High Blood Pressure & Cardiovascular Prevention (2023) 30:191–198
https://doi.org/10.1007/s40292-023-00576-3

REVIEW ARTICLE

Beta-Blockers and Hypertension: Some Questions and Answers

Francesco Fici[1,2] · Nicolas Roberto Robles[3] · Istemihan Tengiz[4] · Guido Grassi[5]

Received: 21 February 2023 / Accepted: 17 April 2023 / Published online: 11 May 2023

Abstract

Introduction International guidelines have removed b-blockers from first-line treatment of hypertension, limiting their use to patients with compelling indications. The position of guidelines stems from the results of studies performed with the 1st and 2nd generation of b-blockers, which concluded that these drugs have lower cardiovascular protection, compared with other antihypertensive agents.

Aim The aim of our mini review is to answer to some questions about the effect of b-blockers on hypertension and cardiovascular protection and if these effects are different from those of other antihypertensive drugs, particularly in young and elderly patients.

Methods We evaluated the relevant systematic reviews and meta-analyses, which reported the effectiveness of b-blockers on blood pressure and cardiovascular outcomes, compared with placebo/no treatment and with other antihypertensive agents.

Results Beta-blockers, decreased high blood pressure with no significant difference from other common antihypertensive agents. Moreover b-blockers, compared with placebo, lowered the risk of major cardiovascular outcomes, while, compared with other drug classes, the reported results are very heterogeneous. Therefore it is difficult, globally, to find a difference between b-blockers and other drug classes.

Conclusions Rather than looking for differences in the cardiovascular protective effect between b-blockers and other antihypertensive agents, we have to consider the different pathophysiology of hypertension in young [sympathetic hyperactivity] and elderly patients [arterial stiffness, high aortic systolic pressure]. Considering these aspects, non-vasodilating b-blockers are preferred, as first-line, in young/middle aged hypertensive subjects, while vasodilating b-blockers, are most appropriate, in elderly patients, for the favourable hemodynamic profile.

Keywords Beta-blockers · Hypertension · Cardiovascular outcomes

1 Introduction

Hypertension is a leading cause of cardiovascular morbidity and mortality worldwide. Treatment of elevated blood pressure [BP] decreases the risk of target organ damage, because the most important benefit of antihypertensive therapy is the reduction of blood pressure, until the targets recommended by several guidelines [1–3]. Globally 10 mmHg reduction of systolic blood pressure [SBP] or 5 mmHg of diastolic blood pressure [DBP], are associated with a statistically significant reduction of major cardiovascular [CV] events [4–6]. This result can be obtained with all antihypertensive drugs, regardless of baseline BP values and gender of patients [7–9]. Diuretics, ACE inhibitors [ACEi], calcium channel blockers, [CCBs] angiotensin II receptor blockers [ARBs], and beta-blockers, [b-blockers] have similar antihypertensive efficacy [1, 10], therefore ESC/ESH current guidelines [1] recommend that the five major classes of drugs should form the basis of antihypertensive therapy. However the role of b-blockers, as initial therapy for hypertension, has been and remains questioned, because some currently international guidelines [2, 3, 11] have removed b-blockers from first-line treatment of hypertension, by restricting their use only in

✉ Nicolas Roberto Robles
nrrobles@yahoo.es

1 Department of Cardiovascular Risk, Salamanca University, Salamanca, Spain

2 Milano-Bicocca University, Milan, Italy

3 University Hospital, of Badajoz, Badajoz, Spain

4 Cardiology and Hypertension Department, Medical Park Hospital, Izmir University, Izmir, Turkey

5 Clinica Medica, Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

patients with previous or concomitant cardiovascular [CV] disease or, as did NICE guidelines [12], limiting their use to younger hypertensive subjects, with increased sympathetic tone. The conflictual position of guidelines stems from the results of landmark studies [1, 13], performed with the 1st and 2nd generation of b-blockers, [propranolol, atenolol, pindolol, metoprolol, oxiprenolol], which have shown a lower cardiovascular protection, particularly on the risk of stroke and coronary heart disease [CHD], compared with other antihypertensive agents. This position has been reaffirmed by a recent review [14] which concluded that b-blockers must be used in hypertensive patients with concomitant CV disease. However it is important to mention that the restriction in using b-blockers to treat hypertension goes against the indications approved by FDA and EMA, which do not suggest that b-blockers should be used only in patients with concomitant cardiovascular disease.

Therefore the relationship between b-blockers and hypertension poses still today many doubts and has undefined aspects.

