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Special Article

European and US guidelines for arterial hypertension: similarities and differences

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ABSTRACT

Hypertension is one of the most common chronic diseases in adults and a leading cause of disability and mortality worldwide. Recently, new Guidelines for the diagnosis and management of hypertension have been released in Europe and in the United States, with changes regarding how to diagnose and treat the condition, and the extent to which intensive blood pressure control should be pursued.

Important differences between the Guidelines exist in the classification of blood pressure levels and definition of treatment goals. Diagnosis of hypertension starts at 140/90 mmHg for the European Guidelines, and 130/80 mmHg for the US Guidelines. Besides, the European guidelines introduced the concept of "safety boundaries", consisting of BP thresholds not to be exceeded towards lower levels (120 mmHg for age < 65 years, 130 mmHg for older people) because of the fear of important adverse events associated with overtreatment. Such discrepancies can indeed have an impact on treatment attitudes and outcome incidence. Hence, we appraised facts in favor and against each of these controversial issues. In conclusion we believe that, instead of fixing rigid BP targets and boundaries, modern hypertension management should be aimed to achieve in each patient an optimal balance between intensive BP reduction and treatment safety.

1. Introduction

Hypertension is a major, but modifiable, contributory factor in cardiovascular (CV) disease [1]. It remains the most powerful predictor of mortality and progressed from rank #4 in year 1990 to rank #1 in year 2010 as a global risk factor for death, disability-adjusted life years and years of life lost [1,2].

New Guidelines for the diagnosis and management of hypertension have been recently released in Europe [3] and in the United States [4], with changes regarding how to diagnose and treat the condition, and the extent to which intensive blood pressure (BP) control should be pursued. Of note, some of the proposed recommendations by European Society of Cardiology (ESC) and European Society of Hypertension (ESH) Guidelines [3] are out of step with those released by American hypertension experts' panel last year [4].

The main differences may be found in (i) the classification of hypertension, (ii) the treatment goals, and (iii) the concept of "safety boundaries". Such discrepancies can indeed have an impact on treatment attitudes and outcome incidence in hypertensive patients. Thus, facts in favor and against each of these controversial aspects and positions [3,4] are summarized and critically appraised.

2. Definition of hypertension

The ESC/ESH Guidelines [3] maintained traditional BP categories, with grade 1 hypertension starting at an office BP of 140/90 mmHg. Conversely, the American College of Cardiology (ACC) and American Heart Association (AHA) Guidelines for the Prevention, Detection, Evaluation, and Management of High BP in adults [4] lowered the threshold for hypertension (Table 1).

The definition of normal BP did not change from the previous document, but the new ACC/AHA Guidelines [4] eliminate the classification of prehypertension and sub-divide the BP levels previously labelled 'prehypertension' into 'elevated BP' (systolic BP between 120 and 129 and diastolic BP < 80 mmHg), and 'Stage 1 hypertension' (systolic BP 130–139 or a diastolic BP of 80–89 mmHg).

Obviously and inevitably, such shift in definition of hypertension by US Guidelines [4] leads to classify more subjects as hypertensive

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Table 1
Blood pressure categories according to the 2017 American College of Cardiology/American Heart Association and 2018 European Society of Cardiology/European Society of Hypertension Guidelines [3,4].

Category	2017 ACC/AHA			2018 ESC/ESH		
	SBP (mmHg)		DBP (mmHg)	SBP (mmHg)		DBP (mmHg)
Optimal	–	–		< 120	and	< 80
Normal	< 120	and	< 80	120–129	and or	80–84
High-N	–	–	–	130–139	and or	85–89
Elevated	120–129	and	< 80	–	–	–
Hypertension Stage/Grade[a]						
1	130–139	or	80–89	140–159	and or	90–99
2	≥140	or	≥90	160–179	and or	100–109
3	–	–	–	≥ 180	and or	≥110
ISH	–	–	–	≥ 140	and	< 90

SBP = systolic blood pressure; DBP = diastolic blood pressure; High-N = high normal

[a] 'Stage' for ACC/AHA; 'Grade' for ESC/ESH; ISH = Isolated systolic hypertension.

worldwide. For instance, a recent analysis of the REasons for Geographic And Racial Differences in Stroke (REGARDS) study [5] showed that when the new definition of hypertension by the ACC/AHA Guidelines [4] is being adopted, the overall prevalence of hypertension would approximately double and the number of individuals requiring pharmacotherapy would increase. Specifically, participants were grouped into 3 mutually exclusive categories based on their BP: (1) systolic BP < 130 mmHg and diastolic BP < 80 mmHg; (2) systolic BP between 130 and 139 mmHg or diastolic BP between 80 and 89 mmHg; and (3) systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg. Among the 14,039 patients not taking antihypertensive medications, 29.9% had hypertension according to the 2017 ACC/AHA Guidelines [4] compared with 15.7% by the ESH/ESC Guidelines [3].

