The 2023 hypertension guidelines of the European Society of Hypertension: a commentary

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The 2023 hypertension guidelines of the European Society of Hypertension (ESH) have been published in the December issue of the official Journal of the Society (Journal of Hypertension),[1] where they are freely available online. Compared to the guidelines published 5 years ago,[2] the new guidelines address issues never or only marginally addressed before, including a large number of comorbidities to hypertension that may change the approach to antihypertensive management. This accounts for their large dimension, *i.e.*, almost 200 pages, more than 1700 references, and many general and specific diagnostic and treatment recommendations, which may support, strengthen but also differ from previous recommendations, based on evidence obtained during the last 5 years.

The new guidelines remain fully adherent to the three fundamental principles that have guided previous guidelines. One, the role of hypertension guidelines should not be coercive for physicians' prescriptions because i) in many cases the scientific evidence is far from being undisputable, and recommendations derive from expert opinion and consensus; ii) this is the case even when evidence is sufficiently solid, *e.g.*, it is based on consistent findings from high quality randomized trials, because trials rely on averaging data from study groups, which may not apply to individual patients in clinical practice. Two, guidelines should primarily have an educational role, which means that the evidence and rationale guiding recommendations and choices should be provided; iii) evidence should not be limited to outcome-based randomized trials which provide the top level of information but also suffer from serious limitations, such as the absence of data in several medical conditions, *e.g.*, younger patients, patients under prolonged antihypertensive treatment, frail patients, patients with different blood pressure (BP) phenotypes, *etc*. Furthermore, because of their conduction in ideal or almost ideal situations, the result of trials may not precisely reflect what happens in clinical practice. All sources of information from randomized trials to observational studies, clinical cases and even mechanistic data should thus be used when necessary, with special emphasis to "real life" data. In the 2023 ESH guidelines "real life" research is mentioned as a promising approach to many current gaps in knowledge on hypertension, such as the extent and changes in adherence to treatment, therapeutic inertia, and absence of trial-based evidence in many hypertension demographic and clinical subgroups.[3]

As shown in Table 1, the 2023 guidelines are characterized by many elements of novelty as well as by considerable incremental knowledge in areas ad-

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dressed by guidelines in the past. To make a few examples, the strength of a recommendation has been made more accurate by classifying trials not only by their design but also by the quality of the provided information, *e.g.*, statistical adequacy, risk of bias, relevance and number of clinical data, *etc*. Stratification of cardiovascular risk by the SCORE-2 approach is supported but it also recognized that medical knowledge of the patient requires information on a much larger number of risk factors and conditions,[4,5] sometimes also apparently unrelated [*e.g.*, non-alcoholic fatty liver disease][6] to the cardiovascular system. As in the past, the search for subclinical organ damage is strongly supported because of its high prevalence in the hypertensive population as well as its association with a high cardiovascular risk.[7-9] Old but also new measures of organ damage are mentioned and evidence is provided not only of their relationship to clinical outcomes, sensitivity, reproducibility, and time to detection of changes, but also to the new evidence on the prognostic value of their treatment-induced changes, an element that may help to decide on continuation or modification of the antihypertensive treatment regimen during the follow-up.

Table 1. Elements of novelties in the European Society of Hypertension guidelines document 2023 (modified from Mancia *et al.*).[1]

1.	Modified and simplified criteria for evidence grading recommendations
2.	Pathophysiological background of primary hypertension
3.	Clinical blood pressure measurements by different methods and in different settings and clinical conditions
4.	Thorough description of office, ambulatory and home blood pressure measurements and value in different demographic and clinical conditions
5.	Upgrading of out-of-office blood pressure measurements in hypertension management
6.	New target organ damage measurements and their clinical value in hypertension work-up
7.	New cardiovascular risk factors and update on cardiovascular risk assessment
8.	Update and comprehensive summary of secondary forms of hypertension
9.	Update on lifestyle interventions
10.	Update on threshold and targets for antihypertensive drug treatment, including their possible heterogeneity in demographic and clinical subgroups of patients
11.	Confirmation of preferred use of renin angiotensin blockers, calcium antagonists and thiazide/thiazide-like diuretics, for treatment. Inclusion of β blockers among the major antihypertensive drugs
12.	Update on available combination-based drug treatment strategies, including the quadpill and the polypill
13.	Emphasis and update on the diagnosis and management of true resistant hypertension
14.	Update on use and position of renal denervation for antihypertensive treatment
15.	Impact of hypertension and its treatment on cognitive dysfunction and dementia
16.	Management of hypertension in older people according to the frailty and functional level
17.	Update on treatment of hypertension in heart failure
18.	New diagnostic approaches to diagnosis and treatment in hypertensive patients with atrial fibrillation
19.	Update on treatment in chronic kidney disease, including kidney transplantation
20.	Update and novel treatment approaches to patients with type 2 diabetes
21.	Epidemiology, diagnosis and treatment in different BP phenotypes
22.	Diagnosis, treatment and follow-up of hypertension in demographic and clinical conditions not or only marginally addressed in previous guidelines: a. Children/adolescents and transition to adulthood b. Young patients c. Sex-related differences d. Pregnancy and puerperium e. Peripheral artery disease f. Aortic aneurism g. Valvular heart disease h. Treatment of hypertension in acute cerebrovascular diseases i. Hypertensive emergencies/urgencies j. Perioperative hypertension k. Obesity l. COVID-19 m. Chronic inflammatory diseases n. Hypertension in oncology o. Baroreflex failure and dysautonomia p. Glaucoma
23.	Recommendations on patients' follow-up strategies, including assessment of nonadherence and clinical inertia
24.	Mention of new potential approaches to the treatment of hypertension and containment of hypertension-related workload (tele-health, team-based treatment, role of pharmacists, etc)

