hypertension. 2010;55:1314–22. https://doi.org/10.1161/hypertensionaha.109.148999.

22 Santarelli P, Biscione F, Natale A, Manzoli A, Lanza GA. Electrophysiologic effects of amlodipine vs. diltiazem in patients with coronary artery disease and beta-blocking therapy. Cardiovasc Drugs Ther. 1994;8:653–8. https://doi.org/10.1007/bf00877419.

23 Ferguson JD, Ormerod O, Lenox-Smith AJ. Bisoprolol alone and in combination with amlodipine or nifedipine in the treatment of chronic stable angina. Int J Clin Pract. 2000;54:360–3.

24 Pehrsson SK, Ringqvist I, Ekdahl S, Karlson BW, Ulvenstam G, Persson S. Monotherapy with amlodipine or atenolol versus their combination in stable angina pectoris. Clin Cardiol. 2000;23:763–70. https://doi.org/10.1002/clc.4960231014.

25 Woodmansey PA, Stewart AG, Morice AH, Channer KS. Amlodipine in patients with angina uncontrolled by atenolol. A double blind placebo controlled cross over trial. Eur J Clin Pharmacol. 1993;45:107–11. https://doi.org/10.1007/bf00315489.

26 Dunselman PH, van Kempen LH, Bouwens LH, Holwerda KJ, Herweijer AH, Bernink PJ. Value of the addition of amlodipine to atenolol in patients with angina pectoris despite adequate beta blockade. Am J Cardiol. 1998;81:128–32. https://doi.org/10.1016/s0002-9149(97)00877-1.

27 Davies RF, Habibi H, Klinke WP, Dessain P, Nadeau C, Phaneuf DC, et al. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. J Am Coll Cardiol. 1995;25:619–25. https://doi.org/10.1016/0735-1097(94)00436-t.

28 Frishman WH, Glasser S, Stone P, Deedwania PC, Johnson M, Fakouhi TD. Comparison of controlled-onset, extended-release verapamil with amlodipine and amlodipine plus atenolol on exercise performance and ambulatory ischemia in patients with chronic stable angina pectoris. Am J Cardiol. 1999;83:507–14. https://doi.org/10.1016/s0002-9149(98)00904-7.

29 Knight CJ, Fox KM. Amlodipine versus diltiazem as additional antianginal treatment to atenolol. Centralised European Studies in Angina Research (CESAR) Investigators. Am J Cardiol. 1998;81:133–6. https://doi.org/10.1016/s0002-9149(97)00893-x.

30 Rocha P, Pathé M, Bernaud C, Zannier D, Baron B, Marchand X, et al. Acute hemodynamic effects of amlodipine 15 days after a myocardial infarction in normotensive patients treated with atenolol. Cardiovasc Drugs Ther. 1997;11:139–47. https://doi.org/10.1023/a:1007732830753.

31 Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665. https://doi.org/10.1136/bmj.b1665.

32 Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122:290–300. https://doi.org/10.1016/j.amjmed.2008.09.038.

33 Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J. 2005;26:967–74. https://doi.org/10.1093/eurheartj/ehi190.

34 Hsia J, Larson JC, Ockene JK, Sarto GE, Allison MA, Hendrix SL, et al. Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study. BMJ. 2009;338:b219. https://doi.org/10.1136/bmj.b219.

35 Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010;376:886–94. https://doi.org/10.1016/s0140-6736(10)61259-7.

36 Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104. https://doi.org/10.1093/eurheartj/ehy339.

37 Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227–337. https://doi.org/10.1093/eurheartj/ehab484.

38 Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. Hypertension. 2021;77:692–705. https://doi.org/10.1161/hypertensionaha.120.15781.

39 Weisser B, Predel HG, Gillessen A, Hacke C, Vor dem Esche J, Rippin G, et al. Single pill regimen leads to better adherence and clinical outcome in daily practice in patients suffering from hypertension and/or dyslipidemia: results of a meta-analysis. High Blood Press Cardiovasc Prev. 2020;27:157–64. https://doi.org/10.1007/s40292-020-00370-5.

