Hypertension

REVIEW

Rationale for the Inclusion of β-Blockers Among Major Antihypertensive Drugs in the 2023 European Society of Hypertension Guidelines

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ABSTRACT: We address the reasons why, unlike other guidelines, in the 2023 guidelines of the European Society of Hypertension β-blockers (BBs) have been regarded as major drugs for the treatment of hypertension, at the same level as diuretics, calcium channel blockers, and blockers of the renin-angiotensin system. We argue that BBs, (1) reduce blood pressure (the main factor responsible for treatment-related protection) not less than other drugs, (2) reduce pooled cardiovascular outcomes and mortality in placebo-controlled trials, in which there has also been a sizeable reduction of all major cause-specific cardiovascular outcomes, (3) have been associated with a lower global cardiovascular protection in 2 but not in several other comparison trials, in which the protective effect of BBs versus the other major drugs has been similar or even greater, with a slightly smaller or no difference of global benefit in large trial meta-analyses and a similar protective effect when comparisons extend to BBs in combination versus other drug combinations. We mention the large number of cardiac and other comorbidities for which BBs are elective drugs, and we express criticism against the exclusion of BBs because of their lower protective effect against stroke in comparison trials, because, for still uncertain reasons, differences in protection against cause-specific events (stroke, heart failure, and coronary disease) have been reported for other major drugs. These partial data cannot replace global benefits as the main deciding factor for drug choice, also because in the general hypertensive population whether and which type of event might occur is unknown. ***(Hypertension.* 2024;81:1021–1030. DOI: 10.1161/HYPERTENSIONAHA.124.22821.)** • **Supplement Material**.

Key Words: antihypertensive drugs ■ blood pressure ■ coronary disease ■ heart failure ■ hypertension ■ stroke

It seems that one of the major novelties of the recently published 2023 guidelines on hypertension of the European Society of Hypertension (ESH)[1] is the upgrading of β-blockers (BBs) for use in the general hypertensive population, that is, their positioning at the same level as the other major antihypertensive drug classes, such as thiazides or thiazide-like (chlortalidone and indapamide) diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs). This contrasts with the recommendations of several other hypertension guidelines, which placed BBs in the second, third, and even fourth treatment step.[2–4] However, it should not be dismissed that BBs have been regarded as important drugs for the initiation and maintenance of antihypertensive treatment also in previous ESH guidelines, which were issued jointly with the European Society of Cardiology since 2003. In the 2018 guidelines,[5] for example, it was mentioned that, like other antihypertensive drugs, BBs have demonstrated the ability to effectively reduce blood pressure (BP) and cardiovascular events in randomized controlled trials and can thus be indicated as one of the main antihypertensive drugs in parallel and with the same background evidence as the other 4 drug classes.

However, in the 2018 guidelines, BBs were not included in the front line of the main antihypertensive treatment algorithm and their recommended use was primarily restricted to special conditions such as associated cardiac diseases (heart failure (HF), angina, post myocardial

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Nonstandard Abbreviations and Acronyms

ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
BB	β-blocker
CCB	calcium channel blocker
DBP	diastolic blood pressure
HF	heart failure
LIFE	Losartan Intervention For Endpoint reduction in hypertension
MI	myocardial infarction
SBP	systolic blood pressure

infarction (MI), and atrial fibrillation) or to young women with or planning pregnancy, favoring the impression of a subordinate use.[5] There is no question that the 2023 ESH guidelines make the inclusion of BBs among the major antihypertensive drugs more clear adding to the previous guidelines that this extends to drug combinations (which are recommended as the antihypertensive treatment strategy for the majority of the hypertensive population), as well as to a large number of additional cardiac, vascular, and nonvascular hypertension-associated comorbidities. The reasons of the 2023 ESH guidelines for considering BBs as an antihypertensive drug class equally important as the other classes are discussed in the present article.

ABILITY TO REDUCE BP

BBs reduce office systolic BP (SBP) and diastolic BP (DBP) as effectively as the other major antihypertensive drugs,[6] and, as it can be found in the references quoted by the 2023 ESH guidelines,[1] evidence is available that their BP-lowering effectiveness extends to out-of-office (ambulatory and home) BP values and use in combination treatment. This is an issue of paramount importance for antihypertensive treatment recommendations because the protective effect of BP-lowering interventions in patients with a BP elevation largely depends on BP reduction per se, regardless how it is obtained. This can be inferred from the observation that, despite major differences in the antihypertensive drugs used, the BP reduction documented by meta-analyses of antihypertensive treatment trials exhibits a linear relationship with the reduction of hypertension-related cardiovascular outcomes.[7,8]

