When should antihypertensive drug treatment be started? Discrepancies between the 2023 European Society of Hypertension and the 2024 European Society of Cardiology guidelines

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One of the most important recommendations from the guidelines on hypertension is to decide when to lower blood pressure (BP) through antihypertensive treatment. On this issue, the guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) seem to agree that there is no BP threshold for non-pharmacological interventions,[1,2] *i.e.*, that correction of inappropriate lifestyles should be implemented at any BP level, based on its potential to reduce BP, lower cardiovascular (CV) risk, and attenuate the risk of future development of a persistent BP elevation. On the other hand, the two guidelines exhibit a profound difference in the recommended BP level at which to start prescribing BP-lowering drugs.

The ESH guidelines recommend considering a BP threshold >140 mmHg systolic (SBP) and/or >90 mmHg diastolic (DBP) in patients aged 18 to 79 years, based on the multiple trials that have shown that, at or above these BP levels, BP reduction is accompanied by a reduction of CV fatal and non-fatal outcomes compared to placebo or less intensive BP-lowering treatment. The 2023 ESH guidelines also emphasize that a single BP threshold does not fit all patients and address a number of conditions in which the BP value at which to start drug treatment may differ from the one adopted for the more general hypertensive population. To cite two important examples, in patients with a history of CV events, trial-based evidence is available that BP-lowering treatment may also be beneficial when starting at >130 mmHg SBP or 85 mmHg DBP (high normal BP range),[3] which means that the recommended BP threshold for drug treatment is lower in the secondary compared to the primary CV prevention setting.

Furthermore, although the 140/90 mmHg BP threshold remains a reference threshold, the 2023 ESH guidelines do not rule out the use of more conservative BP thresholds, *i.e.*, ≥150 mmHg SBP, in older patients (≥65 years) with isolated systolic hypertension and in patients aged ≥80 years because under these circumstances the risk of treatment-related adverse effects may be greater, in isolated systolic hypertension possibly also due to the concomitantly low DBP values. Most importantly, in isolated systolic hypertension and in patients aged 80 years or beyond, antihypertensive treatment benefits have been mainly documented by trials recruiting patients with baseline SBP values higher than those from trials in younger patients, *i.e.*, 160 mmHg or above. Finally, additional BP threshold diversifications are mentioned for other specific conditions or patients (children, acute hemorrhagic stroke, acute ischemic stroke, *etc.*), while no precise threshold value is provided for a condition such as a patient's frailty in which BP reduction seems to be protective,[4,5] but no trial-based evidence on BP threshold and target for treatment is available.

A table grading the frail patient's ability to live an independent life is provided as guidance to treatment initiation only based, however, on clinical considerations.[1] These recommendations substantially replicate the recommendations issued by the European guidelines published in 2018 that 140/90 mmHg and 130/85 mmHg are the BP thresholds for drug treatment in primary and secondary CV prevention, respectively, when patients are aged 18-79 years.[6] They expand on previous recommendations in several specific conditions, however, including isolated systolic hypertension and very old age, by providing details from previously unavailable new evidence.

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The approach to antihypertensive drug treatment initiation is markedly different in the 2024 ESC guidelines, which extend the use of antihypertensive drugs to much wider BP strata of the population. In the first place, these guidelines modify the traditional BP classification by considering three categories of subjects, *i.e.*, those with a <120/70 mmHg BP, those with a 120-139/70-89 mmHg BP, and those with ≥140/90 mmHg BP, termed, respectively, non-elevated BP, elevated BP, and hypertensive categories. Next, BP-lowering drug treatment is extended from individuals with ≥140/90 mmHg to individuals belonging to the "BP elevation" category (120-139/70-89 mmHg), in the latter case provided that their CV risk is high, a condition identified by the presence, among others, of subclinical organ damage, moderate-to-severe chronic kidney disease, diabetes mellitus, or a calculated total 10-year CV risk >10%, according to the, SCORE-2, and SCOPE-OP methods for risk quantification in the European population. Finally, antihypertensive drug treatment is further considered in individuals with "elevated BP" in whom there is a SCORE-related CV risk between 6% and 10% in the presence of a wide and heterogeneous list of upward modifiers of the current or even future CV risk shown in Table 1, after attempt to reduce BP by a non-pharmacological approach for few months.

Table 1. Upward risk modifiers that favor antihypertensive drug therapy according to the 2024 European Society of Cardiology guidelines.

