European Journal of Internal Medicine 121 (2024) 4–8

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Beyond the Guidelines

Rationale of treatment recommendations in the 2023 ESH hypertension guidelines

ARTICLE INFO

Keywords
Guidelines

ABSTRACT

No abstract available.

We thank Drs. Verdecchia, Grossmann and Whelton for their interest and comments on the 2023 Guidelines on Hypertension of the European Society of Hypertension (ESH) [1]. The points they raise are important both for the structure of guidelines in general and, more specifically, for the issues related to patients with a blood pressure (BP) elevation [2]. We have elected to reply to the points, which seem to us to manifest a view that differs more or less substantially from the view of the ESH guidelines. This will give us also a chance to further clarify the rationale guiding some of the guidelines choices and recommendations.

1. Criteria for scoring the strength of the recommendations

Verdecchia and colleagues [2] correctly note that we have used the class of recommendations and the level of evidence criteria that have been used by several previous guidelines. It should be mentioned, however, that these criteria have been somewhat modified. One, the class II recommendation has been simplified by eliminating the "a" and "b" sub scoring, because, application to clinical practice appears easier with one homogenous class of recommendation. Moreover, according to previous experience, assignment to this sub scoring is highly variable between members of a guidelines Task Force, thus having a pronounced subjective component. Two, reflecting the approach used by the Grade guidelines [3], we added to the level of evidence a third criterion, which considered the "quality" of the study beyond its design, e.g. factors such as the statistical power, the risk of bias and the accuracy and number of the relevant variables that were measured. It is well known that trials with a "valid" design may nevertheless differ for the above characteristics (including the accuracy and standardization of BP measurements) and it seemed appropriate to consider this aspect when deciding the strength of evidence. Finally, an important aspect is also the assignment of the level of evidence A only to data from randomized controlled trials, documenting the effect of interest by cardiovascular disease outcomes.

2. Guidelines clarity and simplicity

This aspect of the guidelines is emphasized by Verdecchia and colleagues [2], and we agree with their comments on the need to issue clear and simple recommendations. In this regard, a shorter version of the 2023 ESH guidelines will be made available in the near future. However, in our opinion, guidelines should also pursue an educational goal, which means that the evidence behind the diagnostic and treatment recommendations, and thus their rationale, should be addressed. This seems to us necessary also because only a minority of the recommendations is based on undisputable evidence, such as that originated from consistent results of several high quality randomized trials [4]. In the remaining cases data may be partly or totally conflicting, trials may have limitations or evidence may be based on observational studies and thus open to potential confounders. We believe that it is important for the physician to know how the guidelines found the "thread of Ariadne" among this sometimes complex material, and thus be aware of the dependence of a given recommendation from direct evidence or from data interpretation or extrapolation. Guidelines with an educational value (which includes a correct perception of their limitations) may also help against what Verdecchia and colleagues appropriately mention as the current tendency to make use of guidelines as inculpatory or exculpatory documents in malpractice litigations, and thus to assign them an inappropriate coercive value. This clashes with the above- mentioned limitations of the available evidence as well as with fact that guidelines address diseases in general. Both the past and the present ESH guidelines have never failed to mention that, in individual patients, decisions may depart from the general ones recommended by guidelines.

It is true that extending recommendations to their rationale can lead to longer and more complex guidelines. However, use can be made of final short and clear recommendations that fulfill the physician's need to receive quick diagnostic and treatment advices, with the chance, however, to receive information also on the essential background on which the advice is based. This is what many guidelines now do, and in the 2023 ESH guidelines this approach has been widely used by adding simple and short recommendations at the end of any major diagnostic and treatment section or subsection.

