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REVIEW ARTICLE

The current position of β-blockers in hypertension: guidelines and clinical practice

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ABSTRACT

The benefits of improved clinical outcomes through blood pressure (BP) reduction have been proven in multiple clinical trials and meta-analyses. The new (2023) guideline from the European Society of Hypertension (ESH) includes β-blockers within five main classes of antihypertensive agents suitable for initiation of antihypertensive pharmacotherapy and for combination with other antihypertensive agents. This is in contrast to the 2018 edition of ESH guidelines that recommended β-blockers for use primarily in patients with compelling indications such as cardiovascular comorbidities, e.g. coronary heart disease, heart failure. This change was based on the fact that the magnitude of BP reduction is the most important factor for adverse cardiovascular outcomes, over and above the precise manner in which reduced BP is achieved. The ESH guideline also supports the use of β-blockers for patients with resting heart rate (>80 bpm); high resting heart rate is a sign of sympathetic overactivity, an important driver of adverse cardiac remodelling in the setting of hypertension and heart failure. Hypertension management guidelines support for the use of combination therapies for almost all patients with hypertension, ideally within a single-pill combination to optimise adherence to therapy. Where a β-blocker is prescribed, the inclusion of a dihydropyridine calcium channel blocker within a combination regimen is rational. These agents together reduce both peripheral and central BP, which epidemiological studies have shown is important for reducing the burden of premature morbidity and mortality associated with uncontrolled hypertension, especially strokes.

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Introduction

Five main classes of antihypertensive agents are currently available: angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers (CCB), and diuretics (mainly thiazides and thiazide-like diuretics)[1,2]. Achieving adequate control of blood pressure (BP) links to marked and clinically significant improvements in long-term clinical outcomes in patients with hypertension with reductions in the risk of myocardial infarction (MI), heart failure, stroke and chronic kidney disease (CKD)[3].

The 2023 Guideline for the management of hypertension from the European Society for Hypertension (ESH) considers that the magnitude of BP lowering is the key factor in improving outcomes[1]. Accordingly, any of the main classes of antihypertensive drugs can be prescribed first-line to achieve this, with additional agents added as necessary to bring BP to the individual patient's target. Previous guidelines jointly from the European Society of Cardiology (ESC) and the ESH in 2018[4] and in 2017 from the American Heart Association (AHA)/American College of Cardiology (ACC)[2] made more specific recommendations on various types of antihypertensive agent in terms of their place in the algorithms for hypertension. Here, β-blockers were recommended for first-line use - primarily for patients with cardiovascular disease such as coronary artery disease (CHD) and heart failure, although the heterogeneous nature of the β-blocker class provides an opportunity for selection of a particular agent to support an individualised therapeutic approach for patients with various comorbid conditions[5,6].

This article reviews the place of β-blockers in current hypertension guidelines. We will focus mainly on the latest guideline from the ESH and, for comparison, guidance from the USA and from China[7,8]; taken together, these major guidelines oversee the care of more than 600 million people with hypertension around the world[9,10].

Clinical outcome benefits from blood pressure lowering in hypertension

Current blood pressure targets in major hypertension guidelines

The recent ESH guideline has taken an increasingly intensive approach to the management of BP in patients receiving

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antihypertensive therapy[1]. Initially, BP should be reduced to <130/80 mmHg for adults with hypertension aged <65 years. A less stringent target is proposed for older patients (≥65 years), where SBP should be reduced to <140 mmHg, checking carefully for side-effects in the older group[1]. The ESH guideline includes separate targets of <140/80 mmHg for patients aged 65 years, or of 140–150/80 mmHg for patients aged >80 years, though the SBP target can be reduced by 10 mmHg in either case, if this can be achieved safely[1].

The 2017 AHA/ACC guideline takes a similar, if slightly less intensive approach[2]. Here, reducing BP to <130/80 mmHg is *recommended* for patients with cardiovascular disease or 10-year cardiovascular risk of at least 10%, and deemed *reasonable* for patients with hypertension and no additional cardiovascular disease[2]. The Chinese guideline is similar, with a general goal of reducing BP to <140/90 mmHg, with the aspiration to achieve <130/80 mmHg where this is possible, or when the patient is at elevated cardiovascular risk[7]. In China, elderly patients with hypertension should be controlled initially to <150/90 mmHg, and then to <140/90 mmHg where tolerated, unless the patent is very elderly or frail[8].