Arterial stiffening
Plaques at imaging
Calcium coronary content
Family history of premature atherosclerotic disease
Natriuretic – troponin peptide elevation
Autoimmune disease
Human immunodeficiency virus
Complications of pregnancy
Unfavorable economic conditions
High risk ethnic group
Mental illness

According to the 2024 ESC guidelines, all these recommendations apply without any age limit, *i.e.*, with an extension to subjects above 80 years of age. If implemented, these recommendations will lead to an enormous increase in the number of candidates to lifetime assumption of antihypertensive drugs because i) BP values ≥120/70 mmHg represent the predominant fraction of the population and ii) a CV risk ≥10% extends to virtually all males aged ≥70 years and females aged ≥75 years. The expansion of antihypertensive drug treatment will become astronomical by considering as treatable individuals in the 120-129/70-79 mmHg BP range with intermediate levels of risk (6-9%), plus upward present and future risk modifiers, sometimes of ill-defined nature. To exemplify, according to the 2024 ESC guidelines, octogenarians with a 122 mmHg SBP should be regarded as having an "elevated" SBP and be prescribed antihypertensive drugs. This may also apply to middle-aged individuals with a moderate increase in the CV risk profile in whom a condition such as "economic disadvantage" is identified.

A "*sine qua non*" requirement for guidelines' recommendations is to be based on scientific evidence. In this context, it should be made clear that no "*ad hoc*" trial supports the abovementioned 2024 ESC guidelines' recommendations on initiation of antihypertensive drug treatment. In other words, no trial has ever documented that, in untreated younger or older patients with a BP of 120-139/70-89 mmHg plus diabetes, subclinical organ damage, chronic kidney disease, a CV risk ≥10% or a 6-9% risk plus a variety of upward risk modifiers, antihypertensive drug treatment reduces CV outcomes. Likewise, no trial provides support for antihypertensive drug treatment in patients aged 80-85 years who exhibit a BP<140/90, a threshold that expands to much lower BP values the results of the only placebo-controlled trial in octogenarians (mean age 83 years) in which treatment-related CV protection was shown in patients with a baseline SBP≥160mmHg (average 170 mmHg).[7] The 2024 ESC guidelines position is only supported by a large meta-analysis of randomized trials in which an SBP reduction of 5 mmHg was accompanied by a reduction of CV outcomes at baseline SBP values from >170 mmHg to <120 mmHg.[8] However, these results are affected by serious limitations, some of which are reported in Table 2.[9] Firstly, the meta-

Table 2. Meta-analysis of randomized controlled trials: limitations.

[Lancet 2021; 397:1625-1636] META-ANALYSIS OF RCTs: treatment-related
No data on treatment side effects
No data on treatment discontinuation at any baseline BP
Exclusion of BP values but not of outcomes during the 1st treatment year
Outcome effects of treatment at different baseline SBP values highly heterogeneous
Data from lowest baseline SBP values (<120 mmHg) limited, *i.e.*, 2% of the total population of the meta-analysis
In primary prevention population CV risk 31.9%
Inclusion of both BP-lowering placebo-controlled RCTs and drug comparison RCTs (in which BP difference between group non-intentional or minimal)
Risk similar or higher at baseline SBP <120 *vs.* >160-170 mmHg, *i.e.* poor representativity of the general population
In comparison trials minimal BP differences regarded as responsible for outcomes
Outcome effects blown up by amplification of SBP reduction to 5 mmHg
If analysis limited to BP-lowering trials outcome effects not significant in primary prevention
Inclusion of trials with patients already under drug treatment at baseline
About 50% of outcome-based RCTs not included

RCTs, randomized controlled trials; CV, cardiovascular; BP, blood pressure; SBP, systolic blood pressure.