40 Lee H, Yano Y, Cho SMJ, Heo JE, Kim DW, Park S, et al. Adherence to antihypertensive medication and incident cardiovascular events in young adults with hypertension. Hypertension. 2021;77:1341–9. https://doi.org/10.1161/hypertensionaha.120.16784.

41 Bouvier JM, Rabot D, Herrero G. Effect of bisoprolol and acebutolol on resting blood pressure and on exercise blood pressure profile in hypertensive patients: a comparative, single-blind study. J Cardiovasc Pharmacol. 1990;16 Suppl 5:S179–83.

42 Neaton JD, Grimm RH, Jr., Prineas RJ, Stamler J, Grandits GA, Elmer PJ, et al. Treatment of mild hypertension study. Final results. Treatment of mild hypertension study research group. Jama. 1993;270:713–24. https://doi.org/10.1001/jama.1993.03510060059034.

43 Zhou WJ, Wang RY, Li Y, Chen DR, Chen EZ, Zhu DL, et al. A randomized controlled study on the effects of bisoprolol and atenolol on sympathetic nervous activity and central aortic pressure in patients with essential hypertension. PLoS One. 2013;8:e72102. https://doi.org/10.1371/journal.pone.0072102.

44 Wheeldon NM, MacDonald TM, Prasad N, Maclean D, Peebles L, McDevitt DG. A double-blind comparison of bisoprolol and atenolol in patients with essential hypertension. Qjm. 1995;88:565–70.

45 Leeman M, van de Borne P, Collart F, Vandenhoven G, Peeters L, Mélot C, et al. Bisoprolol and atenolol in essential hypertension: effects on systemic and renal hemodynamics and on ambulatory blood pressure. J Cardiovasc Pharmacol. 1993;22:785–91. https://doi.org/10.1097/00005344-199312000-00002.

46 Neutel JM, Smith DH, Ram CV, Lefkowitz MP, Kazempour MK, Weber MA. Comparison of bisoprolol with atenolol for systemic hypertension in four population groups (young, old, black and nonblack) using ambulatory blood pressure monitoring. Bisoprolol Investigators Group. Am J Cardiol. 1993;72:41–6. https://doi.org/10.1016/0002-9149(93)90216-y.

47 Lithell H, Selinus I, Hosie J, Frithz G, Weiner L. Efficacy and safety of bisoprolol and atenolol in patients with mild to moderate hypertension: a double-blind, parallel group international multicentre study. Eur Heart J. 1987;8 Suppl M:55–64. https://doi.org/10.1093/eurheartj/8.suppl_m.55-a.

48 Neutel JM, Smith DH, Ram CV, Kaplan NM, Papademetriou V, Fagan TC, et al. Application of ambulatory blood pressure monitoring in differentiating between antihypertensive agents. Am J Med. 1993;94:181–7. https://doi.org/10.1016/0002-9343(93)90181-n.

49 Lewis R, Maclean D, Ioannides C, Johnston A, McDevitt DG. A comparison of bisoprolol and atenolol in the treatment of mild to moderate hypertension. Br J Clin Pharmacol. 1988;26:53–9. https://doi.org/10.1111/j.1365-2125.1988.tb03363.x.

50 Bühler FR, Berglund G, Anderson OK, Brunner HR, Scherrer U, van Brummelen P, et al. Double-blind comparison of the cardioselective beta-blockers bisoprolol and atenolol in hypertension: the Bisoprolol International Multicenter Study (BIMS). J Cardiovasc Pharmacol. 1986;8 Suppl 11:S122–7. https://doi.org/10.1097/00005344-198511001-00022.

51 Dixon MS, Thomas P, Sheridan DJ. A randomized double-blind study of bisoprolol versus atenolol in mild to moderate essential hypertension. Eur J Clin Pharmacol. 1990;38:21–4. https://doi.org/10.1007/bf00314797.

52 Schiffrin EL, Pu Q, Park JB. Effect of amlodipine compared to atenolol on small arteries of previously untreated essential hypertensive patients. Am J Hypertens. 2002;15:105–10. https://doi.org/10.1016/s0895-7061(01)02290-7.