OVERALL PROTECTIVE EFFECT OF BB IN PLACEBO-CONTROLLED BP-LOWERING TRIALS

BBs have been the drugs of interest in several antihypertensive treatment trials, in which patients were randomized to a BB (mainly but not exclusively atenolol) versus placebo or an untreated group. In most trials, the use of BB was associated with a statistically and clinically significant reduction of major cardiovascular outcomes and mortality, an observation that has been confirmed by randomized trial-based meta-analyses.[7–9]

An example refers to a meta-analysis of placebo-controlled trials published in 2015 (Figure 1), in which patients randomized to BB showed a 25% and 23% significant reduction in the risk, respectively, of cardiovascular outcomes and cardiovascular mortality, for a ≈10 to 11 mm Hg SBP reduction, with a corresponding 13% nonsignificant reduction of all-cause mortality.[10] In the same meta-analysis, significant outcome reductions were seen also when BP was reduced by other major antihypertensive drugs, except for cardiovascular and all-cause mortality in patients treated with ARBs, whose risk was numerically reduced without attaining statistical significance.

Further documentation of the overall protective effect of BBs was provided by a meta-analysis published in 2020 (Figure 2) that included virtually all available trials in patients with hypertension or other cardiovascular diseases in whom BB-treated patients were compared with a placebo or an untreated group.[9] When all trials were included in the analysis (top lines) BB treatment showed a significant reduction in the risk of cardiovascular outcomes (—15%), cardiovascular mortality (—23%), and all-cause mortality (—19%), the reduction of cardiovascular mortality being in contrast with the claim that cardiovascular mortality is not affected by BBs.[10] Furthermore, as shown by the other 4 lines of Figure 2, the BB-related outcome reduction was retained when different meta-analytic approaches were adopted, that is, if the meta-analysis, (1) only considered trials on HF or post-MI patients, (2) excluded trials on these 2 diseases, or (3) limited the analysis to trials that recruited hypertensive patients with the primary aim to reduce BP and see the consequences of this reduction on outcomes. The separate analysis of patients with HF or after MI was in line with the protective effect of BBs in these diseases, and thus with their known beneficial use in secondary cardiovascular prevention,[11,12] whereas the analyses made after the exclusion of patients with HF and post-MI made more stringent the documentation of their protective effect in primary cardiovascular prevention, including patients with a BP elevation. Indeed, because baseline BP ranged from markedly high to high normal or normal values (Figure 2), this meta-analysis provided evidence that BBs exert their protective effect over a wide range of pretreatment BP values.

OVERALL PATIENT PROTECTION IN TRIALS COMPARING BB WITH OTHER ANTIHYPERTENSIVE DRUGS

Numerous trials have compared BBs to other major antihypertensive drugs, with somewhat discrepant results.