The aim of our mini review is to answer to 5 questions:

(1) Do b-blockers have an antihypertensive effect?
(2) Is this effect similar to that of other antihypertensive agents?
(3) Do b-blockers have CV protective effect in hypertensive patients?
(4) Is the CV protective effect of beta-blockers different from that of other antihypertensive drugs?
(5) There is a difference on CV protection between young and elderly patients?

To answer to these questions we used the data of most relevant systematic reviews and meta-analyses, to avoid the results of individual studies, which are very heterogeneous.

2 Do Beta-Blockers Have an Antihypertensive Effect?

Seminal studies have investigated the antihypertensive efficacy of b-blockers in patients with mild-moderate hypertension [1, 13]. These studies have been included in well performed large meta-analyses [10, 13, 15–17] that have proven that b-blockers, albeit some differences between studies, lowered SBP by an average of 9.2–18.0 mmHg and DBP by 5.6–11.0 mmHg, compared with placebo or no treatment. Similar magnitude has been confirmed by a recent meta-analysis [18] that demonstrated − 10.0/− 8.0 mmHg change in SBP and DBP.

The antihypertensive effectiveness of b-blockers is particularly evident with b1-selective antagonist [16] and with vasodilating b-blockers [19–21], while it seems to be lower with non-selective, or with partial agonist activity [16, 22].

Therefore, globally, there is evidence that treatment with b-blockers, significantly decrease BP in hypertensive patients, supporting the indication approved by FDA and EMA.

3 Is this Effect Similar to that of Other Antihypertensive Agents?

Many reviews and meta-analyses have shown not statistically significant difference in SBP/DBP [0.6–1.4/0.3–0.6 mmHg] between b-blockers and other BP lowering drugs [5, 18]. In particular the difference in SBP/DBP, between b-blockers and CCBs [+ 1.0/+ 0.7 mmHg], RAS inhibitors [+ 0.8/− 0.5 mmHg] and diuretics [+ 0.6/− 0.2 mmHg], has no clinical relevance.

Therefore there is evidence that the efficacy of b-blockers is no different from the common antihypertensive drugs and are, therefore, clinically beneficial in hypertensive patients.

4 Have Beta-Blockers a Cardiovascular Protective Effect in Patients with Hypertension?

To evaluate the [CV] protective effect of beta-blockers we have analyzed meta-analyses and reviews which reported the comparison with placebo or no treatment. The relative risk and the 95% confidence interval [CI] for the assessed outcomes is reported in Table 1.

Stroke: eight meta-analyses [5, 13, 15, 17, 18, 23–26] have proven that treatment with b-blockers was associated with 17–27% lower risk of stroke.
Total CV events: b-blockers decreased the risk of cardiovascular events by 11–14% [17, 24], but no significant difference was found with atenolol [25] and in old patients [24].
CHD: although not different from placebo [5, 13, 15, 17, 18], the risk showed a trend in favor of b-blockers [17, 18], considering that the upper border of CI was very near to1.
MI: the rate of MI was lowered by 20% [26] or was not different from placebo [24, 25].
HF: the rate of HF was reduced by 43–46% [15, 18].
CV mortality: the risk of CV mortality was decreased by 23% [15] or there was no significant difference [13, 18, 26]
Composite outcome: stroke + CHD, and stroke + CHD + HF were significantly decreased by 16% and 22%, respectively [18].

Table 1 Beta-blockers compared with placebo or no treatment.

Author	Stroke	Tot.CV events	CHD	MI	HF	CV death	All cause death
Wisonge (2017)	0.80 [0.66–0.96]	0.88 [0.79–0.97]	0.93 [0.81–1.07]			0.93 [0.80–1.09]	0.99 [0.88–1.11]
Wright (2018) [17]	0.83 [0.72–0.97]	0.89 [0.81–0.98]	0.90 [0.78–1.03]				0.96 [0.86–1.07]
Tomopoulus (2015)	0.73 [0.58–0.91]		0.88 [0.77–1.01]		0.54 [0.39–0.76]	0.77 [0.60–0.99]	0.87 [0.74–1.02]
Tomopoulus (2020)	0.77 [0.61–0.97]		0.88 [0.77–1.01]		0.57 [0.35–0.91]	0.84 (0.68–1.04)	0.95 [0.84–1.06]
Wei (2020) [26]	0.80 [0.67–0.98]	0.83 [0.70–0.98]		0.80 [0.65–0.90]		0.99 [0.87–1.13]	
Kuyper (2014) [25] [atenolol]	0.78 [0.63–0.98]	0.89 [0.75–1.05]		0.98 [0.83–1.16]			0.91 [0.74–1.12]
Kuyper (2014) [25] [non-atenolol]	0.84 [0.65–1.10]	0.86 [0.75–0.99]		0.86 [0.71–1.03]			0.94 [0.79–1.11]
Khan [young] (2006) [24]	0.84 [0.65–1.10]	0.86 [0.74–0.99]		0.85 [0.71–1.03]	1.05 [0.72–1.54]		0.94 [0.79–1.10]
Khan [old] (2006) [24]	0.78 [0.63–0.98]	0.89 [0.75–1.05]		0.98 [0.83–1.16]	0.54 [0.37–0.81]		0.91 [0.74-1.12]
Law (2009) [5]	0.83 [0.70-0.99]		0.89 [0.78–1.02]				