Finally, the reader should note that all of the above recommendations for achieving BP targets refer to office BP, rather than ambulatory BP monitoring (ABPM), or home BP monitoring. Most of the cardiovascular outcomes trials used to define BP targets employed measurement of office BP only, and there is currently no evidence-based equivalents for ABPM derived from randomised, controlled trials. Nevertheless, the guidelines recognise that out-of-clinic BP monitoring is used frequently and of importance[11]. The ESH guideline supports the use of home BP monitoring in addition to office BP measurement, as this provides supplementary information, although the lack of evidence to base treatment decisions on home BP measurement in randomised trials is acknowledged[1]. The 2017 AHA/ACC guideline provides a table for ABPM or home BP measurements that correspond to office BP measurements in the hypertensive range[2]. Further, the 2017 ACC/AHA guideline supports the use of automated BP measurement systems that allow the patient to remain alone and undisturbed while the measurement is underway[2].

Blood pressure control and clinical outcomes

The clinical benefit from controlling BP in hypertension is solidly proven. Indeed, the 2018 ESC/ESH guideline noted that the benefit is supported by "*very solid evidence, underpinned by the largest number of outcome-based RCTs in clinical medicine*"[4]. Meta-analyses have demonstrated similar benefits from control of hypertension, with one showing that treatment of 1,000 patients for 5 years was calculated to prevent 17 strokes (95%CI 14 to 20), 28 cardiovascular events (95%CI 19 to 35), and 8 deaths (95%CI 4 to 12)[12,13]. A large meta-analysis (of 123 studies that enrolled >600,000 people with hypertension) showed that these benefits were apparent irrespective of the initial level of cardiovascular risk, as indicated by the degree of elevation of BP before treatment, or the presence or absence of cardiovascular disease[3]; however, this meta-analysis has been criticised for its inclusion of individuals already on antihypertensive therapy who may therefore have been at higher cardiovascular risk that suggested by their BP levels at baseline[1].

The concept of hypertension-mediated organ damage – to the heart and vascular organs and tissues caused by long-term elevations of BP – provides a compelling pathophysiologic link between hypertension and adverse clinical outcomes[14,15]. Hypertension-mediated organ damage is found commonly in hypertension. For example, a study of 150 newly-diagnosed patients with essential hypertension in the tertiary care setting documented that substantial proportions of the population already had evidence of left ventricular hypertrophy (LVH; 21% diagnosed using the ECG and 29% diagnosed using echocardiography), retinopathy (21%), macroalbuminuria (45%), or left ventricular diastolic dysfunction (21%)[16]. A larger observational study of 1,078 patients with hypertension found LVH to be present in 10% and CKD to be present in 51%[17]. The 2023 ESH guideline identified LVH as detected by ECG or echocardiography, and a reduction of eGFR and microalbuminuria, as the most consistent predictors of adverse outcome inpatients with hypertension-mediated organ damage[4].

LVH in hypertension develops as an attempted protective mechanism in the setting of increased cardiac afterload, as a thickening of the left ventricular wall reduces the excess strain on individual cardiomyocytes[14]. Numerous studies have demonstrated the adverse effect of LVH on the subsequent risks of cardiovascular morbidity and mortality[18]. Hypertension and LVH are common risk factors for developing heart failure, particularly heart failure with preserved left ventricular ejection fraction (HFpEF). LVH also interacts with other manifestations of hypertension-mediated organ damage and further increases cardiovascular risk: one study showed that the age- and gender adjusted HRs for major cardiovascular events were 0.95 (95%CI 0.24 to 3.7) for CKD, 1.62 (95%CI 0.44 to 10.95) for LVH, and 2.45 (95%CI 1.09 to 5.49) for comorbid LVH plus CKD over 7 years of follow-up[17]. Adding measurement of left ventricular mass index (LVMI; a principal diagnostic measure of LVH) to home BP measurement has been shown to be superior to home BP measurement alone in stratifying patients with hypertension for an elevated risk of cardiovascular events[19].