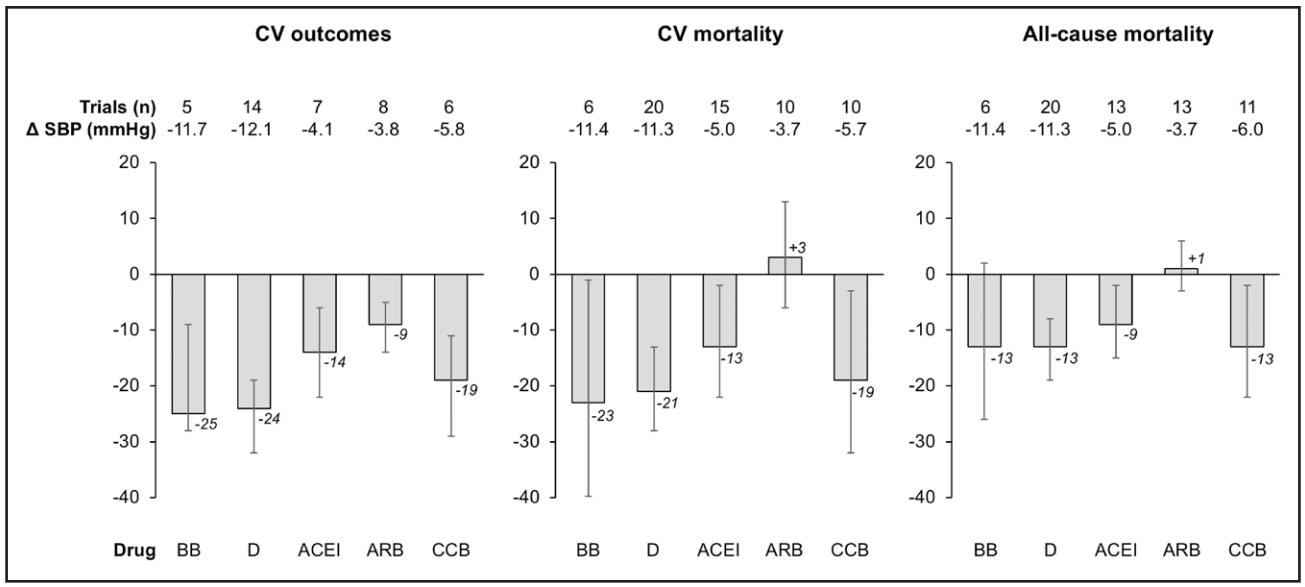

Figure 1. Meta-analysis of changes in the risk of pooled cardiovascular (CV) events, CV mortality, and all-cause mortality in patients initially treated with β-blockers (BB), diuretics (D), angiotensin-converting enzyme inhibitors (ACEI), calcium channel blockers (CCB), or angiotensin receptor blockers (ARB).

Data are shown as mean values and 95% CIs from trials in which patients were randomized to a placebo or untreated group. The number of trials and treatment-induced mean systolic blood pressure (SBP) changes are also shown. Failure of 95% CIs to touch or cross the no-change line indicates statistical significance. Data derived from Thomopoulos et al.[7]

Namely, in 2 trials, that is, LIFE (Losartan Intervention For Endpoint reduction in hypertension) and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), BBs were associated with a greater risk of cardiovascular outcomes than the comparison drug, which in the former trial was an ARB and in the latter a CCB.[13,14] However, this was not observed in other trials in which BBs were compared with diuretics, dihydropyridine, and nondihydropyridine CCBs or ACEIs.[15–21] In these trials, a similar risk of cardiovascular outcomes was observed between the compared groups, and indeed, in a trial on patients with diabetes and hypertension [21] BB treatment showed a trend to greater protection than ACEI treatment, which became significant during the trial prolongation.[22] Furthermore, in another trial, BB was superior to diuretic treatment against the risk of MI and sudden death.[17]

The discrepancies between individual trials are reflected by the heterogeneous results of trial

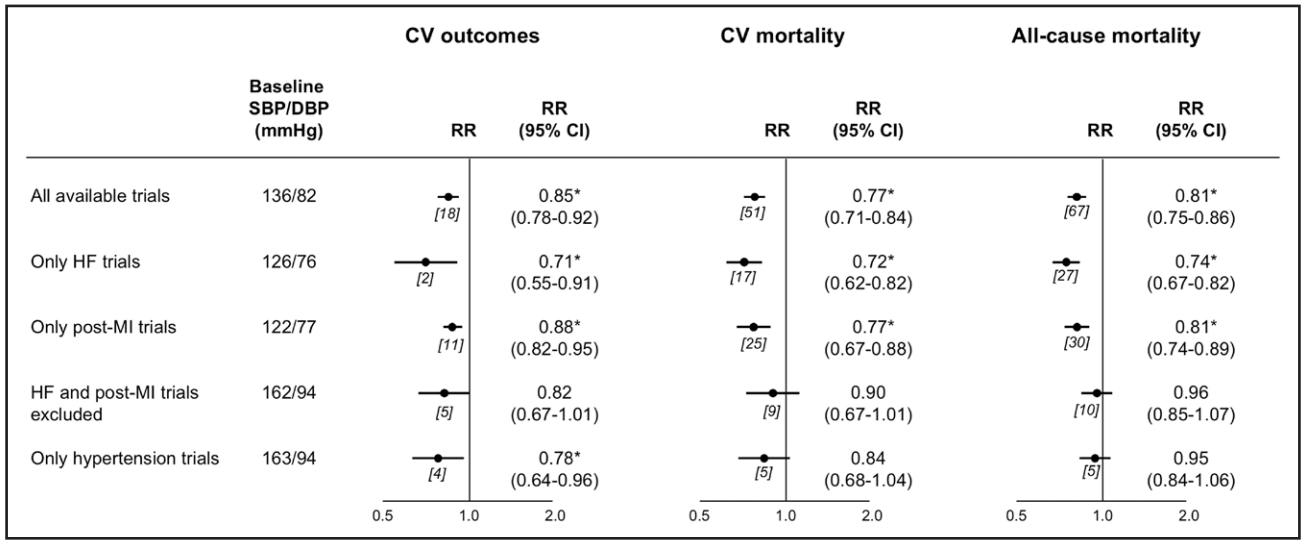

Figure 2. Meta-analysis of risk reduction (RR) of pooled cardiovascular (CV) outcomes, CV mortality, and all-cause mortality in patients initially randomized to β-blockers vs a placebo or untreated group.