Relative Risk [95% Confidence Interval]

CHD Coronary heart disease, *MI* Myocardial infarct, *HF* heart failure, *CV* cardiovascular

All cause of death: no significant difference

Globally, albeit some differences between the meta-analyses, b-blockers, compared with placebo, lowered the risk of major CV outcomes, particularly stroke, which has been the major reason for the retrogression of these drugs from first-line treatment of hypertension.

5 Is the Cardiovascular Protective Effect of Beta-Blockers Different from that of Other Antihypertensive Drugs?

Seven meta-analyses [5, 13, 15, 18, 25, 27, 28] have evaluated the difference between b-blockers and other antihypertensive drugs (Table 2).

Stroke: the risk of stroke was not significantly different from diuretics, atenolol and non-atenolol [13, 23, 25], but it was increased by 18–32%, comparing b-blockers with RAS inhibitors, CCBs and other treatments [5, 13, 15, 27, 28].

Total CV events: the rate of total CV events resulted not significantly different between b-blockers, diuretics, RAS inhibitors, and other active treatments [15, 25], whereas it was increased by 18% comparing b-blockers with CCBs [13].

CHD: there was no difference in the risk between b-blockers, diuretics, CCBs, RAS inhibitors and other treatments [5, 13].

MI: the rate were similar between b-blockers, RAS inhibitors and other active treatments [18, 25, 28]. However in patients treated with non-atenolol b-blockers, there was a trend to decrease the risk of MI by 14%, compared with other drugs [25].

HF: no significant difference comparing b-blockers with RAS inhibitors, CCBs or other antihypertensive compounds [18, 23, 28].

CV mortality: no significant difference between b-blockers, diuretics, CCBs, RAS inhibitors and other antihypertensive agents [13, 18, 23, 25].

Therefore the cardiovascular protective effect of b-blockers, compared with other drug classes, shows a great variability, because not all the meta-analyses assessed the same outcomes and did same comparisons, only the risk of stroke has been evaluated in all the meta-analyses, reported in our review, and also for this outcome the results are not homogeneous. Thus it is difficult to answer to the question as to whether one class of drugs is superior or not in protecting hypertensive patients from cardiovascular risk.

Table 2 Beta-blockers compared with other antihypertensive agents.