53 Frishman WH, Brobyn R, Brown RD, Johnson BF, Reeves RL, Wombolt DG. Amlodipine versus atenolol in essential hypertension. Am J Cardiol. 1994;73:50a–4a. https://doi.org/10.1016/0002-9149(94)90275-5.

54 Tham TC, Herity N, Guy S, Silke B. Haemodynamic comparison of amlodipine and atenolol in essential hypertension using the quantascope. Br J Clin Pharmacol. 1993;36:555–60. https://doi.org/10.1111/j.1365-2125.1993.tb00414.x.

55 Johnson BF, Frishman WH, Brobyn R, Brown RD, Reeves RL, Wombolt DG. A randomized, placebo-controlled, double-blind comparison of amlodipine and atenolol in patients with essential hypertension. Am J Hypertens. 1992;5:727–32. https://doi.org/10.1093/ajh/5.10.727.

56 Frishman WH, Brobyn R, Brown RD, Johnson BF, Reeves RL, Wombolt DG. A randomized placebo-controlled comparison of amlodipine and atenolol in mild to moderate systemic hypertension. J Cardiovasc Pharmacol. 1988;12 Suppl 7:S103–6. https://doi.org/10.1097/00005344-198812007-00023.

57 Eguchi K, Hoshide S, Kario K. Effects of celiprolol and bisoprolol on blood pressure, vascular stiffness, and baroreflex sensitivity. Am J Hypertens. 2015;28:858–67. https://doi.org/10.1093/ajh/hpu245.

58 Yang T, Jiang Y, Hao Y, Zhou S, Xu X, Qu B, et al. Comparison of bisoprolol to a metoprolol CR/ZOK tablet for control of heart rate and blood pressure in mild-to-moderate

hypertensive patients: the CREATIVE study. Hypertens Res. 2017;40:79–86. https://doi.org/10.1038/hr.2016.101.

59 Haasis R, Bethge H. Exercise blood pressure and heart rate reduction 24 and 3 hours after drug intake in hypertensive patients following 4 weeks of treatment with bisoprolol and metoprolol: a randomized multicentre double-blind study (BISOMET). Eur Heart J. 1987;8 Suppl M:103–13. https://doi.org/10.1093/eurheartj/8.suppl_m.103.

60 Shi J, Yuan Y, Deng X, Pan Y, He M, Liu G, et al. Metoprolol has a similar therapeutic effect as amlodipine on BP lowering in hypertensive patients with obstructive sleep apnea. Sleep Breath. 2019;23:227–33. https://doi.org/10.1007/s11325-018-1688-5.

61 Czuriga I, Riecansky I, Bodnar J, Fulop T, Kruzsicz V, Kristof E, et al. Comparison of the new cardioselective beta-blocker nebivolol with bisoprolol in hypertension: the Nebivolol, Bisoprolol Multicenter Study (NEBIS). Cardiovasc Drugs Ther. 2003;17:257–63. https://doi.org/10.1023/a:1026180325278.

62 Mazza A, Gil-Extremera B, Maldonato A, Toutouzas T, Pessina AC. Nebivolol vs amlodipine as first-line treatment of essential arterial hypertension in the elderly. Blood Press. 2002;11:182–8. https://doi.org/10.1080/080370502760050421.

63 Bracchetti D, Gradnik R, Alberti A, Brunelli A, Orselli L, Leonardi G, et al. A double-blind comparison of bisoprolol and captopril for treatment of essential hypertension in the elderly. Cardiovasc Drugs Ther. 1990;4:261–4. https://doi.org/10.1007/bf01857642.

64 Velasco M, Urbina A, Silva H, Fonseca R, Guevara J, Hernandez R, et al. A double-blind, parallel, comparative evaluation of amlodipine vs. captopril in the monotherapeutic treatment of mild and moderate essential hypertension. J Cardiovasc Pharmacol. 1991;17 Suppl 1:S19–21. https://doi.org/10.1097/00005344-199117001-00007.

65 Lacourcière Y, Poirier L, Provencher P. Comparison of the effects of amlodipine and captopril on clinic and ambulatory blood pressure. J Hum Hypertens. 1992;6 Suppl 1:S25–8.