Similar results were also obtained by a recent cross-sectional analysis of the US National Health and Nutrition Examination Survey (NHANES) and China Health and Retirement Longitudinal Study (CHARLS) [6], examining the effect of the 2017 ACC/AHA hypertension Guidelines [4] on the prevalence of hypertension and eligibility for initiation and intensification of treatment.

Adoption of the 2017 ACC/AHA hypertension Guidelines [4] in the US would label 70.1 (95% confidence interval [CI] 64.9–75.3) million people in the 45–75 year age group as having hypertension, representing 63% (60.6–65.4%) of the population in this age group. Their adoption in China would lead to classify 266.9 (252.9–280.8) million people or 55% (53.4–56.7%) of the same age group as having hypertension. This represents an increase in prevalence of 26.8% (23.2–30.9%) in the US and 45.1% (41.3–48.9%) in China (Fig. 1). Furthermore, on the basis of treatment patterns and current Guidelines, 8.1 (6.5–9.7) million Americans with hypertension are untreated, which would be expected to increase to 15.6 (13.6–17.7) million after the implementation of the ACC/AHA Guidelines [4]. In China, on the basis of current treatment patterns, 74.5 (64.1–84.8) million patients with hypertension are untreated, estimated to increase to 129.8 (118.7–140.9) million. Finally, even among people receiving treatment, the proportion that are candidates for intensification of treatment is estimated to increase by 13.9 (12.2–15.6) million (from 24.0% to 54.4% of treated patients) in the US, and 30 (24.3–35.7) million (41.4–76.2% of treated patients) in China, if the ACC/AHA treatment targets are adopted [4].

3. Treatment strategies

The joint ESC/ESH [3] recommendations emphasize the use of at least two drugs to initiate treatment in the vast majority of patients by means of single-tablet combinations to enhance compliance, which will ultimately boost BP control rates. Specifically, the European Guidelines [3] recommend either an angiotensin-converting enzyme inhibitor (ACE-I), or an angiotensin receptor blocker (ARB) associated with either a calcium channel blocker (CCB) or a diuretic as first step (with some exceptions in which monotherapy is still indicated), a triple combination with either an ACE-I or ARB plus a CCB plus a diuretic as second step and a triple combination plus spironolactone, or an alpha blocker or a beta-blocker, as a third step in patients with resistant hypertension. The algorithm in the new ESC/ESH Guidelines [3] to help guide clinicians is depicted in Fig. 2.

Indications from the ACC/AHA Guidelines [4] do not substantially differ: they recommend diuretics, CCBs, ACEIs and ARBs as equally valid for first line treatment, and suggest that a 2-drug combination should be initiated if BP is at least 20/10 mmHg higher than the target in that specific group. In this context, physicians should consider some specific features of combination therapy.

First, the CV protection exerted by the combination of an ACE-I with a CCB is supported by recent findings in this area [7–9]. The Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [8] compared the effects of two different antihypertensive combinations on major fatal and nonfatal CV events. In total, 11,400 men and women aged 55 years or older with systolic BP > 160 mmHg or who were currently on antihypertensive therapy and who had evidence of CV or renal disease or target-organ damage were randomized to the fixed combination of benazepril plus hydrochlorothiazide or benazepril plus amlodipine. At 36 months, BP levels were significantly improved, with > 75% of patients in both treatment arms having BP levels < 140/90 mmHg. The combination treatment with ACE-I and CCB significantly reduced the primary CV outcome, defined as CV death, fatal/nonfatal myocardial infarction, fatal/nonfatal stroke, hospitalization for unstable angina, and coronary revascularization, by 20%, compared with those treated with an ACE inhibitor plus a diuretic [8]. Similarly, the BP-lowering