Data are shown as mean values and 95% CIs. Calculation was made for all available trials, or for only heart failure (HF) trials, post-MI trials, or hypertension trials. The number in parentheses below the RR values indicates the number of trials. Asterisks indicate statistical significance. Baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) values are also shown. Data derived from Thomopoulos et al.[9]

meta-analyses, which in some cases showed a similar but in others a lesser overall protective effect of BB versus the comparison treatment, albeit usually with a difference of limited size. To quote some examples, in a large meta-analysis of randomized trials published in 2008 by the Blood Pressure Lowering Treatment Trialists' Collaboration, BB-treated patients aged < or ≥65 years showed, for a similar BP reduction, a similar risk of cardiovascular outcomes compared with treatment with any other major drug class.[23] This was the case also in a large meta-analysis published in 2015,[24] although in a subsequent meta-analysis by the same authors a smaller protective effect of BBs on cardiovascular outcomes in older patients was reported.[25] A smaller protective effect of BBs was also reported by a large meta-analysis (about 614 000 patients from trials in hypertension or other cardiovascular diseases), in which treatment with these drugs was associated with a significantly greater risk of cardiovascular outcomes (+17%) and all-cause mortality (+6%) than treatment with the other major antihypertensive drugs together.[26] However, this has not been found in the previously quoted 2020 meta-analysis,[9] which addressed the outcome effects of BBs versus other drugs by including all available comparison trials, excluding HF and post-MI trials, or limiting the analysis to hypertension trials. With all analytic approaches, there was a modest significant increase (6%) of all-cause mortality in patients treated with BBs (Table 1), whereas the risk of cardiovascular mortality never showed a significant between-treatment difference and the greater risk of cardiovascular outcomes with BBs was no more significant after exclusion of HF and post-MI trials or when only hypertension trials were analyzed. The large number of comparison trials in virtually all analytic steps provided the results with scientific strength.

BB AND TRIALS WITH COMBINATION OF ANTIHYPERTENSIVE DRUGS

No specifically designed trial has compared the protective effect of combination treatment versus placebo or an untreated patient group. However, in virtually all placebo-controlled trials showing a reduction of cardiovascular outcomes, most patients randomized to the treatment group were given a second and even ≥3 antihypertensive drugs after the initial monotherapy, leaving no doubt as to the protective effect of the combination treatment strategy. This has been also documented by a meta-analysis of trials in which outcomes were analyzed in relation to the intensity of BP-lowering treatment[27]; in this analysis, reduced outcomes by treatment with ≥3 versus ≈2 drugs or by ≥2 versus ≈1 antihypertensive drug were shown.[27] It has also been emphasized[1] that in at least 3 placebo-controlled trials BBs have been used in combination with diuretics[19,28–30] and that this has resulted into a major reduction of cardiovascular outcomes, including a 40% to 42% reduction of stroke in old patients with isolated systolic hypertension (Table 2, first 3 lines).

There is a paucity of trials specifically designed to compare different drug combinations by their systematic use in both treatment arms either from the beginning or as addition to initial monotherapy. This said, the 2023 ESH guidelines emphasize that, in trials comparing different treatment regimens, most if not all combinations have been used by a stepped care or randomized approach, in most instances without major differences in benefits. This includes the combination of a BB and a diuretic, which lost the confrontation with the CCB/ACEI combination in ASCOT,[14] as well as with the ARB/diuretic combination in LIFE[13] but showed no significant difference in the risk of cardiovascular outcomes in several other trials. With the caveat that most trials do not provide randomized comparisons, Table 2 shows that there has been a total of 10 comparisons in which the alternative to BB/diuretic treatment (a CCB/diuretic, an ACEI/diuretic, and an ACEI/CCB) was not associated with a better outcome. No significant difference in cardiovascular outcomes has also been observed in trials comparing a BB/diuretic combination versus a CCB/diuretic or a CCB/ARB combination.[18,20,31–35] According to the 2023 ESH guidelines,[1] the evidence from the above-mentioned placebo-controlled and comparison trials strongly supports the inclusion of BBs among the major antihypertensive drugs to be considered for BP-lowering therapy as well as their use in combination with all other major antihypertensive drugs. This is of critical importance for guidelines that

Table 1. Risk Ratios and 95% CIs of CV Outcomes, CV Mortality, and All-Cause Mortality for Treatment With BB Versus Treatment With Other Major Antihypertensive Drugs (Diur, CCB, ACEI, ARB) Combined

Outcomes	Baseline SBP/DBP	CV outcomes	CV mortality	All-cause mortality
All trials	153/93 mm Hg	1.10 (1.01–1.21) [13]*	1.06 (0.95–1.18) [18]	1.06 (1.01–1.11) [22]*
After the exclusion of HF and post-MI trials	159/93 mm Hg	1.09 (0.99–1.18) [11]	1.05 (0.93–1.19) [4]	1.06 (1.01–1.12) [16]*
Only hypertension trials	160/94 mm Hg	1.09 (0.99–1.18) [11]	1.06 (0.93–1.21) [12]	1.06 (1.01–1.12) [14]*

Baseline mean SBP and DBP values are shown in column 2. Meta-analysis from (1) all available randomized trials, or (2) after exclusion of trials on HF and post-MI trials or (3) only from hypertension trials. Numbers in brackets beside the risk ratios indicate the number of trials included in the analysis. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; CV, cardiovascular; DBP, diastolic blood pressure; Diur, diuretic; HF, heart failure; MI, myocardial infarction; and SBP, systolic blood pressure. Data derived from Thomopoulos et al.[9]

*Statistical significance values.