Author	Stroke	Tot CV events	CHD	MI	HF	CV death	All cause death
Wisonge (2017)	1.17 [0.65–2.09] Bb vs D	1.13 [0.99–1.28] Bb vs D	1.12 [0.82–1.54] Bb vs D			1.09 [0.90–1.32] Bb vs D	1.04 [0.91–1.19] Bb vs D
	1.24 [1.11–1.4] Bb vs CCBs	1.18 [1.08–1.29] Bb vs CCBs	1.05 [0.96–1.15] Bb vs CCBs			1.15 [0.92–1.46] Bb vs CCBs	1.07 [1.0–1.14] βb vs CCBs
	1.30 [1.11, 1.53] Bb vs RAS	1.00 [0.72–1.38] Bb vs RAS	0.90 [0.76–1.06] Bb vs RAS			1.09 [0.92–1.29] Bb vs RAS	1.10 [0.98–1.24] Bb vs RAS
Law (2009) [5]	1.18 [1.03–1.36] Bb vs others		1.04 [0.92–1.17] Bb vs others				
Thomopoulos (2015)	1.25 [1.11–1.40] Bb vs CCBs		1.04 [0.95–1.14] Bb vs CCBs		1.04 [0.80–1.34] Bb vs CCBs	1.17 [0.93–1.48] Bb vs CCBs	1.08 [0.98–1.18] Bb vs CCBs
	1.32 [1.13–1.54] Bb vs RAS		0.92 [0.78–1.08] Bb vs RAS		1.04 [0.85–1.28] Bb vs RAS	1.10 [0.80–1.50] Bb vs RAS	1.08 [0.95–1.24] Bb vs RAS
	0.85 [0.58–1.25] Bb vs D		0.93 [0.75–1.16] Bb vs D		0.76 [0.47–1.24] Bb vs D	1.03 [0.77–1.38] Bb vs D	0.99 [0.86–1.15] Bb vs D
Chen (2018) [28]	0.75 [0.63–0.88] RAS vs Bb	0.88 [0.80–0.98] RAS vs Bb		1.05 [0.86–1.27] RAS vs Bb	0.95 [0.76–1.18] RAS vs Bb		0.89 [0.78–1.01] RAS vs Bb
Thomopoulos (2020)	1.21 [1.07–1.38] Bb vs others		1.02 [0.93–1.12] Bb vs others		1.05 [0.94–1.17] Bb vs others	1.06 [0.93–1.21] Bb vs others	1.06 [1.01–1.12]
Zhu (2022) [27]	0.77 [0.67–0.88] CCBs vs Bb	0.84 [0.77–0.92] CCBs vs Bb		0.90 [0.79–1.02] CCBs vs Bb	0.83 [0.67–1.04] CCBs vs Bb	0.90 [0.81–0.99] CCBs vs Bb	0.94 [0.88–1.00] CCBs vs Bb
Kuyper (2014) [25]	1.07 [0.94–1.23] Atenolol vs others	1.05 [0.99–1.12] Atenolol vs others		1.07 [0.98–1.17] Atenolol vs others			1.04 [0.98–1.11] Atenolol vs others
	1.19 [0.66–2.14] non-atenolol vs others	0.99 [0.88–1.11] non-atenolol vs others		0.86 [0.73–1.01] non-atenolol vs others		0.99 [0.82–1.21] non-atenolol vs others	

Relative Risk [95% Confidence Interval]

Bb beta-blockers, *D* Diuretics, *CCBs* Calcium channel blockers, *RAS* Renin Angiothensin System inhibitors, *CHD* coronary heart disease, *MI* myocardial infarct, *HF* heart failure, *CV* cardiovascular

6 Is the Cardiovascular Protection of b-blockers Different in Young and Old Hypertensive Patients?

Four meta-analyses (Table 3) reached opposite conclusions.

(a) The first [24] has shown that in young patients [< 60 years] b-blockers, compared with placebo (Table 1), significantly decreased the composite cardiovascular outcome [MI, stroke and death] by 14%, whereas compared with other antihypertensive treatments there was no difference in all CV events (Table 3). In elderly [≥ 60 years] patients, indeed, comparing b-blockers with placebo (Table 1), there was a significant 22% and 46% reduction of stroke, and HF, respectively, whereas compared with other antihypertensive agents, b-blockers were associated with a no significant difference in the composite cardiovascular outcome [MI, stroke and death], but with 18% increased risk of stroke (Table 3).

(b) The second [29], instead, has shown no significant difference in cardiovascular events between younger [age < 65 years] and elderly [≥ 65 years] subjects.

(c) The third [25] reported (Table 3) that both in elderly and young patients there was no significant difference

Table 3 Beta-blockers compared with other antihypertensive agents in patients younger [<60 years] and older [≥ 60 yrs]