66 Gosse P, Roudaut R, Herrero G, Dallocchio M. Beta-blockers vs. angiotensin-converting enzyme inhibitors in hypertension: effects on left ventricular hypertrophy. J Cardiovasc Pharmacol. 1990;16 Suppl 5:S145–50.

67 Liu G, Li M, Shi X, et al. Efficacy of domestic bisoprolol, enalapril and nifedipine retard in mild to moderate hypertension: a randomized double-blind multicenter clinical trial in China. Zhonghua Nei Ke Za Zhi. 2002;41:450–2.

68 Rasmussen S, Borrild N, Vang Andersen J. Efficacy and safety of 24 weeks of therapy with bendroflumethiazide 1.25 mg/day or 2.5 mg/day and potassium chloride compared with enalapril 10 mg/day and amlodipine 5 mg/day in patients with mild to moderate primary hypertension : a multicentre, randomised, open study. Clin Drug Investig. 2006;26:91–101. https://doi.org/10.2165/00044011-200626020-00004.

69 Webster J, Fowler G, Jeffers TA, Lyons D, Witte K, Crichton WA, et al. A comparison of amlodipine with enalapril in the treatment of isolated systolic hypertension. Br J Clin Pharmacol. 1993;35:499–505. https://doi.org/10.1111/j.1365-2125.1993.tb04176.x.

70 Fowler G, Webster J, Lyons D, Witte K, Crichton WA, Jeffers TA, et al. A comparison of amlodipine with enalapril in the treatment of moderate/severe hypertension. Br J Clin Pharmacol. 1993;35:491–8. https://doi.org/10.1111/j.1365-2125.1993.tb04175.x.

71 Kraiczi H, Hedner J, Peker Y, Grote L. Comparison of atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan for antihypertensive treatment in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2000;161:1423–8. https://doi.org/10.1164/ajrccm.161.5.9909024.

72 Omvik P, Thaulow E, Herland OB, Eide I, Midha R, Turner RR. A double-blind, long-term, comparative study on quality of life, safety, and efficacy during treatment with amlodipine or enalapril in mild or moderate hypertensive patients: a multicenter study. J Cardiovasc Pharmacol. 1993;22 Suppl A:S13–9.

73 Tomlinson B, Woo J, Thomas GN, Chau YM, Critchley JA. Randomized, controlled, parallel-group comparison of ambulatory and clinic blood pressure responses to amlodipine or enalapril during and after treatment in adult chinese patients with hypertension. Clin Ther. 2004;26:1292–304. https://doi.org/10.1016/s0149-2918(04)80145-0.

74 Farsang C. Blood pressure control and response rates with zofenopril compared with amlodipine in hypertensive patients. Blood Press Suppl. 2007;2:19–24. https://doi.org/10.1080/08038020701561737.

75 Vaïsse B, Herpin D, Asmar R, Battistella P, Zannad F, Boutelant S, et al. Assessment of antihypertensive effect by blood pressure monitoring: applications to bisoprolol and lisinopril in a double-blind study. J Cardiovasc Pharmacol. 1997;29:612–7. https://doi.org/10.1097/00005344-199705000-00008.

76 Saku K, Liu K, Takeda Y, Jimi S, Arakawa K. Effects of lisinopril and bisoprolol on lipoprotein metabolism in patients with mild-to-moderate essential hypertension. Clin Ther. 1995;17:1136–46. https://doi.org/10.1016/0149-2918(95)80092-1.

77 Reisin E, Graves JW, Yamal JM, Barzilay JI, Pressel SL, Einhorn PT, et al. Blood pressure control and cardiovascular outcomes in normal-weight, overweight, and obese hypertensive patients treated with three different antihypertensives in ALLHAT. J Hypertens. 2014;32:1503–13; discussion 13. https://doi.org/10.1097/hjh.0000000000000204.

78 Cushman WC, Ford CE, Einhorn PT, Wright JT, Jr., Preston RA, Davis BR, et al. Blood pressure control by drug group in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich). 2008;10:751–60. https://doi.org/10.1111/j.1751-7176.2008.00015.x.

79 Stanton AV, Chapman JN, Mayet J, Sever PS, Poulter NR, Hughes AD, et al. Effects of blood pressure lowering with amlodipine or lisinopril on vascular structure of the common carotid artery. Clin Sci (Lond). 2001;101:455–64.