Antihypertensive therapy, together with lifestyle interventions such as weight loss or restricted sodium intake, is effective in promoting regression of LVH and improving outcomes[20]. An observational study demonstrated that the risk of a composite cardiovascular endpoint reduced as on-treatment LVMI decreased (hazard ratio 0.78 [95%CI 0.65 to 0.94], $p = 0.009$] for a decrease of 1 standard deviation in LVMI *over and above* that expected from reduced BP alone)[21]. A retrospective analysis of the same population confirmed the adverse effect of LVH on cardiovascular prognosis and supported the cardiovascular outcomes benefit derived from inducing regression of LVH[22]. A meta-analysis (5 studies 3,149 patients), showed that the adjusted risk of

cardiovascular events in subjects with regression of LVH (or without LVH at baseline) was 46% lower as compared with persistent or progressing LVH[23].

The key to successful management of hypertension is therefore to achieve early and sustained control of BP to prevent the development of hypertension-mediated organ organ damage, which will in turn preserve long-term cardiovascular outcomes.

Place of β-blockers in current major hypertension management guidelines

Overview of guideline recommendations

Table 1 summarises important recommendations for the management of hypertension in current guidelines from Europe, the USA and China[1,2,4,7,8]. The 2023 ESH[1] guideline states that major cardiovascular outcomes are improved similarly with any of the five main classes of antihypertensive drugs (although some experts still advocate the approach to selection of therapy made in earlier guidelines and disagree with the use of β-blockers as first-line agents in the absence of compelling indications)[24]. Hence, all of them can be used alone or in combination to reduce BP. Such therapy should be initiated using a renin-angiotensin-aldosterone-system (RAAS) blocker together with a dihydropyridine CCB or thiazide-like diuretic, other options can be used as appropriate for the individual patient[1]. β-blockers are described as particularly useful for managing hypertension in several specific patient groups: patients with established CHD (symptomatic angina, post-MI, or heart failure with reduced ejection fraction [HFrEF]), and for hypertensive women planning pregnancy or of child-bearing potential, for whom ACEI or ARB are contraindicated[1].

The ESH guidelines also identify elevated resting heart rate (>80 bpm) as a marker of elevated cardiovascular risk. High heart rate is indicative of an overactive sympathetic nervous system, which drives hypertension and adverse cardiac remodelling primarily *via* overstimulation of the β_1-adrenoceptor[25]. The guideline notes that elevated resting heart rate is common among patients with hypertension, associated with increased risk of adverse clinical cardiovascular outcomes and of atrial fibrillation, and represents a clinical phenotype that supports the prescription of a β-blocker[1]. β-blockers also appear to be effective in hypertension with obstructive sleep apnoea, another condition associated with excessive activation of the sympathetic nervous system[26].

Severe asthma, heart rate <60 bpm, and high-grade atrioventricular or supraventricular conduction block are described as absolute contraindications for β-blockers, according to the ESH; caution is advised regarding their use in patients with asthma or glucose intolerance and in especially physically active patients, due to the possibility of fatigue[1]. It should be noted that highly β_1-adrenoceptor selective β-blockers are unlikely to have major effects on glucose metabolism or the airways at clinically approved doses, although the cautious, pragmatic approach recommended by the guidelines remains appropriate[27]. Bisoprolol and metoprolol are contraindicated for severe asthma, according to their European labelling, consistent with these guidelines. The implications of higher or lower selectivity for the β_1-adrenoceptor are discussed in more detail below.

Recommendations from the US (AHA/ACC)[2] and China[7,8] are generally similar to those from Europe, described above, with the principal uses of β-blockers being in patients with ischaemic heart disease or HFrEF (Table 1). According to the 2017 AHA/ACC guidelines, cardioselective agents are preferred for the management of hypertension in patients with HFrEF, and β-blockers with intrinsic sympathomimetic activity should be avoided in this indication. The guideline from China also supports the use of β-blockers in patients with increased sympathetic activation[7], or in elderly patients with high resting heart rate and pre-existing cardiovascular disease[8]. Contraindications and precautions again relate mainly to avoiding the risk of bronchospasm and bradycardia.