Author	Stroke	Tot CV events	MI	HF	CV death	All cause death
Khan (2006) [24] [<60 yrs]	0.99 [0.67–1.44] Bb vs others	0.97 [0.88–1.07] Bb vs others	0.97 [0.86–1.10] Bb vs others	0.93 [0.64–1.34] Bb vs others		0.97 [0.83–1.14] Bb vs others
Khan (2006) [24] [≥60 yrs]	1.18 [1.07–1.30] Bb vs others	1.06 [1.01–1.10] Bb vs others	1.06 [0.94–1.20] Bb vs others	0.98 [0.87–1.11] Bb vs others		1.05 [0.99–1.11] Bb vs others
Turnbull (2008) [8] [<65 yrs]		1.03 [0.88–1.20] ACEi or CCBs vs Bb				
Turnbull (2008) [8] [≥ 65 yrs]		0.94 [0.84–1.06] ACEi or CCBs vs Bb				
Kuyper (2014) [25] [≤60 yrs]	0.78 [0.64–0.95] atenolol vs others	0.96 [0.85–1.07] Atenolol vs others	1.05 [0.89–1.24] atenolol vs others			0.94 [0.72–1.24] atenolol vs others
Kuyper (2014) [25] [>60 yrs]	1.17 [1.05–1.30] atenolol vs others	1.07 [1.00–1.15] atenolol vs others	1.07 [0.96–1.20] atenolol vs others			1.05 [0.98–1.11] atenolol vs others
Kuyper (2014) [25] [≤60 yrs]	0.90 [0.24–3.39] non-atenolol vs others	1.02 [0.81–1.28] non-atenolol vs others	0.87 [0.67–1.11] non-atenolol vs others			0.81 [0.39–1.68] non-atenolol vs others
Kuyper (2014) [25] [>60 yrs]	1.22 [0.99–1.50] non-atenolol vs others	0.98 [0.86–1.12] non-atenolol vs others	0.85 [0.69–1.05] non-atenolol vs others			1.06 [0.82–1.39] non-atenolol vs others
Bangalore (2008) [30] [<60 yrs]	0.78 [0.65–0.94] Bb vs others		1.01 [0.88–1.17] Bb vs others		1.06 [0.86–1.31] Bb vs others	0.98 [0.85–1.13] Bb vs others
Bangalore (2008) [30] [≥60 yrs]	1.19 [1.11–1.28] Bb vs others		1.03 [0.96–1.10] Bb vs others		1.05 [0.98–1.12] Bb vs others	1.03 [0.99–1.08] Bb vs others

Relative Risk [95% Confidence Interval]

Bb beta-blockers, *CCBs* Calcium channel blockers, *ACEi* ACE inhibitors, *CHD* coronary heart disease, *MI* myocardial infarct, *HF* heart failure, *CV* cardiovascular disease

between non atenolol b-blockers in all CV outcomes, compared with other treatments. On the contrary in young subjects [≤ 60 years], atenolol, compared with other treatments, decreases the risk of stroke by 22%, but, instead, it increased by 17% in elderly patients [> 60 years].

(d) The forth meta-analysis [30] proved that in subjects < 60 years of age the risk of stroke decrease by 32%, whereas it increased by 19% in subjects ≥ 60 years, comparing b-blockers with other drugs. No significant changes were reported in other outcomes.

7 Discussion

The results of our overview can be summarized as following:

(a) in patients with hypertension, b-blockers, compared with placebo, decrease SBP/DBP, proving to have an antihypertensive effect;

(b) the antihypertensive activity of b-blockers is not different from that of CCBs, RAAS inhibitors and diuretics;

(c) compared with placebo, b-blockers, including atenolol, generally lower the risk of stroke**,** total cardiovascular events, heart failure**,** but not significantly coronary heart disease, myocardial infarct**,** cardiovascular mortality and all cause of death;

(d) several clinical trials and meta-analyses have evaluate as to whether one class of antihypertensive agents is superior to b-blockers in decreasing the risk of cardiovascular events. The results have been variable and controversial, therefore we are obliged to navigate between Scylla and Charybds. The pioneering studies [1, 13] have been performed with different protocols, statistical procedures, mean follow-up periods, cardiovascular outcomes, blood pressure targets and using traditional, b1selective b-blockers, especially atenolol. Therefore the comparison of b-blockers with other antihypertensive agents could be misleading**.** Atenolol, does not provide a 24 h blood pressure reduction, because its short half-life [6–9 h]; moreover once-daily dosing does not control blood pressure variability and, particularly, morning blood pressure surge [31, 32], which is

correlated with cerebrovascular events [33, 34]. However, whether atenolol or all b-blockers are involved in the low capacity to protect hypertensive patients from stroke and other cardiovascular events, is not yet well clarified, because head to head comparison between different b-blockers is lacking. A meta-analysis [25], evaluated the effect of studies performed with atenolol and non-atenolol, b-blockers on the risk of cardiovascular outcomes. Atenolol, differently from non-atenolol b-blockers, decreased the risk of stroke compared with placebo or with other antihypertensive agents only in young people [≤ 60 years], whereas the risk increased in elderly [> 60 years] patients. Non atenolol b-blockers were, instead, associated with no significant difference in all the cardiovascular outcomes, in young and elderly patients.