3. Blood pressure measurements

The 2023 ESH guidelines devote much space to the different approaches to BP measurement that have been made available by years of intensive and fruitful research. It seems to us that Verdecchia and

https://doi.org/10.1016/j.ejim.2023.12.015
Received 25 November 2023; Received in revised form 5 December 2023; Accepted 12 December 2023
Available online 12 January 2024

colleagues agree with our position to (i) emphasize the predominant importance of office or clinic BP because of its almost exclusive use in large scale epidemiological studies, randomized outcome-based trials and definition of BP thresholds and target treatment values. Verdecchia and colleagues also appear to agree on the decision of the 2023 ESH guidelines to consider out-of-office BP as a source of information that importantly increases medical knowledge of the patient by the physician. For this reason, the 2023 ESH guidelines recommend to collect out-of-office BP data whenever possible, thereby upgrading use of this approach compared to the recommendation made in the past. It should be noticed, however, that our guidelines avoided to mention that out-of-office BP allows a better diagnosis of hypertension, a more accurate definition of the BP values at which to start antihypertensive treatment or a more reliable BP target to pursue with treatment, i.e. advantages mentioned in a number of guidelines. This seemed to us to contradict that (i)the diagnosis of hypertension and treatment-related threshold and target values derive from trials that have used office BP and (ii) despite their large use, out-of-office BP has never been tested in randomized outcome trials, except for data collection in small and non-randomized subgroups [5]. This has been largely due to the fear that including out-of-office BP measurements might not only make trials more expensive but also increase patients' obligations, with detrimental effects on their adherence to treatment and cooperation within trials. Failure to adequately emphasize these important limitations of out-of-office BP by previous guidelines may have contributed to the persistence of these serious research gaps.

Among out-of-office BP measurements, Verdecchia and colleagues emphasize the importance and peculiar advantages of home BP. We agree with their considerations, and the 2023 ESH guidelines have described the pros and cons of home (and ambulatory) BP in detail in the section devoted to BP measurement. Further advantages of home BP measurements have been reported in the sections on long-term BP control in children and adolescents, patients under anti-cancer treatment and long-term patient follow-up. It may be of interest, however, to additionally note, that, after describing the relative advantages of home vs ambulatory BP as well as the conditions in which home or ambulatory BP might be preferentially considered, ESH guidelines favor collection of both types of BP data, whenever possible. This can be justified by their discrepant identification of a BP elevation in a nonmarginal number of subjects [6,7] as well as by some evidence that this discrepancy may have clinical significance [7].

4. Initiation of antihypertensive drug treatment

A small error made by Verdecchia et al. [2] is that in the nice algorithm of their Figure 2, they refer to the office BP threshold for drug treatment recommended by the ESH guidelines for the general hypertensive population as ≥140mmHg systolic or ≥80mmHg diastolic. Reference to a systolic BP threshold for drug treatment of ≥140mmHg is correct, but the ESH 2023 guidelines indicate the diastolic BP threshold as ≥90 (not 80) mmHg, because this has been the entry diastolic value used by a large number of trials that have shown the beneficial effects of BP-lowering treatment. To be fair, Verdecchia and colleagues mention the 140/90mmHg threshold in their Figure 1 and also correctly report in the text these threshold BP values, but an error in a figure may have particularly misleading consequences. When office BP is ≥140mmHg systolic or ≥90mmHg diastolic the ESH 2023 guidelines stand for an immediate and concomitant non-pharmacological and pharmacological treatment, except when BP is in the low grade 1 range (BP < 150/95mmHg), there is no organ damage and added CV risk is relatively low. In this case the 2023 ESH guidelines consider the possibility for physicians to use non-pharmacological treatment alone, adding antihypertensive drugs after 3 months if BP control is not achieved. In addition the guidelines recommend that (i) patients on exclusive non-pharmacological treatment should be under close follow-up to account for the well know low adherence to non-pharmacological interventions, and (ii) antihypertensive drugs should be quickly added to the treatment regimen if treatment failure becomes evident. These seem to us reasonable and safe recommendations, although we acknowledge that their basis does not lay on dedicated evidence from controlled trials. If our reading is correct, Verdecchia and colleagues do not substantially disagree, but rather find our recommendations on this issue too restrictive for non-pharmacological treatment, i.e. they support the possibility of exclusive use of non-pharmacological treatment in the entire grade 1 hypertensive population and in individuals with a moderate CV risk, such as with a combination of grade 1 hypertension, male sex and 1 or 2 cardiovascular risk factors. With the caution required by the limited ability of lifestyle changes to lower BP as well as by the patient's poor adherence to these measures, an expansion of non-pharmacological treatment to a wider grade 1 BP range should not be altogether dismissed. However, a meta-analysis of randomized trials [8] and a more recent subgroup analysis of grade 1 hypertension in largely untreated hypertensive patients with a moderate cardiovascular risk [9] has documented the protective effect of antihypertensive treatment in patients with an average initial systolic BP greater than 150mmHg. This supports drug use in grade 1 hypertension with initial BP values in the upper grade 1 BP range.