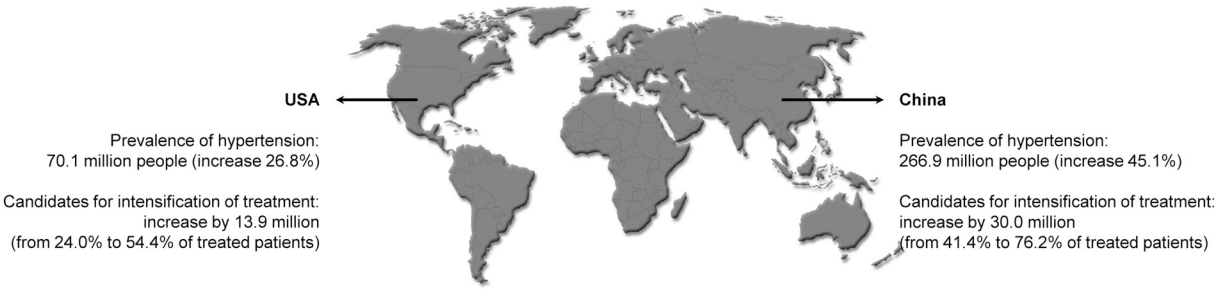

Fig. 1. Effects of the 2017 American College of Cardiology/American Heart Association hypertension Guidelines on the prevalence of hypertension and eligibility for initiation and intensification of treatment in nationally representative populations from the United States and China. Data from ref.[6].

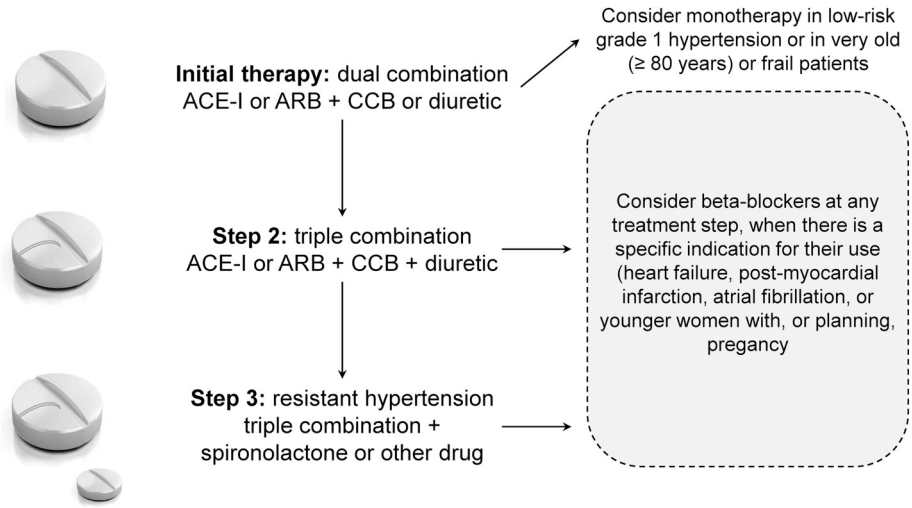

Fig. 2. Drug-treatment strategy for uncomplicated hypertension as recommended by the ESC/ESH Guidelines (see text for details) [3]. ACE-I = angiotensin converting enzyme-inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) [7] showed that antihypertensive therapy based on a "newer" regimen of the CCB amlodipine and the ACE-I perindopril confers significant advantages over a "traditional" regimen of a beta-blocker, atenolol, and thiazide diuretic, bendroflumethiazide, in terms of effects on both CV mortality and all-cause mortality.

Second, combination therapy may be administered separately or in a fixed combination. Notwithstanding its convenience, it is not entirely clear whether fixed combinations of two antihypertensive agents in a single tablet provide a greater benefit than the corresponding components given separately. In other words, it is not clear if the use of fixed combinations translates into a clearly improved BP control and CV prevention in clinical practice [10,11]. Fixed dose combinations may simplify the treatment regimen by reducing the number of pills and, thus, may improve compliance with medications [10]. In this context, a systematic overview and meta-analysis [10] compared single-pill combinations of two antihypertensive agents with free combinations; the outcome measure was the achievement of better BP control and compliance. Fifteen studies comparing fixed-dose combinations with the same free drug (or class) components were included in the analysis for a total of 32,331 hypertensive patients. Nine of the 15 studies were clinical trials and six were retrospective cohort studies. Overall, compliance with medications was modestly higher with fixed-drug combinations compared with free-drug combinations (odds ratio [OR]: 1.21; 95% CI: 1.03–1.43). However, fixed-drug combinations did not result in a significantly longer persistence with treatment when compared with free-drug combinations (OR: 1.54; 95% CI: 0.95–2.49).

Finally, although attractive for many hypertensive patients, a few specific aspects of fixed-dose combinations need to be considered [11,12]. The first issue is the cost of fixed combinations. Branded fixed combinations may be more expensive than equivalent free combinations. In addition, the use of fixed combinations implies less flexibility in modifying the doses of individual components and the exposure of patients to unnecessary therapy. Moreover, should a patient develop side effects to one component, the entire combination should be discontinued and replaced by free drugs.