Table 2. Trials Showing the Effect of BB in 2 Drug Combinations Versus Placebo or Other 2 Drug Combinations (ACEI, ARB, CCB, Diur)

Trial	Treatment	Comparator	ΔSBP (mm Hg)	Outcomes (Δ, relative risk)
Coope and Warrender	BB+Diur	Placebo	−18	−42% strokes (P<0.03)
SHEP	BB+Diur	Placebo	−13	−36% strokes (P<0.0001)
STOP	BB+Diur	Placebo	−23	−40% CV outcomes (P=0.003)
CAPPP	BB+Diur	ACEI+Diur	−3	No difference in CV outcomes
LIFE	BB+Diur	ARB+Diur	+1	+26% strokes (P<0.001)
ALLHAT	BB+Diur	ACEI+BB	−2	No difference in CV outcomes
ALLHAT	BB+Diur	CCB+BB	−1	No difference in CV outcomes
CONVINCE	BB+Diur	CCB+Diur	0	No difference in CV outcomes
NORDIL	BB+Diur	ACEI+CCB	−3	No difference in CV outcomes
INVEST	BB+Diur	ACEI+CCB	0	No difference in CV outcomes
ASCOT	BB+Diur	ACEI+CCB	+3	+16%, CV outcomes (P<0.001)
ELSA	BB+Diur	CCB+Diur	0	No difference in CV outcomes
STOP-2	BB+Diur	ACEI or Conv. T.	0	No difference in CV outcomes
COPE	BB+CCB	CCB+ARB	−0.8	No difference in CV outcomes/stroke
COPE	BB+CCB	CCB+Diur	−0.7	No difference in CV outcomes/stroke

ΔSBP (mm Hg) refers to the difference between SBP reduction in the BB-arm versus the comparison arm. The minus and plus signs indicate greater and smaller reductions with the combination treatment, respectively. ACEI indicates angiotensin-converting enzyme inhibitor; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ARB, angiotensin receptor blocker; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CAPPP, Captopril Prevention Project; CCB, calcium channel blocker; Conv. T., conventional therapy; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPE, Combination therapy of hypertension to Prevent cardiovascular Events; CV, cardiovascular; ELSA, European Lacidipine Study on Atherosclerosis; INVEST, International Verapamil-Trandolapril Study; LIFE, Losartan Intervention For Endpoint reduction in Hypertension; NORDIL, Nordic Diltiazem; SBP, systolic blood pressure; SHEP, Systolic Hypertension in the Elderly Program; and STOP, Swedish Trial in Old Patients with hypertension. Data derived from Mancia et al.[1].

recommend combination treatment, rather than monotherapy, in most patients with hypertension.

BB AND CAUSE-SPECIFIC OUTCOMES IN PLACEBO-CONTROLLED TRIALS

A major and unfortunately widely spread argument against the use of BBs in hypertension is that these drugs do not protect against stroke, that is, a cause-specific outcome closely related to BP elevations.[36] However, this is by no means what randomized outcome trials comparing BBs with placebo have shown. This is exemplified by the results of a large meta-analysis (Figure 3) published in 2009,[37] as well as by the meta-analysis published in 2015,[7] which have both documented a significant reduction in the risk of stroke by BBs compared with a placebo or untreated group. It is further exemplified by the 2020 meta-analysis,[9] which compared placebo with BB-treated patients and showed an almost always significant and sizeable reduction in the risk of stroke throughout the various meta-analytic steps (Table 3).

In the 2009 and 2015 meta-analyses,[7,37] a significant stroke reduction was observed also with the other major antihypertensive drugs classes, and all 5 drug classes significantly reduced other main cause-specific outcomes such as HF and coronary disease (Figure 3; Table 3). Although multiple differences (demography, clinical aspects, baseline and achieved BP values, background cardiovascular medicines, etc.) make comparisons across placebo-controlled trials of limited value, it may be of interest that in these 2 meta-analyses the reduction in the risk of stroke by BBs (−17% and −27%) was less than that by diuretics (−38% and −37%) and CCBs (−34% and −34%) but not less than the risk of stroke associated with use of ACEIs (−22% and −21%) or ARBs, for which data were available in only 1 meta-analysis,[7] showing a 10% reduction of stroke risk.