What we do not know

Heterogeneity of the β-blocker class

β-blockers are a diverse class of drugs, differentiated by varying (or absent) selectivity for blockade of β_1- vs. β_2-adrenoceptors, intrinsic sympathomimetic activity at either or both of these receptors, the presence or absence of additional vasodilator mechanisms (actions of β_3-adrenoceptors that stimulate nitric oxide formation or blockade of α_1-adrenoceptors), and differences in their physicochemical properties (e.g. lipophilicity vs. hydrophilicity, which determines the extent to which the drug can penetrate the central nervous system)[28]. Heterogeneity exists even within the cardioselective (β_1-selective) group of β-blockers, with bisoprolol, nebivolol and metoprolol demonstrating a higher degree of β_1-adrenoceptor selectivity than atenolol[29–34]. A substantial proportion of the clinical evidence base for the use of β-blockers in the management of hypertension has come from studies that employed atenolol, which is not cardioselective at the higher of the two doses recommended for clinical use[25]. Unfortunately, the short-acting agent, atenolol, was administered once daily in most of these trials, in comparison with long-acting RAAS blockers. Without the certainty of 24-h BP lowering effect with once daily dose of atenolol, an inferior result may have been expected. The ASCOT BPLA cardiac outcome trial serves as an example of this phenomenon, where amlodipine ± perindopril was compared with atenolol ± hydrochlorothiazide in patients with hypertension and additional cardiovascular risk factors[35]. The average BP was higher in the atenolol-based arm throughout the study period. The trial was terminated early due to the emergence of a mortality benefit for amlodipine-perindopril during routine trial monitoring. There was a non-significant trend towards a lower incidence of the primary end point (non-fatal myocardial infarction [MI] and coronary heart disease [CHD] death) for amlodipine-perindopril vs. atenolol-hydrochlorothiazide, with benefits for the amlodipine-based regimen in seven secondary end points. When data from the UK cohort enrolled in the ASCOT LEGACY study were published 16 years later, most of these benefits had attenuated, including an earlier benefit for all-cause mortality, CVD death, CHD death[36]. Only the risk of stroke remained lower with

Table 1. Overview of recommendations relating to initiation of pharmacologic antihypertensive therapy, including those specifically relevant to β-blockade for the management of hypertension in major guidelines from Europe, the USA and China.

	2023 ESH	2017 USA	2018–2019 China
Initiation of pharmacologic antihypertensive therapy	Initiate for SBP >140 mmHg and/or DBP >80 mmHg; consider higher individualised threshold for SBP ≤160 mmHg for the elderly (≥80 y) Consider initiation at high-normal BP levels (≥130/≥80 mmHg) for patients with established CVD (especially CAD)	Prescribe for Stage 1 hypertension[a] and elevated cardiovascular risk and all with stage 2 hypertension[b] Consider 2-drug combination therapy for "the overwhelming majority" with Stage 2 hypertension	Immediate antihypertensive therapy for all "high risk" and "very high risk" patients, and for "moderate risk" patients with BP ≥160/100 mmHg Prescribe for patients >65 y and BP ≥140/90 mmHg, for >80 y with BP ≥150/90 mmHg, and for very elderly or frail with BP ≥150/90 mmHg; use lower doses for older patients and titrate carefully
Choice of initial antihypertensive therapy	Any of the 5 main antihypertensive classes can be used first; ideally include a RAAS blocker with a CCB or thiazide-like diuretic within an initial combination regimen;	Choose from ACEI, ARB, thiazide diuretic, CCB	Initiate with β-blocker, ACEI, ARB, CCB, or diuretic
When to consider a β-blocker	• For all with hypertension, as per above • β-blocker or RAAS inhibitor is favoured for patients with CAD; β-blockers and CCB are preferred for patients with angina • β-blockers, RAAS inhibitors, CCB can be used in patients with MI without obstructive CAD • Combine β-blockers, MRA, ARNI, RAAS inhibitors and SGLT2i for patients with HFrEF; all major classes can be used to manage hypertension in HFpEF • RAAS inhibitors and β-blockers can be used in patients with AF to limit recurrence • High resting heart rate (>80 bpm), indicative of sympathetic overactivation	• Ischaemic heart disease • HFrEF (bisoprolol, metoprolol or carvedilol preferred)	• Stable angina pectoris • Cardiac dysfunction (HFrEF) • Increased sympathetic activation • High resting heart rate if CHD or HF is present (elderly patients)
Contraindications or precautions to clinical use of β-blockers	• Severe asthma • Any high-grade sinoatrial or atrioventricular block • Bradycardia (e.g. heart rate <60 bpm) • Use with caution in any asthma, glucose intolerance, athletes or very physically active patients	• Use a cardioselective agent for patients at risk of bronchospasm • Avoid β-blockers with ISA in ischaemic heart disease or HFrEF • Bradycardia • Risk of dysglycaemia with "traditional" β-blockers	• Grade 2–3 AV block • Asthma • Caution in COPD, PVD, dysglycaemia, athletes • Avoid high doses of β-blocker in patients with non-ST-elevation ACS