5. Target BP for treatment

The 2023 ESH guidelines recommend to lower BP to <130/80mmHg in patients aged 18 to 64 years. However, and similarly to the principle used by the 2020 hypertension guidelines of the International Society of Hypertension [10], in patients aged 65 to 79 years a sequential "two target" concept is adopted. Lowering BP to < 140/80mmHg is recommended as a first or "must" target because at this target reduction of hypertension-related CV outcomes is already pronounced [11] and the balance between treatment-related protection, safety and tolerability is a favorable one. Nevertheless, in these patients, physicians are invited to consider a second target, i.e. a systolic BP reduction to values <130mmHg, because reducing systolic BP to <130mmHg leads to further outcome reduction, albeit of a magnitude that is less than that obtained when BP is reduced from higher values to <140mmHg [11]. This second target should be pursued only if treatment is well tolerated, due to the evidence that more marked BP reductions or absolute systolic BP values <130mmHg are associated with a considerable increase in the incidence of side effects, including those leading to treatment discontinuation, and thus to a possible rebound increase of fatal and nonfatal outcomes. No active treatment to reduce BP to < 120/70mmHg is recommended because at these low values side effects are maximized and evidence of patients' incremental protection is inconsistent. Furthermore, reports from trial data-bases have frequently shown that BP reductions to <120/70mmHg can be associated with an increased risk of cardiovascular events and mortality, known as the J curve phenomenon [12–15].

Verdecchia and colleagues acknowledge the rationale behind the target BP values that has guided the 2023 ESH guidelines, i.e. the dependence of the treatment decision not only on the achievable outcome reductions but also on patient's safety and well-being. Their disagreement with the ESH 2023 guidelines focuses on our use for target BP recommendations also of evidence from post-hoc analysis of trials, with thus the possibility of a bias associated with comparison of non-randomized patient groups. The ESH 2023 guidelines mention that the non-randomized nature of post-hoc data analyses represents a limitation and that this should be reflected in a lower strength of related recommendations. It is argued, however, that in guidelines evidence cannot be drawn only from randomized trials because randomized trial data are not available in many important hypertension areas (long term benefits of antihypertension treatment, treatment of young hypertensives, treatment of frail patients, treatment of hypertension phenotypes etc.), making information from post-hoc analysis of trials, other types of observational studies, real life data, and in few circumstances even

mechanistic data necessary to fill what otherwise would be substantial guidelines gaps. Furthermore, the 2023 ESH guidelines express the belief that a more cautious attitude adopted for the target BP to be reached with treatment, is supported by important and diversified evidence. First, the marked increase of serious side effects and treatment discontinuation with greater BP reductions is undisputable because of its documentation by randomized trials [16]. Furthermore, benefits should be expected by BP reductions within lower BP ranges because the relationship between BP and the number of CV events flattens at lower BP values, the linear reduction of outcomes down to a BP of about 110/70mmHg reported by a popular meta-analysis of epidemiological studies being the effect of quantifying outcomes on a logarithmic rather than on an arithmetic scale [17]. Finally, it is also undisputable that below a certain BP level vital organ perfusion is compromised, which means that what should be under discussion is not the existence of a J curve but only at which BP level this may occur and which patients may be affected. In this context, the frequent description of an increased risk of outcomes at on-treatment BP values <120/70mmHg cannot be dismissed because of the post-hoc nature of the data whose main limitation is the inability to clarify whether the increase in outcomes is due to the adverse consequences for organ perfusion of too low on-treatment BP or to a greater initial cardiovascular risk and a frailty status that favor clinical events [18].