BB AND CAUSE-SPECIFIC OUTCOMES IN RANDOMIZED COMPARISON TRIALS

The 2023 ESH guidelines have not omitted to mention that meta-analyses of trials comparing BBs with other antihypertensive drugs have consistently found that BBs reduce the risk of stroke less than other antihypertensive agents, with a relative increase of BB-related risk.[9,24–26,37,38] However, they also mention that this is just one of the between-drug differences in the ability of major antihypertensive agents to protect against cause-specific outcomes that have emerged in the meta-analysis era. ACEIs have also been found to be significantly less protective than other drugs

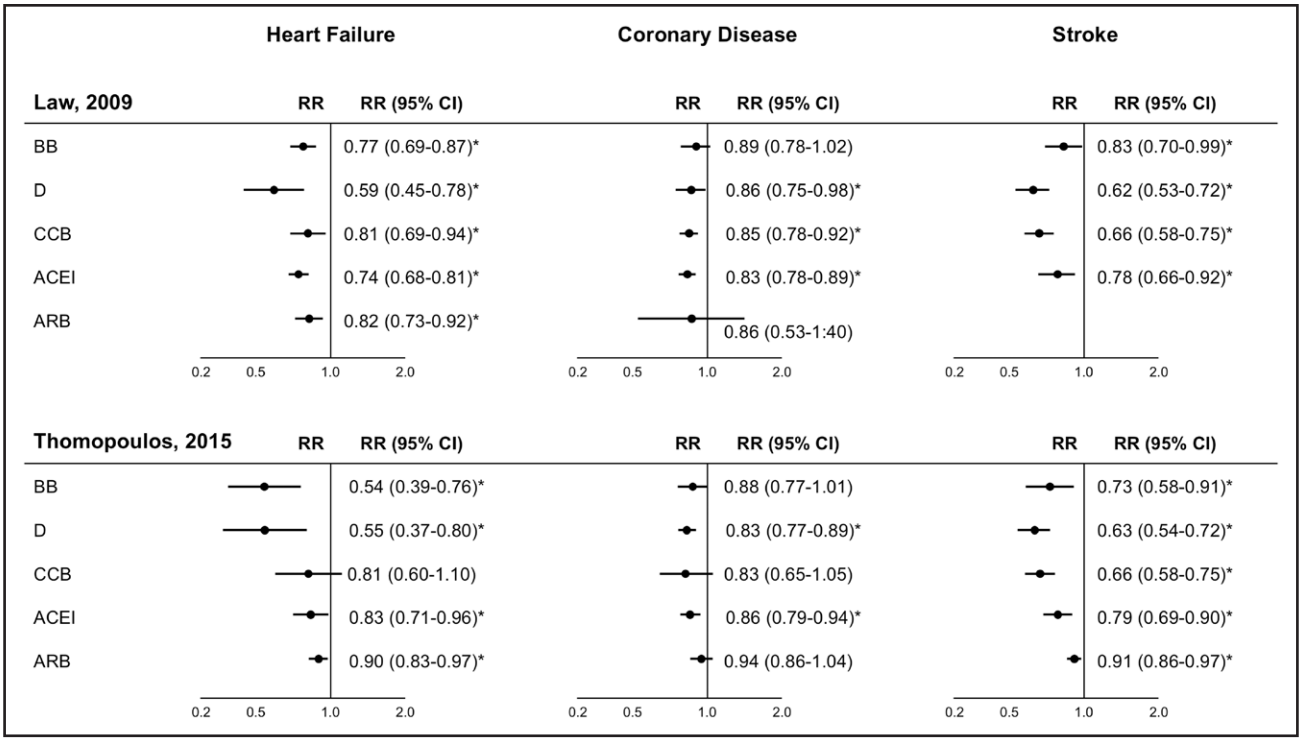

Figure 3. Risk reductions of heart failure, coronary diseases, and stroke in patients randomized to initial treatment with β-blockers (BB), diuretic (D), angiotensin-converting enzyme inhibitor (ACEI), calcium channel blocker (CCB), or angiotensin receptor blocker (ARB) vs placebo or untreated patients.
Asterisks indicate statistical significance. Data derived from the meta-analyses of Law et al.[37] and Thomopoulos et al.[9]