Finally, using fixed-dose combinations, the physician cannot easily titrate one component without changing the other [11,12].

4. Blood pressure targets

There is a continental divide as far as treatment goals and targets are concerned. The Europeans appear to favor less tight BP targets [3]. This may reflect some skepticism in current evidence on the potential benefits of lowering BP more intensively than previously recommended.

Conversely, the 2017 ACC/AHA Guidelines [4] recommend a systolic BP target < 130/80 mmHg in almost all hypertensive patients. Notably, the recommendations for stage 1 hypertension treatment are guided by the patients' underlying CV risk. Only those with established CV disease, diabetes, renal failure, age ≥65 years or estimated cardiovascular risk of 10% or more would be offered drug treatment. The remaining subjects would be given life-style changes only [4]. In principle, such recommendation endorses the results of the Systolic Blood Pressure Intervention Trial (SPRINT) [13]. Briefly, the SPRINT [13] trial enrolled 9361 participants aged 50 years and older, including a substantial proportion of elderly (≥75 years), those with chronic kidney disease (CKD) or preexisting CV disease. The study was terminated early due to overwhelming evidence of benefit of intensive systolic BP control on the primary outcome, a composite of myocardial infarction (MI), acute coronary syndrome (ACS), stroke, congestive heart failure (CHF), or cardiovascular (CV) death. The patients in the intensive treatment arm (systolic BP target < 120 mmHg) had a 25% risk reduction in the primary composite outcome and a 27% risk reduction in mortality compared with those in the standard treatment arm (systolic BP target < 140 mmHg) [13].

Although trial evidence accumulated so far (Fig. 3) clearly supports the notion that even a small decrease in BP reduces risks of CV morbidity and mortality and that an intensive BP-lowering strategy significantly reduces the risk of CV mortality without evidence of harm [9,14–18], for the ESC/ESH Guidelines [3] the main priority for all patients remains to get BP below 140/90 mmHg (I A recommendation). More importantly, the European document [3] establishes target ranges, recommending a systolic target of 130 mmHg, but not lower than 120 mmHg, for most adults younger than 65 years (I A recommendation). For adults 65 and older, regardless of comorbidities, the treatment target range is the same as the one in younger patients with diabetic or non-diabetic CKD: < 140 mmHg, but no lower than 130 mmHg [19]. Practically, the European Guidelines [3] introduced the concept of 'safety boundaries', not to be crossed towards lower BP levels in treated patients.

5. Safety boundaries in clinical practice

As discussed above, the BP targets recommended by the ACC/AHA Guidelines [4] considerably differ from the indications released by the ESC/ESH Guidelines [3]. Lowering the threshold for diagnosis of hypertension and the BP targets, as recommended by the ACC/AHA