According to the 2023 ESH guidelines, in some patient categories BP threshold and target for treatment differ from those recommended for the general hypertensive population, again based on the attempt to reach a favourable balance between evidence of protection and treatment-related safety. Compared to the general hypertensive population, .higher BP targets are recommended for patients aged 80 years or more and the same is done for old patients (65–79 years of age) with isolated systolic hypertension in whom the caution required to avoid an excessive reduction of diastolic BP is also mentioned. A lower BP threshold (high normal BP) is recommended in patients with with a previous clinically manifest cardiovascular disease (secondary prevention) and higher BP targets are indicated as the optimal goal in those with left ventricular hypertrophy [19] and pregnancy. Completely different BP threshold and target criteria are recommended for use in children and adolescents up to 16 years of age while no threshold and target BP indications are given for frail patients due to absence of relevant data. Verdecchia and colleagues note that this may make compliance to treatment recommendations more difficult, and we agree. However, to be in line with available evidence this seems to us inevitable and a somewhat greater complexity of treatment recommendations may be acceptable in order to avoid issuing simplistic rather than simple guidelines.

6. Antihypertensive drugs

Verdecchia and colleagues do not raise any criticism against the treatment strategies recommended by the 2023 ESH guidelines: two drug combination as initial treatment, increased dosing of the combination components and three drug combinations as subsequent steps, use of single pill combinations whenever possible, and initial monotherapy in few patient categories, i.e. very old patients, frail patients, patients with a very modest BP elevation or patients with a high normal BP and a very high cardiovascular risk. They do not raise any criticism also on the acceptance by the 2023 ESH guidelines of treatment options such as the polypill and renal denervation nor do they criticize the recommendations issued for the treatment of specific conditions such as heart failure with reduced or preserved ejection fraction, chronic kidney disease or resistant hypertension, in which the recommended drugs (see use of SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists or ARNI) and treatment strategies depart substantially from those recommended for the general hypertensive population. On the other hand, they hold a different view on the antihypertensive drugs that should be listed for general first step use. The 2023 ESH guidelines consider beta-blockers among the major drug classes to be used for initiation and maintenance of antihypertensive treatment, together with diuretics, ACE-inhibitors, angiotensin receptor blockers and calcium channel blockers while Verdecchia et al. are for exclusion of beta-blockers and limitation of the major drugs to be considered for initial treatment to the remaining four drug classes only. We acknowledge that exclusion of beta-blockers from first step treatment is in line with the recommendations of other guidelines, including those issued by the American College of Cardiology and the American Heart Association [20]. It is, in part, also in line with the 2018 guidelines issued by ESH with the European Society of Cardiology, which considered the evidence in favor of beta-blockers as valid as that of the other four drug classes in the text, but excluded beta-blockers from the main treatment algorithm [21]. Nevertheless, and despite the association of beta-blockers with some inconveniences and contraindications (from which also the other drug classes are not immune), we think that regarding beta-blockers as suitable at any treatment step and both for monotherapy and combination therapy is justified. The reasons for the beta-blocker up-grading are addressed in detail in the text, based on old and recent reviews and specific data [22,23]. One, beta-blockers, alone and in combination, have the same ability as the other drug classes to lower BP, an effect that accounts “per se” for most of the antihypertensive treatment benefits. Two, the protective effect of beta-blockers against hypertension-related outcomes is documented by several placebo-controlled trials. Three, although in two outcome trials [24,25] beta-blockers lost the confrontation with the comparison drugs, in several other trials they showed a similar or even greater [26] protective ability, the various trial meta-analyses showing either an equivalent or only a slightly smaller reduction of pooled cardiovascular events with beta-blockers compared to other drugs [27–30]. Mention is also made that, although beta-blockers have been consistently shown to be less protective against stroke than other major antihypertensive drugs, this has been the case also for ACE inhibitors while calcium channel blockers have been consistently associated with less protection against heart failure. Only for beta-blockers, however, cause-specific disadvantages have been used as a weapon against their inclusion among the major antihypertensive drugs, dismissing their more important similarity or only small difference from other drugs on the statistically more powerful and clinically more meaningful global cardiovascular protection. The 2023 ESH guidelines also emphasize that the lower protective effect of beta-blockers on stroke has some puzzling aspects because beta-blockers (i) have never been shown to exert damaging effects on the brain or impair cerebral blood flow autoregulation, (ii) their use in placebo controlled antihypertensive treatment trials is accompanied by a sizeable reduction of stroke [30,31] and (iii) in a large meta-analysis of randomized comparison trials the lower protection against stroke was mainly evident vis-a-vis calcium channel blockers rather than vis-a-vis other major antihypertensive drugs [31], raising the possibility of its origin from lesser BP reduction in beta-blocker treated compared to calcium channel blocker treated patients which has actually occurred in a large comparison trial [25]. Finally, an important consideration made by the 2023 ESH guidelines is that use of beta-blockers is mandatory not only in several clinically important cardiac diseases or conditions generated by or frequently associated with hypertension (post--myocardial infarction, angina pectoris, heart failure, atrial fibrillation, patients with increased heart rate and aortic aneurysm) but also that their use extends to many vascular and non-vascular conditions, representing frequent hypertension comorbidities [22,23]. According to the 2023 ESH guidelines, this makes beta-blockers a “de facto” major antihypertensive drug class as well as a drug class that helps to tailor treatment to the individual medical status and needs. Unfortunately, the treatment algorithm shown by Verdecchia et al. in their Figure 2 [2] does not reflect the above evidence because beta-blockers are positioned at the same level as mineralocorticoid receptor antagonists or alpha-blockers, i.e. drugs with worse tolerability problems and contraindications, that have never been tested in outcome based randomized