against the risk of stroke[24] as well as more protective against the risk of coronary disease.[24] BBs have been shown to be less protective[26] and blockers of the renin-angiotensin system to be more protective against the progression of kidney disease to kidney failure.[39] CCBs have been associated with a greater protection against stroke but with lower protection than other drugs against HF[24,37] while diuretics have been associated with a greater reduction in the risk of HF,[24,37] compared with all other drugs together, and particularly compared with CCBs. In one of the largest available meta-analyses[37] BBs were reported to provide significantly greater protection against coronary disease than all other drugs in patients with a history of a recent MI. Furthermore, in the same meta-analysis, the increase in the risk of stroke seen when BBs were compared with all other major antihypertensive drugs was no more significant when CCBs were excluded and BBs were compared with pooled data from ACEIs, ARBs, and diuretics, which in turn showed an almost significant increase in stroke when compared with CCBs.[37] With these diversified data, to focus only on the lower protective effect of BBs against stroke and decide on their exclusion as a major antihypertensive drug class reflects a double standard of judgment, which should by all means be avoided. In addition, these diversified drug-related effects make cause-specific data an unsuitable criterion for the selection of the drugs to be primarily recommended for antihypertensive treatment, at least in the European hypertensive population, in which stroke, coronary outcomes, and HF are all common.[40] According to the 2023 ESH guidelines, this selection needs to be guided by the overall protective effect of drugs against hypertension-related outcomes because; (1) if lower

Table 3. Risk Ratios and 95% CIs for the Risk of Stroke, Coronary Disease, and Heart Failure (HF) in Randomized Trials on Antihypertensive Treatment With BB Versus Placebo or an Untreated Group

Outcomes	Heart failure	Coronary disease	Stroke
All trials	0.82 (0.74–0.92)*	0.75 (0.69–0.81)*	0.86 (0.72–0.98)*
After the exclusion of HF and post-MI trials	0.80 (0.36–1.79)	0.88 (0.78–1.01)	0.78 (0.64–0.94)*
Only hypertension trials	0.57 (0.35–0.91)*	0.88 (0.77–1.01)	0.77 (0.61–0.97)*

Meta-analysis of all available trials or after exclusion of trials on HF and post-MI or of hypertension trials only. Data derived from Thomopoulos et al.[9]
*Statistical significance values.

protection against a cause-specific outcome coexists with a similar overall cardiovascular protection, it is obvious that reduced protection against one cause-specific outcome is compensated by increased protection against other outcomes; (2) in the general hypertensive population physicians do not know whether and which outcome a patient will experience in the future, which makes overall protection a compelling choice; and (3) data on overall protection are based on a larger number of outcomes and thus provide a greater statistical power than cause-specific data, which are considerably more variable between trials than data on overall protection.

FACTORS INVOLVED IN DIFFERENT CAUSE-SPECIFIC OUTCOME PROTECTION BY ANTIHYPERTENSIVE DRUGS

Another major problem of drug-related differences in cause-specific outcomes is that the factors responsible are largely speculative and that confounders cannot be excluded. As far as HF is concerned, the greater protective effect of diuretics might be ascribed to diagnostic limitations, that is, to the ability of diuretics to reduce or even temporarily eliminate the HF-dependent symptoms and signs, which implies that diuretics may just make the identification of HF more difficult. The lesser protective effect of CCBs on HF may originate from the negative inotropic effect of these drugs[41] as well as from their inability to reduce the HF-dependent neurohumoral activation and its adverse consequences.[42] However, also for CCBs confounding factors cannot be excluded, one of them being a spurious diagnosis of HF by CCB-dependent ankle edema, particularly in patients complaining of shortness of breath, due to overweight and lack of exercise rather than to cardiac functional impairment. These diagnostic problems have been reduced in more recent trials by restricting the diagnosis to hospitalized HF, and at any rate they are not pertinent to the effect on stroke by BBs, because the diagnosis of stroke, like that of coronary disease, is based on specific symptoms and signs as well as on instrumental data. According to the 2023 ESH guidelines, direct damaging influences of BBs on the brain have never been reported in patients treated with BBs, and no data have shown a detrimental effect of BBs on autoregulation of cerebral blood flow when BP is acutely or chronically reduced. A role for greater rate of treatment discontinuation reported for BB-treatment[43] is also unlikely because the detrimental effect of treatment discontinuation should involve all cardiovascular outcomes, and not just stroke.[44] As of today, a potentially important factor to consider is a smaller BP reduction in BB-treated patients than in patients treated with the comparison drugs. This is not an unrealistic possibility because stroke incidence is known to be sensitive to even small BP changes and in the 2 trials that have shown a lower protection against stroke by BBs, that is, LIFE and ASCOT,[13,14] office BP showed a lesser reduction in the BB-group. The difference was small in LIFE (average 0.3 mm Hg SBP, 1.3 mm Hg SBP at the last visit) but considerably greater in ASCOT (average 5 mm Hg SBP during the first year, and 2.9 mm Hg SBP throughout the trial, in which the 23% difference in stroke risk between the 2 treatment arms (BB and CCB-treatment) almost precisely fell on the meta-regression line associating the effect of SBP reduction on the reduction of stroke (Figure S1).[8,45] It should be additionally mentioned that an origin of the lesser stroke protection by BBs from a smaller BP reduction would not be ruled out by a between-group similar office BP reduction, because BB trials have made frequent use of once-daily atenolol, which is known to leave therapeutically uncovered the 24 hours (a prognostically important BP)[46] in numerous patients. Regretfully, this possibility remains untested because in randomized trials ambulatory BP has not been measured or measurements have been limited to a small nonrandomized fraction of the overall trial population and to its outcomes. This is true also for LIFE and ASCOT in which the number of patients in whom ambulatory BP was measured was, respectively, about 1% and 10% of the recruited patients.[47,48] Finally, for a similar reduction of brachial BP, BBs lower central BP less than other major antihypertensive drugs.[49] However, an explanation based on a central BP imbalance suffers from the uncertain prognostic superiority of central vis-à-vis brachial BP.[50]