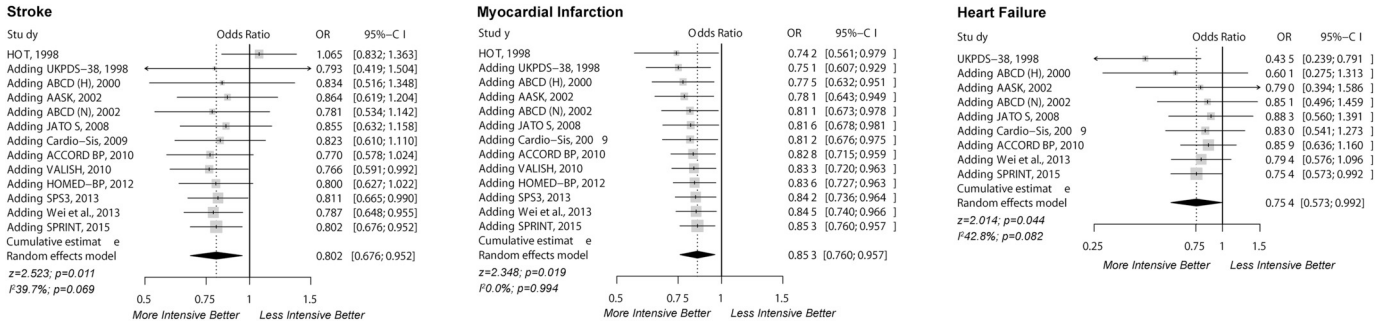

Fig. 3. Effect of more intensive versus less intensive blood pressure reduction on the risk of stroke, myocardial infarction, and heart failure in a cumulative meta-analysis of controlled clinical trials comparing different blood-pressure lowering strategies. Overall, the more intensive BP-lowering strategy was associated with a significant reduction in the cumulative risk of stroke, myocardial infarction and heart failure. There was no significant heterogeneity across the studies. Weights are from random-effect analysis and diamonds represent the 95% confidence interval (CI) for pooled estimate of effect. With permission [14]. CI = confidence interval; OR = odds ratio; AASK indicates African-American Study of Kidney Disease and Hypertension; ABCD, Appropriate Blood Pressure Control in Diabetes; ACCORD-BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure; BP, blood pressure; Cardio-Sis, Italian Study on the Cardiovascular Effects of Systolic Blood Pressure Control; DBP, diastolic blood pressure; HOMED-BP, Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure; HOT, Hypertension Optimal Treatment; JATOS, Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; MAP, mean blood pressure; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; REIN-2, Renoprotection in Patients with Non-diabetic chronic renal disease; RRR, relative risk reduction; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; SPS3, Secondary Prevention of Small Subcortical Strokes; UKPDS, UK Prospective Diabetes Study; and VALISH, Valsartan in Elderly Isolated Systolic Hypertension.

Guidelines [4], may be considered a valuable achievement in the light of evidence that a higher BP is associated with adverse CV outcomes even at levels below 140/90 mmHg [4].

In this context, the aforementioned prospective population-based analysis of the REGARDS study [5], evaluated to what extent the new BP stratum of stage 1 hypertension (systolic/diastolic BP of 130 to 139/80 to 89 mmHg) affects the CV risk in the US population. Specifically, subjects entered the study in years 2003 to 2007 and were followed up to year 2014. Overall, 4094 major CV events occurred. As expected, there was a rise in the rate of CV events across the 3 BP categories defined by the 2017 ACC/AHA hypertension Guidelines [4] (< 130/80, 130–139 and 80–89, and ≥140/90 mmHg). The Authors grouped the subjects by absence or presence of antihypertensive drug treatment at study entry. Subsequently, each of the 2 groups was subdivided by presence or absence of clinical conditions dictating initiation (in untreated subjects) or intensification (in treated subjects) of drug treatment according to the 2017 ACC/AHA Guidelines [4]. An important part of the study was the analysis of untreated subjects with baseline systolic/diastolic BP 130 to 139/80 to 89 mmHg. In this group, the rate of CV disease and all-cause mortality (per 1000 person-years) was 6-fold higher among participants with 2017 AHA/ACC indication [4] to initiate drug treatment (20.5 and 29.6, respectively) than in those without such indication (3.4 and 4.8, respectively). When restricting the analysis to treated subjects with systolic/diastolic BP 130–139/80–89 mmHg, the rate of CV disease and all-cause mortality was considerably higher among those with 2017 ACC/AHA indication [4] to intensify drug treatment (22.4 and 29.9, respectively) than in those without such indication (3.8 and 5.6, respectively).

On the other hand, the use of “safety boundaries”, as suggested by the European Guidelines [3] (i.e., treated systolic BP not below 130 mmHg in subjects aged 65 years or more, and not below 120 mmHg in subjects aged < 65 years), might be counter-productive. In fact, implementation of “safety boundaries” may induce doctors to refrain from achieving more ambitious BP targets that, if well tolerated, would reasonably result in a reduced risk of major complications of hypertension.

More specifically, some important concerns regarding the use of rigid fixed target in specific populations (elderly and CKD) of hypertensive patients need to be discussed. With a rapidly aging population, the prevalence of hypertension continues to rise, and older adults account for the bulk of hypertension-related morbidity and mortality [1,2]. It is well documented that hypertension occurs in more than two thirds of individuals after age of 65 [1,2]. Data from the Framingham Heart Study in men and women free of hypertension at 55 years of age indicate that the remaining lifetime risks for development of hypertension through 80 years are 93% and 91% respectively [20]. In other words, > 90% of individuals who are free of hypertension at 55 years of age will develop it during their remaining lifespan [20,21]. Thus, physicians need to consider specific features of their elderly hypertensive patients [22] regarding the association between elevated BP and the risk of CV disease. Hypertension in the elderly is a major risk factor for vascular dementia and, importantly, for both ischemic stroke and cerebral hemorrhage [23,24]. Furthermore, according to AHA statistics, the majority of coronary deaths occurs in subjects ≥65 years of age and elderly patients with hypertension have higher prevalence of myocardial infarction than elderly patients without hypertension [25,26].