clinical trials or lost the confrontation with diuretic treatment [32].

7. Implementation of guidelines

Verdecchia et al. include in their paper a number of interesting considerations on implementation of hypertension guidelines. We agree that implementation of guidelines is disappointingly low. More than 40 years of guidelines recommending therapeutic BP control as a major step to achieve cardiovascular protection have not made this control substantially better in the hypertensive population. Progress seems to have occurred in some countries but its quantitative dimension is uncertain also because, except for few countries (USA and perhaps UK), unstandardized studies make comparisons of the rate of hypertension control at different times difficult. Efforts by all guidelines to encourage combination treatment in most hypertensive patients, years ago via the step care approach (one initial drug followed by combination treatment) and more recently as first treatment step, do not seem to have substantially modified the way hypertension is commonly treated in real life, i.e. switching from one monotherapy to another. This negatively affects the BP-lowering ability of treatment, keep patients with uncontrolled hypertension numerically majorital and maintain hypertension among the first causes of death worldwide. The 2023 ESH guidelines have tried to contribute to the crucial issue of guidelines implementation and improvement of hypertension care in real life by addressing in a separate section the problem of patients' follow-up, i.e. how hypertensive patients should be followed chronically by doctors and other health care providers. Patients' follow-up has usually been only marginally addressed by guidelines, one reason being that evidence from controlled studies is rare, the study quality is often limited and recommendations are thus largely based on expert consensus rather than data. In the 2023 ESH guidelines advice is given on the most appropriate intervals between visits, laboratory examinations and instrumental examinations according to the clinical characteristics of the patients. Information is provided on how to collect information and deal with the problem of non-adherence to treatment, now recognized as a main barrier to long-term treatment efficacy. Factors involved in physician's therapeutic inertia, i.e. failure to upgrade treatment when hypertension is not controlled, are also addressed together with the possible advantages of different models of chronic patient care: greater use of nurses' medical expertise, involvement of pharmacists, team-based care, telemetric technologies and involvement of excellence hypertension centers. Future guidelines should continue to devote attention to the problems posed by the follow-up of hypertensive patients, hopefully with the help of high quality studies.

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