OTHER THERAPEUTIC ADVANTAGES AND INCONVENIENCES OF BB

Like all therapeutically effective drugs, BBs are not immune from clinical inconveniences. (1) BBs are less effective than other major antihypertensive drugs on the regression of subclinical organ damage.[1] (2) BBs have a less favorable tolerability profile compared with ACEIs and ARBs (reduced exercise ability, fatigue, cold extremities, etc.), in both younger and older patients. This leads to a greater risk of treatment discontinuation because treatment discontinuation is closely associated with the incidence of side effects.[51] (3) BBs favor the development of insulin resistance and type 2 diabetes[52] in predisposed patients, such as those with a metabolic syndrome. Finally, because of a possible reduction of peripheral blood flow and size of the bronchial tree, BBs have for a long time been contra-indicated in conditions such as peripheral artery disease or obstructive lung disease. The 2023 ESH guidelines regard these effects as therapeutic disadvantages that may reduce or avoid the use of BBs in specific conditions or in some patients but do not consider them a reason to exclude BBs from the main antihypertensive treatment algorithm. In this context, relevant

arguments are that, (1) some side effects of BBs have been overestimated[53,54]; (2) it is now widely accepted that BBs can be used with no substantial safety problems for respiratory function or lower limb perfusion[55,56] in obstructive lung disease and peripheral artery disease, where they may provide a better protection against coronary disease, which is common in these patients; (3) drug-related and between-drug differences in side effects are likely to be minimized by the combination treatment recommended by the 2023 ESH guidelines for most patients with hypertension, because side effects are dose-dependent and, in drug combinations, drugs are usually used at lower doses; (4) use of BBs is well established in several cardiovascular conditions frequently associated with and favored by hypertension (MI, angina pectoris, HF, atrial fibrillation, subaortic stenosis, long-QT syndrome, coronary bypass surgery, aortic dissection, aneurysm of the ascending or abdominal aorta, heart rate >80 bpm, etc.), in which they relieve symptoms and play a life-saving role; (5) the number of patients with hypertension in need of BBs is even larger if one considers that these drugs can be important in women with a child-bearing potential age as well as in hypertension disorders of pregnancy, where blockers of the renin-angiotensin system are contra-indicated. Furthermore, in clinical practice prescription of BBs extends to diseases that do not primarily involve the cardiovascular system, but in which BBs exert a favorable effect on their symptoms and signs[57]; (6) the worse tolerability and the other inconveniences of BBs can be minimized by the new β-blocker generation, that is, by BBs with higher β-1 selectivity and an additional vasodilator effect[58]; and (7) although rarely considered by guidelines, it may not be of marginal interest that BBs are a pathophysiological appropriate treatment because hypertension is characterized by sympathetic activation from its early to its late and complicated stages, to which it contributes with both BP-dependent and BP-independent detrimental influences.[59]

PERSPECTIVES

The multiple important data in favor of BBs that have been discussed in this article justify their inclusion among the major drugs to be used for the treatment of hypertension, at the same level as diuretics, ACEIs, CCBs, and ARBs. This also carries the advantage of increasing the number of options available to the physician to effectively lower an elevated BP by mono or combination therapy, achieving cardiovascular protection in a greater number of patients. Although they should be appropriately taken into account, the inconveniences of BBs (treatment discontinuation, lesser protection against subclinical organ damage, dysmetabolic effects) should not be used as an exclusion criterion to avoid the double standard of judgment that has never regarded the same inconveniences a problem for the use of diuretics. The same is true for the lesser protective effect of BBs against stroke that cannot ignore that different protective effects against cause-specific events characterize all major drugs and, in the case of BBs, do not prevent an effective overall cardiovascular protection.

ARTICLE INFORMATION

Affiliations

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