Regarding BP lowering strategies, a recent meta-analysis [27] including 4 high-quality trials involving 10,857 older hypertensive patients (age ≥ 65 years; 5437 patients randomized to intensive BP control and 5420 patients randomized to standard BP control strategy) with a mean follow-up of 3.1 years, evaluated the effect of intensive BP control on the risk of major adverse events, including cardiovascular mortality and heart failure.

Specifically, Bavishi and co-workers demonstrated that intensive BP lowering was associated with a 29% reduction in major adverse CV events (relative risk [RR]: 0.71; 95% CI: 0.60–0.84), 33% in CV mortality (RR: 0.67; 95% CI: 0.45–0.98), and 37% in heart failure (RR: 0.63; 95% CI: 0.43–0.99) compared with standard BP lowering [27]. Importantly, there was no significant difference in the incidence of serious adverse events (RR: 1.02; 95% CI: 0.94–1.09) or renal failure (RR: 1.81; 95% CI: 0.86–3.80) between the 2 groups [27].

Both hypertension and aging may impact on renal function. Elderly patients are more likely to have CKD, usually defined by a measured estimated Glomerular Filtration Rate (eGFR) ≤ 60 mL/min per 1.73 m^2. Of note, 75% of the CKD population is ≥65 years of age and systolic BP is a strong independent predictor of decline in kidney function among older patients with isolated systolic hypertension [28,29].

Just recently, the SPRINT added an important piece of evidence in this area [30]. In SPRINT, 28.3% of participants had non-diabetic CKD at entry, defined by an estimated eGFR between 20 and 59 ml/min per 1.73 m^2. The outcome benefits associated with the more intensive BP targets did not show any significant differences between the patients with and without CKD. Of note, in the subset of patients with CKD, all-

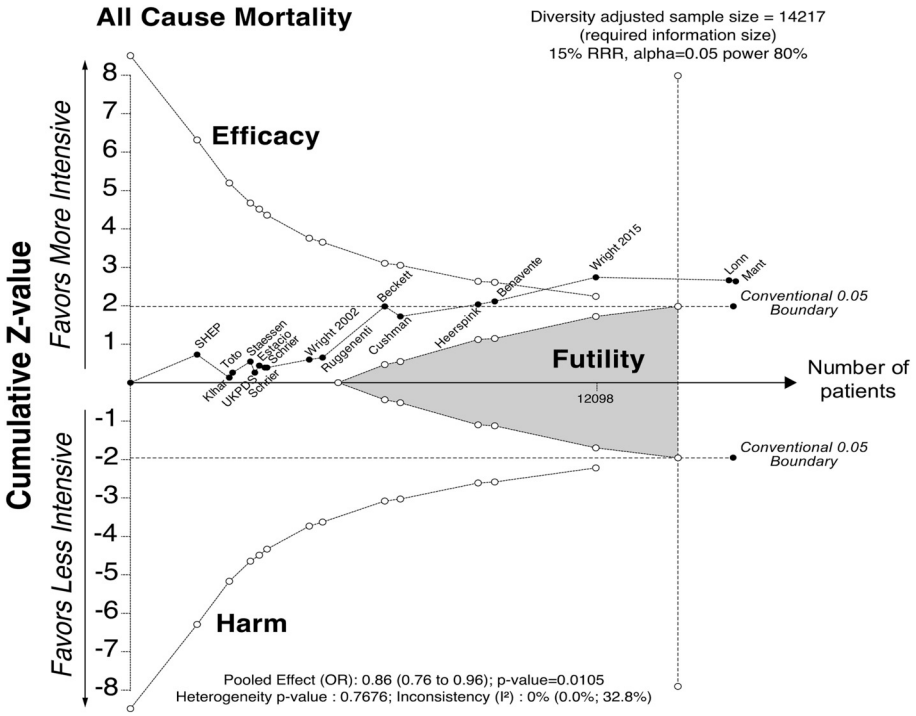

Fig. 4. Trial sequential analysis (TSA) of the effect of more intensive versus less intensive blood pressure reduction on mortality in the studies examined by Malhotra et al. [31]. The mortality benefit remained consistently and steadily above the futility area, and it crossed the sequential monitoring boundary for efficacy before the required information size was reached with no evidence for harmful effect. With permission.
OR = odds ratio; RRR = relative risk reduction. Sequential analysis applied to meta-analysis, and specifically cumulative TSA, can establish whether and when firm evidence favoring a specific intervention has been reached in the literature collected to date. Cumulative TSA requires a prespecified and clinically relevant intervention effect, as well as an overall risk of type I error to be maintained. See Ref.[19] for guidance on TSA and plot interpretation.

cause mortality was reduced by 18% (p = .04) in the more intensive compared with the less intensive treatment group [30].