Therefore these findings, even not confirmed by other studies, raise doubts about the negative role of atenolol on the incidence of stroke and other cardiovascular outcomes, also because in the subgroup analysis of INVEST [35] and in CONVINCE trials [36] there was no significant difference in the composite outcomes between verapamil and atenolol treatment strategy.

In our opinion, rather than looking for differences in cardiovascular protective effect between b-blockers and other drug classes, we have to keep in mind the following important aspects: the underlying pathophysiology of hypertension and the age of patients. The pathophysiology of hypertension in elderly and young subjects is very different. In young subjects hypertension is characterized predominantly by the hyperactivity of sympathetic nervous system [37, 38] with increased heart rate, inotropic cardiac activity and peripheral vascular resistance. In these patients, b-blockers, decrease cardiac output, heart rate, modulate sympathetic outflow, and lower renin secretion from the juxtaglomerular cells [37–39]. This approach is in agreement with the last NICE guidelines [12] which suggest b-blockers as first-line in young patients. On the contrary, in elderly patients hypertension is related to vascular aging, structural and functional changes of arteries properties, and consequently arterial stiffness, and increase central aortic systolic blood pressure [40–42]. High central aortic systolic blood pressure is associated with increased risk of CV events [40, 43]. Therefore central aortic BP have to be considered a therapeutic target in elderly patients with hypertension. Beta-blockers are an heterogeneous class of drugs, that, for the pharmacological properties are classified as selective beta1 receptors antagonists, (e.g., **acebutolol**, **atenolol**, **bisoprolol**, **metoprolol, nebivolol**), and non- selective beta1 receptors antagonists (e.g., **propranolol, carvedilol**, **labetalol**, **oxprenolo**, **pindolol**). Some of these b-blockers display also partial intrinsic sympathomimetic activity (e.g., pindolol, acebutolol, oxprenolol, celiprolol), or vasodilating effect by blocking α1-vascular receptors (**carvedilol, labetalol**) or by increasing endothelial nitric oxide bioavailability (nebivolol) [44]. Non vasodilating b-blockers does not decrease central aortic systolic pressure [45–48], therefore are not indicated in elderly hypertensive patients. This aspect has been well documented in a systematic reviews [24, 25] and other studies [49, 50], comparing young and elderly subjects with hypertension. Evidence from different studies have demonstrated that new 3rd-generation b-blockers with vasodilating activity, [carvedilol, nebivolol, celiprolol], decrease central aortic systolic pressure, augmentation index [AIx], peripheral vascular resistance and cardiac afterload, without affecting cardiac output, therefore, are particularly indicated in elderly patients [47, 51–53]. In addition several studies have reported that carvedilol and nebivolol decrease the risk of cardiovascular events and hospitalization [54–56].

8 Conclusions

In conclusion the findings of our review suggest that the antihypertensive effect of b-blockers is not different, compared with other antihypertensive agents. Furthermore b-blockers compared with placebo or no treatment decrease the risk of cardiovascular events. The results of studies which compared b-blockers with other drug classes, are not homogeneous for several reasons, and particularly because most early studies have enrolled, especially, elderly patients which were treated mainly with atenolol. The pathophysiology of hypertension suggest that non vasodilating β-blockers are preferred, as first-line, in young/middle aged hypertensive patients (< 60 years), to decrease sympathetic hyperactivity and consequently high BP, while vasodilating b-blockers, are most appropriate, as first choice, in elderly patients (> 60 years), for the favourable hemodynamic profile. To achieve BP goal, both type b-blockers can be combined with other antihypertensive drugs, with complementary pharmacological activity.

Funding No funding was received for this work.

Data availability Data sharing not applicable—no new data generated.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval The authors adhere to ethical norms in research and publishing.