80 Terpstra WF, May JF, Smit AJ, de Graeff PA, Havinga TK, van den Veur E, et al. Long-term effects of amlodipine and lisinopril on left ventricular mass and diastolic function in elderly, previously untreated hypertensive patients: the ELVERA trial. J Hypertens. 2001;19:303–9. https://doi.org/10.1097/00004872-200102000-00018.

81 Ranieri G, Andriani A, Lamontanara G, De Cesaris R. Effects of lisinopril and amlodipine on microalbuminuria and renal function in patients with hypertension. Clin Pharmacol Ther. 1994;56:323–30. https://doi.org/10.1038/clpt.1994.143.

82 Wu SC, Liu CP, Chiang HT, Lin SL. Prospective and randomized study of the antihypertensive effect and tolerability of three antihypertensive agents, losartan, amlodipine, and lisinopril, in hypertensive patients. Heart Vessels. 2004;19:13–8. https://doi.org/10.1007/s00380-003-0724-x.

83 Lorimer AR, Lyons D, Fowler G, Petrie JC, Rothman MT. Differences between amlodipine and lisinopril in control of clinic and twenty-four hour ambulatory blood pressures. J Hum Hypertens. 1998;12:411–6. https://doi.org/10.1038/sj.jhh.1000620.

84 Frishman WH, Ram CV, McMahon FG, Chrysant SG, Graff A, Kupiec JW, et al. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study. The Benazepril/Amlodipine Study Group. J Clin Pharmacol. 1995;35:1060–6. https://doi.org/10.1002/j.1552-4604.1995.tb04027.x.

85 Stergiou GS, Makris T, Papavasiliou M, Efstathiou S, Manolis A. Comparison of antihypertensive effects of an angiotensin-converting enzyme inhibitor, a calcium antagonist and a diuretic in patients with hypertension not controlled by angiotensin receptor blocker monotherapy. J Hypertens. 2005;23:883–9. https://doi.org/10.1097/01.hjh.0000163159.22116.ab.

86 Ding YA, Chang SM, Chou TC. Comparison of amlodipine and quinapril on ambulatory blood pressure and platelet function in hypertension. J Hum Hypertens. 1995;9:637–41.

87 Rajzer M, Klocek M, Kawecka-Jaszcz K. Effect of amlodipine, quinapril, and losartan on pulse wave velocity and plasma collagen markers in patients with mild-to-moderate arterial hypertension. Am J Hypertens. 2003;16:439–44. https://doi.org/10.1016/s0895-7061(03)00052-9.

88 Perticone F, Pugliese F, Ceravolo R, Mattioli PL. Amlodipine versus ramipril in the treatment of mild to moderate hypertension: evaluation by 24-hour ambulatory blood pressure monitoring. Cardiology. 1994;85:36–46. https://doi.org/10.1159/000176644.

89 Poirier L, de Champlain J, Larochelle P, Lamarre-Cliche M, Lacourcière Y. A comparison of the efficacy and duration of action of telmisartan, amlodipine and ramipril in patients with confirmed ambulatory hypertension. Blood Press Monit. 2004;9:231–6. https://doi.org/10.1097/00126097-200410000-00001.

90 Neutel JM, Germino FW, Smith D. Comparison of monotherapy with irbesartan 150 mg or amlodipine 5 mg for treatment of mild-to-moderate hypertension. J Renin Angiotensin Aldosterone Syst. 2005;6:84–9. https://doi.org/10.3317/jraas.2005.014.

91 Radchenko GD, Sirenko YM, Kushnir SM, Torbas OO, Dobrokhod AS. Comparative effectiveness of a fixed-dose combination of losartan + HCTZ versus bisoprolol + HCTZ in patients with moderate-to-severe hypertension: results of the 6-month ELIZA trial. Vasc Health Risk Manag. 2013;9:535–49. https://doi.org/10.2147/vhrm.S44568.

92 Parrinello G, Paterna S, Torres D, Di Pasquale P, Mezzero M, La Rocca G, et al. One-year renal and cardiac effects of bisoprolol versus losartan in recently diagnosed hypertensive patients: a randomized, double-blind study. Clin Drug Investig. 2009;29:591–600. https://doi.org/10.2165/11315250-000000000-00000.