A recent meta-analysis by Malhotra and co-workers [31] was focused on all-cause mortality in 18 randomized trials that compared either a more intensive versus a less intensive BP target, or an active BP lowering treatment versus placebo or no treatment. All these trials had been conducted in patients with eGFR < 60 ml/min per 1.73 m^2. Systolic BP at entry was < 140/90 mmHg in 6 of these trials, and 12 trials included patients with diabetes [31]. Overall, systolic BP fell by 16 mmHg from baseline to follow-up in the more intensive arm and by 8 mmHg in the less intensive arm. All-cause mortality during follow-up was 14% lower in the more intensive than in the less intensive arm and results were consistent across several subgroups. In particular, the mortality benefit in the more intensive arm did not differ (p for interaction: 0.56) according to baseline systolic BP (< 120 mmHg vs 120–140 mmHg vs > 140 mmHg) [31].

Finally, a trial sequential analysis [19] on the same study examined by Malhotra and co-workers [31] documented that the mortality benefit remained consistently and steadily above the futility area, and it crossed the sequential monitoring boundary for efficacy before the required information size was reached, thus providing early and firm evidence of the beneficial effect of the more intensive BP strategy (Fig. 4).

6. Conclusions

The recent European Guidelines [3,4] for the diagnosis and management of hypertension differ in some key aspects from the 2017 US Guidelines [4]. These include the definition of hypertension and the BP targets. Although there is agreement between the guideline committees [3,4] regarding patients with BP ≥ 140/90 mmHg, who should be treated at any level of CV risk, the recommendations differ for patients with systolic/diastolic BP between 130/80 and 139/89 mmHg.

In our opinion, the use of low diagnostic thresholds and intensive therapeutic targets, as suggested by the ACC/AHA Guidelines [4], are supported by sound evidence and are safe for clinical use. Conversely, the European recommendations [3], that systolic BP should not be lowered < 130 mmHg in patients aged ≥65 years, and < 120 mmHg in patients aged < 65 years (“safety boundaries”), seem to depends upon a skewed interpretation of clinical trial results.

Some well-done meta-analyses showed that a greater reduction in systolic BP is associated with a greater outcome benefit without any evidence of a J-curve effect [32].

Other findings from network meta-analyses supported the notion that reducing BP to levels below currently recommended targets significantly reduces the risk of cardiovascular disease and all-cause mortality [33,34]. In a recent network meta-analysis of 17 trials comparing different BP targets, systolic BP targets < 120 mmHg and < 130 mmHg ranked #1 and #2, respectively, as the most efficacious for preventing stroke and myocardial infarction [34]. Conversely, systolic BP targets < 140 mmHg and < 150 mmHg ranked as #1 and #2, respectively, for safety. Overall, a systolic BP target < 130 mmHg achieved the best balance between efficacy and safety [34].

Thus, instead of fixing rigid BP targets, the real challenge in a modern management of hypertension should become the best possible balance between the maximal achievable BP reduction and the tolerability of treatment in each single patient [15,35]. The concept of ‘the lower the BP the better, conditional to tolerability of treatment’ should drive our clinical approach to hypertensive patients.

Conflict of interest

None of the authors of this study has financial or other reasons that could lead to a conflict of interest.

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References

[1] Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005;365:217–23.
[2] Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: a systematic review. J Hypertens 2004;22:11–9.
[3] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. List of