Note that all patients should receive advice on improved lifestyles. Abbreviations. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ACS, acute coronary syndrome; AV, atrioventricular; BP, blood pressure; CCB, calcium channel blocker; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HFrEF, heart failure with reduced ejection fraction; PVD, peripheral vascular disease; SA, sinoatrial. Compiled from information presented in references[1,2,4,7,8]. Recommendations are abbreviated and paraphrased for clarity – always check the full guideline before prescribing.

[a]130–139 mmHg/80–89 mmHg.

[b]≥140/90 mmHg.

amlodipine-based therapy. The risk of stroke is highly sensitive to BP: differences in stroke risk between β-blockers and other antihypertensive agents in meta-analyses should be treated with caution, as this may have arisen due to small differences in BP in individual trials that can potentially be avoided by appropriate adjustment of antihypertensive regimens[5]. Moreover, no adverse pathogenetic effect of β-blockers on the cerebral circulation has been described, and β-blockers have been shown to reduce the risk of stroke in randomised, placebo-controlled trials in populations with hypertension[5]. Such findings may trigger discussions about the rationale of downgrading exclusively β-blockers from first-line use as antihypertensive agents[5].

The 2023 ESH guidelines discuss potential benefits of third-generation vs. second-generation cardioselective β-blockers (i.e. with vs. without additional vasodilator mechanisms), based on reports of superior effects on central BP and markers of vascular and metabolic function, based on short-term comparisons between carvedilol or nebivolol with metoprolol. Although evidence from randomised trials is lacking[1], the ESH guideline suggests that third-generation (carvedilol, nebivolol) or highly β_1-adrenoceptor selective β-blockers (bisoprolol) may be better tolerated than other β-blockers. Nebivolol does not appear to be more effective in reducing office BP compared with bisoprolol[37]. A lack of outcomes trials with the newer agents in populations with hypertension means that there is currently no evidence to support additional outcomes benefits with third-generation β-blockers, compared with older agents.

The guidelines also cite a higher incidence of side-effects leading to discontinuation of therapy as a limitation of the

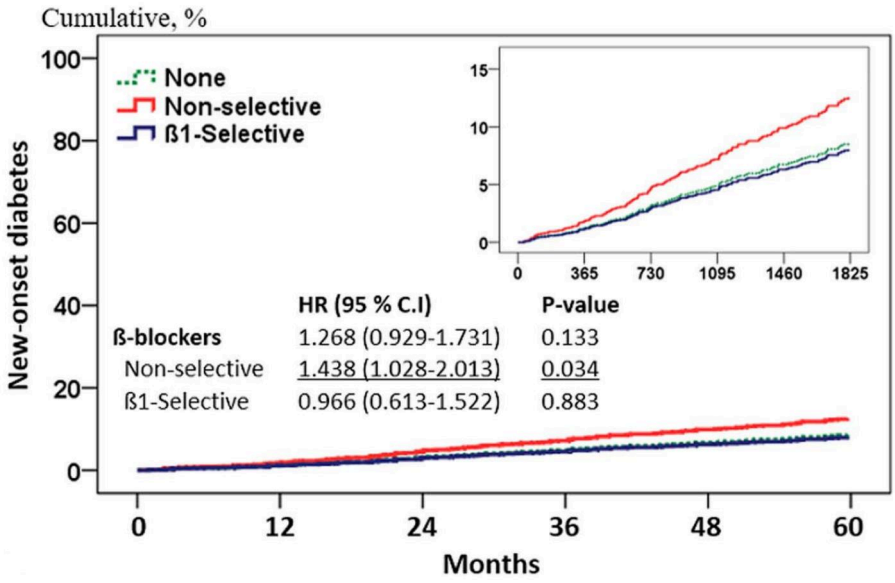

Figure 1. Risk of new-onset diabetes during treatment with a β-blocker in a population of patients with hypertension attending a tertiary care Centre. Data are from cohorts matched using propensity scores. Adjusted for traditional cardiovascular risk factors and receipt of cardiovascular medications. Reproduced with permission from reference[39].