93 Phillips RA, Kloner RA, Grimm RH, Jr., Weinberger M. The effects of amlodipine compared to losartan in patients with mild to moderately severe hypertension. J Clin Hypertens (Greenwich). 2003;5:17–23. https://doi.org/10.1111/j.1524-6175.2003.01416.x.

94 Yasuda G, Ando D, Hirawa N, Umemura S, Tochikubo O. Effects of losartan and amlodipine on urinary albumin excretion and ambulatory blood pressure in hypertensive type 2 diabetic patients with overt nephropathy. Diabetes Care. 2005;28:1862–8. https://doi.org/10.2337/diacare.28.8.1862.

95 Volpe M, Junren Z, Maxwell T, Rodriguez A, Gamboa R, Gomez-Fernandez P, et al. Comparison of the blood pressure-lowering effects and tolerability of losartan- and amlodipine-based regimens in patients with isolated systolic hypertension. Clin Ther. 2003;25:1469–89. https://doi.org/10.1016/s0149-2918(03)80133-9.

96 Lee JW, Choi E, Son JW, Youn YJ, Ahn SG, Ahn MS, et al. Comparison of blood pressure variability between losartan and amlodipine in essential hypertension (COMPAS-BPV). Am J Hypertens. 2020;33:748–55. https://doi.org/10.1093/ajh/hpaa060.

97 Ishimitsu T, Minami J, Yoshii M, Suzuki T, Inada H, Ohta S, et al. Comparison of the effects of amlodipine and losartan on 24-hour ambulatory blood pressure in hypertensive patients. Clin Exp Hypertens. 2002;24:41–50. https://doi.org/10.1081/ceh-100108714.

98 Wilson TW, Lacourcière Y, Barnes CC. The antihypertensive efficacy of losartan and amlodipine assessed with office and ambulatory blood pressure monitoring. Canadian Cozaar Hyzaar Amlodipine Trial Study Group. CMAJ. 1998;159:469–76.

99 Dahlöf B, Lindholm LH, Carney S, Pentikäinen PJ, Ostergren J. Main results of the losartan versus amlodipine (LOA) study on drug tolerability and psychological general well-being. LOA Study Group. J Hypertens. 1997;15:1327–35. https://doi.org/10.1097/00004872-199715110-00018.

100 Oparil S, Barr E, Elkins M, Liss C, Vrecenak A, Edelman J. Efficacy, tolerability, and effects on quality of life of losartan, alone or with hydrochlorothiazide, versus amlodipine, alone or with hydrochlorothiazide, in patients with essential hypertension. Clin Ther. 1996;18:608–25. https://doi.org/10.1016/s0149-2918(96)80212-8.

101 Fogari R, Maffioli P, Mugellini A, Zoppi A, Lazzari P, Derosa G. Effects of losartan and amlodipine alone or combined with simvastatin in hypertensive patients with nonalcoholic hepatic steatosis. Eur J Gastroenterol Hepatol. 2012;24:164–71. https://doi.org/10.1097/MEG.0b013e32834ba188.

102 Formica RN, Jr., Friedman AL, Lorber MI, Smith JD, Eisen T, Bia MJ. A randomized trial comparing losartan with amlodipine as initial therapy for hypertension in the early post-transplant period. Nephrol Dial Transplant. 2006;21:1389–94. https://doi.org/10.1093/ndt/gfk058.

103 Eguchi K, Imaizumi Y, Kaihara T, Hoshide S, Kario K. Comparison of valsartan and amlodipine on ambulatory blood pressure variability in hypertensive patients. Clin Exp Hypertens. 2016;38:721–4. https://doi.org/10.1080/10641963.2016.1200609.

104 Katada E, Uematsu N, Takuma Y, Matsukawa N. Comparison of effects of valsartan and amlodipine on cognitive functions and auditory p300 event-related potentials in elderly hypertensive patients. Clin Neuropharmacol. 2014;37:129–32. https://doi.org/10.1097/wnf.0000000000000042.