authors/Task Force m. 2018 practice guidelines for the management of arterial hypertension of the European society of hypertension and the european society of cardiology: Esh/esc task force for the management of arterial hypertension. J Hypertens 2018;36:2284–309.
[4] Whelton PK, Carey RM, Aronow WS, Casey Jr. DE, Collins KJ, Dennison Himmelfarb C, et al. 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.
[5] Colantonio LD, Booth 3rd JN, Bress AP, Whelton PK, Shimbo D, Levitan EB, et al. 2017 acc/aha blood pressure treatment guideline recommendations and cardiovascular risk. J Am Coll Cardiol 2018;72:1187–97.
[6] Khera R, Lu Y, Lu J, Saxena A, Nasir K, Jiang L, et al. Impact of 2017 acc/aha guidelines on prevalence of hypertension and eligibility for antihypertensive treatment in United States and China: nationally representative cross sectional study. BMJ 2018;362:k2357.
[7] Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the anglo-scandinavian cardiac outcomes trial-blood pressure lowering arm (ascot-bpla): a multicentre randomised controlled trial. Lancet 2005;366:895–906.
[8] Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med 2008;359:2417–28.
[9] Verdecchia P, Reboldi G, Angeli F, Gattobigio R, Bentivoglio M, Thijs L, et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. Hypertension 2005;46:386–92.
[10] Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension 2010;55:399–407.
[11] Angeli F, Verdecchia P, Reboldi G. Intensive blood pressure control in obese diabetic patients: clinical relevance of stroke prevention in the accord trial. Expert Rev Cardiovasc Ther 2012;10:1467–70.
[12] Orloff DG. Fixed combination drugs for cardiovascular disease risk reduction: regulatory approach. Am J Cardiol 2005;96:28K–33K. [discussion 34K-35K].
[13] Group SR, Wright Jr. JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–16.
[14] Verdecchia P, Angeli F, Gentile G, Reboldi G. More versus less intensive blood pressure-lowering strategy: cumulative evidence and trial sequential analysis. Hypertension 2016;68:642–53.
[15] Verdecchia P, Angeli F, Cavallini C, Reboldi G. Keep blood pressure low, but not too much… does evidence support the recommendation of rigid “safety boundaries”? Circ Res 2018;123:1205–7.
[16] Verdecchia P, Gentile G, Angeli F, Mazzotta G, Mancia G, Reboldi G. Influence of blood pressure reduction on composite cardiovascular endpoints in clinical trials. J Hypertens 2010;28:1356–65.
[17] Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, et al. Cardio-Sis i. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (cardio-sis): an open-label randomised trial. Lancet 2009;374:525–33.
[18] Reboldi G, Angeli F, de Simone G, Staessen JA, Verdecchia P. Cardio-Sis I. Tight versus standard blood pressure control in patients with hypertension with and without cardiovascular disease. Hypertension 2014;63:475–82.
[19] Reboldi G, Gentile G, Angeli F, Verdecchia P. The 2018 esc/esh hypertension guidelines: should nephrologists always stop at the lower boundary? J Nephrol 2018;31:621–6.
[20] Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557–62.
[21] Lionakis N, Mendrinos D, Sanidas E, Favatas G, Georgopoulou M. Hypertension in the elderly. World J Cardiol 2012;4:135–47.
[22] Chung N, Baek S, Chen MF, Liau CS, Park CG, Park J, et al. Expert recommendations on the challenges of hypertension in asia. Int J Clin Pract 2008;62:1306–12.
[23] Kannel WB, Dawber TR, Sorlie P, Wolf PA. Components of blood pressure and risk of atherothrombotic brain infarction: the Framingham study. Stroke 1976;7:327–31.
[24] Vinyoles E, De la Figuera M, Gonzalez-Segura D. Cognitive function and blood pressure control in hypertensive patients over 60 years of age: cognipres study. Curr Med Res Opin 2008;24:3331–9.
[25] Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the american heart association. Circulation 2018;137:e67–492.
[26] Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham heart study. Circulation 2001;103:1245–9.
[27] Bavishi C, Bangalore S, Messerli FH. Outcomes of intensive blood pressure lowering in older hypertensive patients. J Am Coll Cardiol 2017;69:486–93.
[28] Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. International comparison of the relationship of chronic kidney disease prevalence and esrd risk. J Am Soc Nephrol 2006;17:2275–84.
[29] Young JH, Klag MJ, Muntner P, Whyte JL, Pahor M, Coresh J. Blood pressure and decline in kidney function: findings from the systolic hypertension in the elderly program (shep). J Am Soc Nephrol 2002;13:2776–82.
[30] Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, et al. Effects of intensive bp control in ckd. J Am Soc Nephrol 2017;28:2812–23.
[31] Malhotra R, Nguyen HA, Benavente O, Mete M, Howard BV, Mant J, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. JAMA Intern Med 2017;177:1498–505.
[32] Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–67.
[33] Bundy JD, Li C, Stuchlik P, Bu X, Kelly TN, Mills KT, et al. Systolic blood pressure reduction and risk of cardiovascular disease and mortality: a systematic review and network meta-analysis. JAMA Cardiol 2017;2:775–81.
[34] Bangalore S, Toklu B, Gianos E, Schwartzbard A, Weintraub H, Ogedegbe G, et al. Optimal systolic blood pressure target after sprint: insights from a network meta-analysis of randomized trials. Am J Med 2017;130. [707-719 e708].
[35] Fuster V. No such thing as ideal blood pressure: a case for personalized medicine. J Am Coll Cardiol 2016;67:3014–5.