β-blocker class. Bisoprolol was better tolerated than carvedilol (non-cardioselective) in patients with HFrEF and chronic obstructive pulmonary disease[38,39]. Caution is needed when attributing clinical effects to β-blockers as a class and when considering the potential effects of additional vasodilator mechanisms.

The ESH guidelines cite glucose intolerance as a caution relating to the prescription of β-blockers, citing a risk of new-onset diabetes[1]. A large retrospective study ($N = 65{,}686$) evaluated the factors associated with an increased risk of new-onset diabetes among patients with hypertension who attended a tertiary medical centre[40]. Non-cardioselective β-blockers were associated with a significantly increased risk of new-onset diabetes, while cardioselective β-blockers were not (Figure 1). Recent real-world evidence suggested that there was no increase in the risk of new-onset diabetes between bisoprolol (highly cardioselective) and other antihypertensive classes[41]. Finally, selective β_1-adrenoceptor blockade in general did not adversely affect glycaemia in patients who already had diabetes[42,43].

Monotherapy vs. combination therapy. The evidence base for improved clinical outcomes with antihypertensive therapy described above was derived almost exclusively from monotherapy trials, with relatively few trials comparing different antihypertensive combinations. However, the use of initial combination therapy is supported for almost all patients by the ESH, and for most patients with Stage 2 hypertension in the US guideline[1,2]. The addition of a second agent to an antihypertensive regimen is more effective for controlling BP than titration of an existing monotherapy, and low-dose combinations are likely to be better tolerated than a high dose of a monotherapy[43]. In addition, single-tablet combination regimens support better adherence to therapy than co-administered combinations[44,45].

The guidelines recommend the use of rational combinations based on the use of antihypertensive combinations of different mechanisms. The relative lack of effect of β-blockers on central BP has been proposed as an explanation for the lower reductions in stroke incidence for these agents in comparison to other classes of antihypertensive classes in the ESH guideline for hypertension management[46]. Several studies have shown that CCBs, for example, lower peripheral and central BP, while β-blockers are more effective in reducing peripheral BP[47–49]. Importantly, a study that compared the haemodynamic effects of amlodipine and bisoprolol alone and in combination showed that the combination was as effective in reducing central BP as amlodipine alone (Figure 2)[49]. Pulse wave velocity, a marker of arterial stiffness, was also reduced following treatment with the combination, compared with bisoprolol monotherapy. This study provides a clear example of how a switch from monotherapy to a combination therapy can improve BP control and increase the magnitude of peripheral BP reductions.

Conclusions

In the 2023 ESH guidelines, β-blockers are included as a first-line management option for patients with hypertension at any step of therapy either as monotherapy or in combination with other drug classes[1]. There remains a compelling indication for β-blockers in patients with comorbid cardiovascular diseases where the β-blocker class has been shown to improve clinical outcomes, such as stable angina, previous MI or left ventricular systolic dysfunction. Elevated heart rate and obstructive sleep apnoea are indicative of sympathetic nervous activation and represent hypertensive phenotypes which may support the use of β-blockers. While guidelines place increasing support for the use of combination therapy, the evidence base for improved outcomes with antihypertensive treatment is based largely on the use of monotherapy, with relatively few studies having compared initial combination regimens. When β-blockers are prescribed, the inclusion of a dihydropyridine CCB within a combination regimen