analysis did not include about 50% of available trials, one of which (the HOPE-3 trial) showed that the risk of CV outcomes was reduced (-27%) by an antihypertensive drug treatment that lowered a baseline SBP of >143.5 mmHg, while no reduction was seen with an antihypertensive treatment of patients with a baseline SBP between 131.6 and 143.5 mmHg (mean 137.6 mmHg, CV risk +8%) or <131.5 mmHg (mean 122.2 mmHg, CV risk +16%).[10] This conclusion was reinforced when data were analyzed after prolongation of treatment from the original 4.2 to 8.7 years.[11] Importantly, in the HOPE-3 trial, at variance from the meta-analysis, the patients were largely untreated at baseline (see criticism of the meta-analysis below) and their CV risk was classified as "intermediate", thus resembling the 6-9% risk level considered for treatment of individuals with "elevated BP" by the 2024 ESC guidelines. Second, in contrast to the HOPE-3 trial, in the meta-analysis, the patients were already under antihypertensive drugs at baseline. In the SPRINT trial, for example, almost all patients were initially on one or two antihypertensive drugs (average 1.8),[12] while in other trials, patients under treatment with up to four drugs were allowed to participate. This is a crucial limitation because baseline antihypertensive drug treatment plainly contradicts the obvious requirement, for studies addressing when to initiate drug treatment, to only deal with treatment-naïve patients or patients in which the effects of treatment have been dissipated by an adequate wash-out period, in the absence of which the native BP of the patient remains unknown. Third, the results of the meta-analysis originated from a mixture of BP-lowering trials against placebo or a control group and between-drug comparison trials, although only in the former case the purpose was to look at the outcome effects of BP reduction, the latter case having the purpose to look at the BP-independent protective properties of some drugs, to be obviously documented in the absence or with minimal BP differences between trial arms. In contrast with the trial design, purpose, and result interpretation of the comparison trials, in the meta-analysis, the CV outcome reductions found in one trial arm compared to the other were entirely ascribed to the slightly greater associated BP reductions rather than to the BP-independent protective properties of the drugs employed. Indeed, the hypothetical outcome effects of these minimally greater BP reductions were blown up by increasing the SBP reduction always to 5 mmHg. To exemplify from a widely quoted comparison trial on hypertensive patients with left ventricular hypertrophy such as LIFE,[13] the 14% reduction of CV outcomes seen in patients treated with losartan *vs.* those treated with atenolol was not ascribed, as in the original publication, to the protective properties of angiotensin receptor blockade but to the 1 mmHg lower SBP seen in the losartan group, with a 5-time amplification of the effect by the increase of SBP reduction to 5 mmHg. Importantly, when the meta-analysis excluded from the calculation comparison trials, a SBP reduction in patients with a baseline SBP<140 mmHg did not have any significant effect on CV outcomes in primary CV prevention individuals, a reduction being observed only in patients with a baseline SBP>170mmHg (Table 3).[8] Fourth, the 10-year CV risk of the primary CV prevention patients included in the meta-analysis was on average 31.9%, an extremely high risk level which seriously weakens the applicability of the results to the general population, and specifically to risk strata around or below 10%. Lastly, there was considerable heterogeneity in the outcome effects of BP reduction at different baseline SBP values. This is exemplified by the finding that, in the primary prevention setting, the risk of CV outcomes was not affected by 5 mmHg SBP reduction when baseline SBP was <140 mmHg [-1%: confidence interval (CI) -8/+7], but it showed a decrease when baseline SBP was <130 mmHg (-11: CI -19/-2) or <120 mmHg (-23: CI -32/-13), a baseline BP level at which the protective effect of treatment was maximal.[9] This and other heterogeneous results were disregarded by the authors of the study because the interactive test for BP levels and effects was found to be neutral throughout different groups of patients. The largest outcome reduction at very low baseline BP values was also disregarded by the 2024 ESC guidelines, which do not recommend treatment at a baseline SBP<120 mmHg, this time in contrast with the results of their reference meta-analysis.

In conclusion, the BP thresholds for antihypertensive drug treatment recommended by the 2023 ESH guidelines appear to be much more strongly supported by evidence than the lower thresholds and much wider treatable population strata recommended by the 2024 ESC guidelines. Further support for the 2023 ESH guidelines' recommendations may originate from their consideration not only of the expected outcome reductions but also of treatment tolerability and incidence of serious side effects, both of which are adversely affected by treatment-related lower BP values. Avoiding serious side effects is a fundamental component of a clinically valid antihypertensive treatment strategy because side effects not only worsen the quality of life but also increase the incidence of treatment discontinuation,[14] which is followed by a rebound increase in outcomes.[15] Given the top position of hypertension among the causes of death worldwide, the possibility that antihypertensive drug treatment is associated with CV benefits in patients with BP values lower than those currently used for

Table 3. Risk of cardiovascular (CV) outcomes with blood pressure (BP) reduction according to baseline systolic BP in patients without previous CV events after removal of comparison drug trials.

Baseline SBP (mmHg)	Outcomes	HR (95% CI)
<120	288	0.86 (0.67-1.11)
120-129	481	0.88 (0.73-1.07)
130-139	800	0.96 (0.83-1.12)
140-149	949	0.92 (0.81-1.05)
150-159	796	0.88 (0.76-1.01)
160-169	1040	0.93 (0.80-1.09)
≥170	1264	0.84 (0.72-0.98)

SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval.

treatment implementation is a question of crucial importance for public health. The answer to this question, however, should come from appropriately designed trials that allow subsequent recommendations to be supported by strong and consistent evidence. In our opinion, this is not the case for the above-discussed meta-analysis and, by reflection, for the guidelines taking it as a reference.

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