References

1. Williams B, Mancia G, Spierin W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus

R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104.
2. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127-248.
3. Al-Makki A, DiPette D, Whelton PK, Murad MH, Mustafa RA, Acharya S, Beheiry HM, Champagne B, Connell K, Cooney MT, Ezeigwe N, Gaziano TA, Gidio A, Lopez-Jaramillo P, Khan UI, Kumarapeli V, Moran AE, Silwimba MM, Rayner B, Sukonthasan A, Yu J, Saraffzadegan N, Reddy KS, Khan T. Hypertension Pharmacological Treatment in Adults: A World Health Organization Guideline Executive Summary for the pharmacological treatment of hypertension in adults. Hypertension. 2022;79:293–301.
4. Blood Pressure Lowering Treatment Trialists Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362:1527–35.
5. 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;338:1–19.
6. Theomopulous C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses and meta-regression analyses of randomized trials. J Hypertens. 2014;32:2285–95.
7. Theomopulous C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 2. Effects at different baseline and achieved blood pressure levels-overview and meta-analyses of randomized trials. J Hypertens. 2014;32:2296–304.
8. Turnbull F, Woodward M, Neal B, Barzi F, Ninomiya T, Chalmers J, Perkovic V, Li N. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. Eur Heart Journal. 2008;29:2669–80.
9. Ong HT. Cardiovascular outcomes in the comparative hypertension drug trials: more consensus than controversy. Singapore Med Review Article J. 2008;49:599–605.
10. Law MR, Wald NJ, Morris K, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326:1–8.
11. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. International Society of Hypertension global hypertension practice guidelines. Hypertension. 2020;2020(75):1334–57.
12. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management. NG136. 2019
13. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2017;1:1–71.
14. Chrysant SG, Chrysant GS. Antihypertensive and cardioprotective effects of three generations of beta-adrenergic blockers: an historical perspective. Hosp Pract. 2022;50:1–7.
15. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4 Effects of various classes of antihypertensive drugs- overview and meta-analysis. J Hypertens. 2015;33:195–211.
16. Wong GWK, Boyda HN, Wright JM. Blood pressure lowering efficacy of beta-1 selective beta blockers for primary hypertension. Cochrane Database Syst Rev. 2016;3:1–130.
17. Wright JM, Musini VM, Gill R. First-line drugs for hypertension. Cochrane Database Syst Rev. 2018;4:1–108.
18. Thomopoulos C, Bazoukis G, Tsioufis C, Mancia G. Beta-blockers in hypertension: overview and metaanalysis of randomized outcome trials. J Hypertens. 2020;38:1669–81.
19. Wong GWK, Laugerotte A, James M, Wright JM. Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension. Cochrane Database Syst Rev. 2015;8:1–43.
20. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. Am J Cardiovasc Drugs. 2008;8:35–44.
21. Frishman WH, Henderson LS, Lukas MA. Controlled-release carvedilol in the management of systemic hypertension and myocardial dysfunction. Vascular Health Risk Manag. 2008;4:1387–400.
22. Wong GWK, Wright JM. Blood pressure lowering efficacy of nonselective beta-blockers for primary hypertension. Cochrane Database Syst Rev. 2014;2:1–68.
23. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 5 Effects head-to-head comparison of various classes of antihypertensive drugs-overview and meta-analysis. J Hypertens. 2015;33:1321–41.
24. Khan N, McAlister FA. Re-examining the efficacy of b-blockers for the treatment of hypertension: a meta-analysis. CMAJ. 2006;174:1737–42.
25. Kuyper LM, Khan NA. Atenolol vs nonatenolol b-blockers for the treatment of hypertension: a meta-analysis. Can J Cardiol. 2014;30:S47-53.
26. Wei J, Galaviz KI, Kowalski AJ, Magee MJ, Haw JS, Narayan KMV, Ali MK. Comparison of cardiovascular events among users of different classes of antihypertension medications. a systematic review and network meta-analysis. JAMA Netw Open. 2020;3:1–12.
27. Zhu J, Chen N, Zhou M, Guo J, Zhu C, Zhou J, Ma M, He L. Calcium channels blockers versus other classes of drugs for hypertension. Cochrane Database of Syst Rev 2022;1: Art. No.: CD003654
28. Chen YJ, Li LJ, Tang WL, Qiu R, Li Q, Xue H, Wright JM. First-line drugs inhibiting the renin angiotensin system versus other first-line antihypertensive drug classes for hypertension. Cochrane Database Syst Rev. 2018;11:1–108.
29. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ. 2008;336:1–7.
30. Bangalore S, Wild D, Parkar S, Kukin M, Messerli FH. Beta-blockers for primary prevention of heart failure in patients with hypertension. J Am Coll Cardiol. 2008;52:1062–72.
31. Neutel JM, Smith DH, Ram CV, Kaplan NM, Papademetriou V, Fagan TC, Lefkowitz MP, Kazempour MK, Weber MA. Application of ambulatory blood pressure monitoring in differentiating between antihypertensive agents. Am J Med. 1993;94:181–7.
32. Frishman WH, Saunders E. β-adrenergic blockers. J Clin Hypertens (Greenwich). 2011;13:649–53.
33. Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensive: a prospective study. Circulation. 2003;107:1401–6.
34. Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke. 1998;29:992–6.

35. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancia G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. JAMA. 2003;290:2805–16.
36. Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, Neaton JD, Grimm RH Jr, Hansson L, Lacourciere Y, Muller J, Sleight P, Weber MA, Williams G, Wittes J, Zanchetti A, Anders RJ, CONVINCE Research Group. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. JAMA. 2003;289:2073–82.
37. Grassi G, Quarti-Trevano F, Seravalle G, Dell'Oro R, Facchetti R, Mancia G. Association between the European Society of Cardiology/European Society of Hypertension heart rate thresholds for cardiovascular risk and neuroadrenergic markers. Hypertension. 2020;76:577–658.
38. Esler M, Lambert G, Esler D, Ika Sari C, Guo L, Jennings G. Evaluation of heart rate as a sympathetic nervous system biomarker in essential hypertension. J Hypertens. 2020;38:1488–95.
39. Mann SJ. Neurogenic hypertension: pathophysiology, diagnosis and treatment. Clin Auton Res. 2018;28:363–74.
40. Chirinos JA, Segers P, Hughes T, Townsend R. Large-artery stiffness in health and disease JACC state-of-the-art review. J Am Coll Cardiol. 2019;74:1237–63.
41. McEniery CM, Yasmin A, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR, ACCT Investigators. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol. 2005;46:1753–60.
42. Zhang Y, Lacolley P, Protogerou AD, Safar ME. Arterial stiffness in hypertension and function of large arteries. Am J Hypertens. 2020;33:291–5.
43. Boutouyrie P, Chowienczyk P, Humphrey JD. Arterial stiffness and cardiovascular risk in hypertension. Circ Res. 2021;128:864–86.
44. Frishman WH. Beta-adreneric blockade in cardiovascular disease. J Cardiovasc Pharmacol Ther. 2013;18:310–9.
45. Polónia J, Barbosa L, Silva JA, Bertoquini S. Different patterns of peripheral versus central blood pressure in hypertensive patients treated with β-blockers either with or without vasodilator properties or with angiotensin receptor blockers. Blood Press Monit. 2010;15:235–9.
46. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation. 2006;113:1213–25.
47. Pedersen ME, Cockcroft JR. The vasodilatory beta-blockers. Curr Hypertens Rep. 2007;9:269–77.
48. Ripley TL, Staseen JJ. β-blockers: a review of their pharmacological and physiological diversity in hypertension. Ann Pharmacother. 2014;48:723–33.
49. Ruwald AC, Westergaard B, Sehestedt T, Kjeldsen SE, Lindholm LH, Wachtell K, Devereux RB, Ibsen H, Nieminen MS, Dahlöf B, Olsen MH. Losartan versus atenolol-based antihypertensive treatment reduces cardiovascular events especially well in elderly patients: the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. J Hypertens. 2012;30:1252–9.
50. Testa G, Cacciatore F, Della-Morte D, Mazzella F, Mastrobuoni C, Galizia G, Gargiulo G, Rengo F, Bonaduce D, Abete P. Atenolol use is associated with long-term mortality in community-dwelling older adults with hypertension. Geriatr Gerontol Int. 2014;14:153–8.
51. 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.
52. Shah NK, Smith SM, Nichols WW, Lo MC, Ashfaq U, Satish P, Johnson JA, Epstein BJ. Carvedilol reduces aortic wave reflection and improves left ventricular/vascular coupling: a comparison with atenolol (CENTRAL Study). J Clin Hypertens (Greenwich). 2011;13:917–22.
53. Kampus P, Serg M, Kals J, Zagura M, Muda P, Karu K, Zilmer M, Eha J. Differential effects of nebivolol and metoprolol on central aortic pressure and left ventricular wall thickness. Hypertension. 2011;57:1122–8.
54. DiNicolantonio JJ, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. Meta-analysis of carvedilol versus beta 1 selective beta-blockers (atenolol, bisoprolol, metoprolol and nebivolol). Am J Cardiol. 2013;111:765–9.
55. Huck DM, Rosenberg MA, Stauffer BL. Nebivolol and incident cardiovascular events in hypertensive patients compared with non-vasodilatory beta blockers. J Hypertens. 2022;40:1019–29.
56. Basile J, Egan B, Punzi H, Ali S, Li Q, Patel M, Neutel J. Risk of hospitalization for cardiovascular events with beta-blockers in hypertensive patients: a retrospective cohort study. Cardiol Ther. 2018;7:173–83.