105 Delles C, Klingbeil AU, Schneider MP, Handrock R, Weidinger G, Schmieder RE. Direct comparison of the effects of valsartan and amlodipine on renal hemodynamics in human essential hypertension. Am J Hypertens. 2003;16:1030–5. https://doi.org/10.1016/j.amjhyper.2003.07.017.

106 Eguchi K, Kario K, Hoshide Y, Hoshide S, Ishikawa J, Morinari M, et al. Comparison of valsartan and amlodipine on ambulatory and morning blood pressure in hypertensive patients. Am J Hypertens. 2004;17:112–7. https://doi.org/10.1016/j.amjhyper.2003.09.008.

107 Zhang Y, Agnoletti D, Safar ME, Blacher J. Effect of antihypertensive agents on blood pressure variability: the Natrilix SR versus candesartan and amlodipine in the reduction of systolic blood pressure in hypertensive patients (X-CELLENT) study. Hypertension. 2011;58:155–60. https://doi.org/10.1161/hypertensionaha.111.174383.

108 Kloner RA, Weinberger M, Pool JL, Chrysant SG, Prasad R, Harris SM, et al. Comparative effects of candesartan cilexetil and amlodipine in patients with mild systemic hypertension. Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators. Am J Cardiol. 2001;87:727–31. https://doi.org/10.1016/s0002-9149(00)01491-0.

109 Imbs JL, Nisse-Durgeat S. Efficacy and tolerability of candesartan cilexetil vs. amlodipine as assessed by home blood pressure in hypertensive patients. Int J Clin Pract. 2005;59:78–84. https://doi.org/10.1111/j.1742-1241.2005.00296.x.

110 Youssef AM, Elghoneimy HA, Helmy MW, Abdelazeem AM, El-Khodary NM. Effect of amlodipine versus bisoprolol in hypertensive patients on maintenance hemodialysis: a randomized controlled trial. Medicine (Baltimore). 2021;100:e28322. https://doi.org/10.1097/md.0000000000028322.

111 Zanchetti A, Omboni S, La Commare P, De Cesaris R, Palatini P. Efficacy, tolerability, and impact on quality of life of long-term treatment with manidipine or amlodipine in patients with essential hypertension. J Cardiovasc Pharmacol. 2001;38:642–50. https://doi.org/10.1097/00005344-200110000-00017.

112 Oliván Martinez J, Garcia MJ, Rodriguez Botaro A, Pizarro JL, Carretero J, Garrido M. Bisoprolol and nifedipine SR in the treatment of hypertension in the elderly. J Cardiovasc Pharmacol. 1990;16 Suppl 5:S95–9.

113 Amabile G, Serradimigni A. Comparison of bisoprolol with nifedipine for treatment of essential hypertension in the elderly: comparative double-blind trial. Eur Heart J. 1987;8 Suppl M:65–9. https://doi.org/10.1093/eurheartj/8.suppl_m.65.

114 Bueno J, Amiguet JA, Carasusan J, Cebollada J, Carretero J. Bisoprolol vs. chlorthalidone: a randomized, double-blind, comparative study in arterial hypertension. J Cardiovasc Pharmacol. 1990;16 Suppl 5:S189–92.

115 Adolphe AB, Vlachakis ND, Rofman BA, Brescia D, Zellner SR. Long-term open evaluation of amlodipine vs hydrochlorothiazide in patients with essential hypertension. Int J Clin Pharmacol Res. 1993;13:203–10.

116 Burris JF, Ames RP, Applegate WB, Ram CV, Davidov ME, Mroczek WJ. Double-blind comparison of amlodipine and hydrochlorothiazide in patients with mild to moderate hypertension. J Cardiovasc Pharmacol. 1988;12 Suppl 7:S98–102. https://doi.org/10.1097/00005344-198812007-00022.

117 Rofman BA. Long-term open evaluation of amlodipine versus hydrochlorothiazide in patients with essential hypertension. J Cardiovasc Pharmacol. 1988;12 Suppl 7:S94–7. https://doi.org/10.1097/00005344-198812007-00021.

118 Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386:2059–68. https://doi.org/10.1016/s0140-6736(15)00257-3.