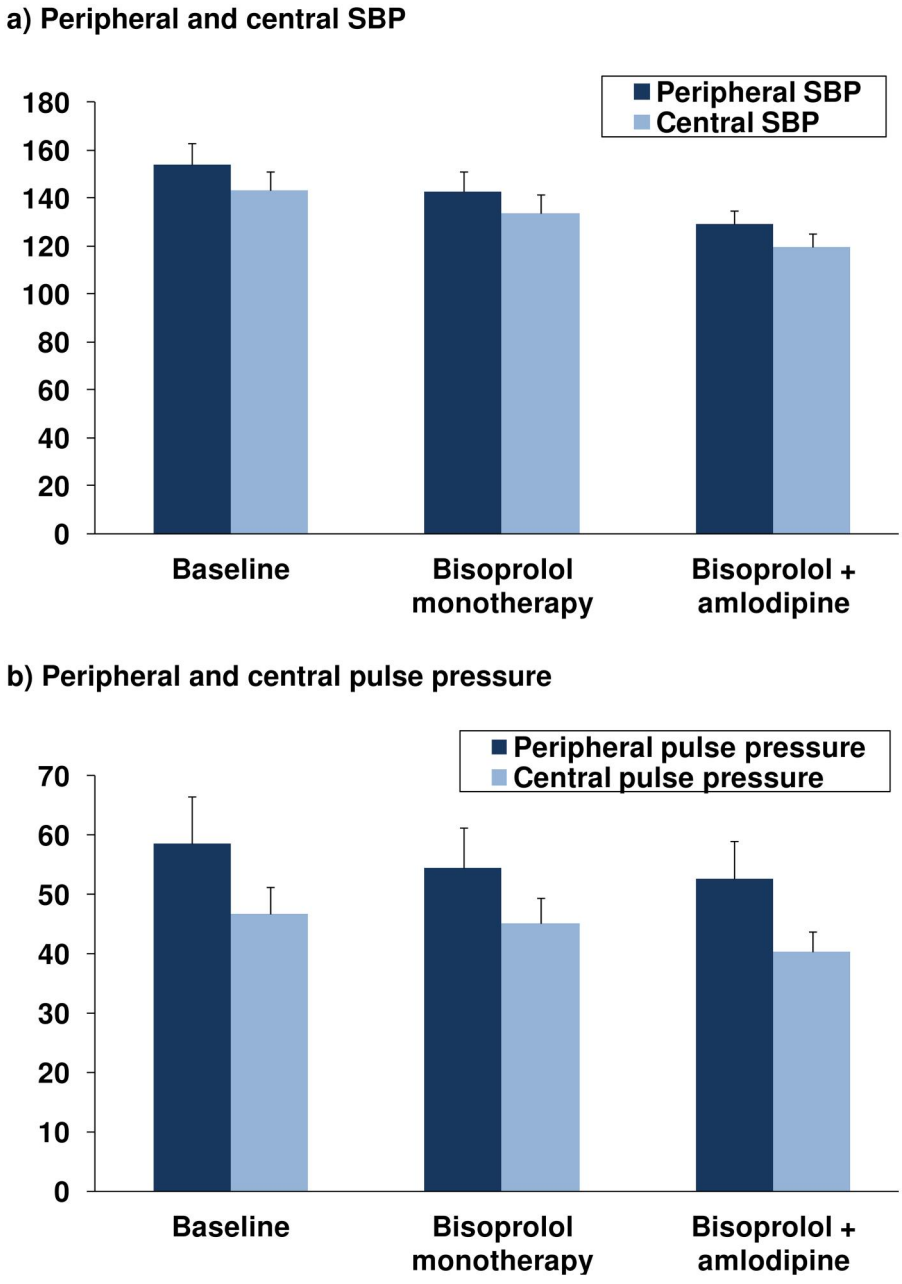

Figure 2. Effects of a cardioselective β-blocker with and without additional treatment with a calcium channel blocker on peripheral and central systolic blood pressure (SBP) and pulse pressure in patients with hypertension. (a) Peripheral and central SBP. (b) Peripheral and central pulse pressure.
Patients received 4 weeks of monotherapy with bisoprolol followed by a further 4 weeks with or without additional amlodipine (each drug was titrated as necessary to optimise BP control). Bars are SD. *P < 0.05 vs. baseline; #p < 0.05 vs. for the combination bisoprolol monotherapy. Drawn from data presented in reference[49].

is rational, as these agents together reduce both peripheral and central BP. Establishing to what extent the pathophysiology of hypertension and its optimal management can be further individualised represents another frontier of research to be addressed by future hypertension and cardiovascular disease management guidelines[50].

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No AI-related technologies were used in the preparation of this article.

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