In the 2023 ESH guidelines, follow-up is given much more attention than in previous guidelines because of its obviously crucial importance for the maintenance of BP control, which is notoriously low in "real life" hypertension. Despite the limited number of studies, recommendations are given on the frequency of visits, out-of-office BP measurements and medical examinations in the various follow-up phases in relation to the patient's clinical status, thus complying with the physicians' requests to have more than the vague mention of this aspect of treatment typical of previous guidelines. A pertinent example is the recommendation not to excessively rarefy the number of annual visits, as suggested in the past for patients with low cardiovascular risk, because of the need to maintain a good patient-physician relationship and reinforce the motivation to keep patient's adherence to treatment high. As mentioned above, the 2023 guidelines do not conceal that in this area randomized trials are virtually absent and even observational studies are only a few. Yet, recommendations based on expertise, experience, common sense and reasonable extrapolations from available data can be useful and stimulate the performance of dedicated studies, *i.e.*, another important educational goal of guidelines. In this context, it can be of further interest to mention that the 2023 guidelines also address the available data, the limitations but also the promise associated with possible novel modalities of chronically sick patients' follow-up: the modality based on greater use of nurses' competence, the integration of pharmacies in the follow-up model, the follow-up by team-based care involving health care professionals, not only physicians, with diversified expertise, and of course the use of telematic technologies.

Finally, as shown in Table 1, guidelines address a large number of conditions for which hypertension is the most common comorbidity, with mention of how this may change the patient's prognosis, the treatment of the comorbid condition, the treatment of hypertension (choice of antihypertensive drugs, BP threshold, and BP target) and the follow-up strategies. However, a fundamental aspect of guidelines remains how to treat hypertension in the general hypertensive population. In this context, the guidelines make it clear that the reference BP values remain those obtained in the physician's office because the largest epidemiological studies and all outcome-based treatment trials have made use of office BP. Although measurements of out-of-office BP are regarded as a source of important information to be collected whenever possible, the use of out-of-office BP for classification of hypertension, assessment of cardiovascular risk, and threshold and target for treatment is not recommended, because of the absence of long-term epidemiological studies with serial BP measurements as well as of outcome trials in which treatment was guided by ambulatory or home BP.[10] While correction of inappropriate lifestyles (non-pharmacological treatment) is advised at any BP value (because of its ability to modestly lower BP, reduce cardiovascular risk, and prevent future hypertension) the threshold for drug treatment is placed at office BP values ³140 mmHg systolic or ³90 mmHg diastolic, *i.e.*, the entry BP criteria adopted in most trials that have documented the protective effect of BP reduction. Based on randomized trial evidence it is recommended to lower BP to <130/80 mmHg in patients aged 18-64 years while (at variance from the more aggressive attitude of some other guidelines),[11] in patients aged 65-79 years the recommendation is to consider two sequential targets. One, an office BP <140/80 mmHg because at this BP level, there is already a good balance between treatment-dependent protection and safety or tolerability. Two, a further office BP reduction to <130/80 mmHg, but only if treatment is well tolerated, given that at these lower BP values serious side effects and treatment discontinuation increase markedly.[12] In all patients, actively aiming at lowering BP to <120/70 mmHg is not recommended because of i) the unfavorable consequences of BP reduction to these low values on the side effect profile and safety of the patients; ii) the questionable evidence of the protective effect on the risk of outcomes as well as the possibility of an increased risk, *i.e.*, of a J curve phenomenon. Mention is also made that threshold or target BP values for treatment should be different (more conservative or more aggressive) in specific conditions, *e.g.*, isolated systolic hypertension, age >80 years, patients with coronary disease, pregnancy, and children or adolescents up to 16 years old.

Concerning how to reach the target BP, guidelines mix novel information with a strengthening of old recommendations. Based on the evidence that the benefit of treatment largely depends on BP lowering "per se", the new guidelines acknowledge that a greater number of antihypertensive drugs favors an effective BP reduction in a larger number of patients. Because of i) a similar ability to lower an elevated BP; ii) a protective effect in placebo-controlled outcome trials; iii) a similar or only slightly different protective effect on cardiovascular morbid and fatal events in comparison trials, the guidelines consider 5 drug classes, *i.e.*, diuretics (both thiazides and thiazide-like), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, calcium channel blockers and β-blockers, as suitable for initiation and maintenance of antihypertensive treatment, the inclusion of β-blockers differing from recommendations by other guidelines.[11,13,14] Although several treatment strategies are regarded as capable of lowering BP (monotherapy, step-care treatment, use of polypill, renal denervation,

and quad-pill) and usable in specific conditions, the guidelines strengthen the previous recommendation to start treatment with two drugs in a single pill combination in most hypertensive patients because of the evidence that, compared to initial monotherapy,[2] initial two combinations improves adherence to treatment and reduces therapeutic inertia.[15,16] This favors long-term use of drug combinations, which lowers BP much more effectively than monotherapy but it is still a minority in most countries. According to the 2023 guidelines, initial monotherapy should be reserved for patients aged ≥80 years, fragile patients, low-risk patients with a BP elevation modestly above 140/90 mmHg, or very high-risk patients with a high normal BP, in the last two conditions because the relatively small BP reduction needed to reach the BP target is achievable with one antihypertensive drug only.

At variance from previous guidelines, and except for the combination between the ACE inhibitors and angiotensin receptor blockers, the 2023 guidelines validate the use of all possible two-drug combinations between the 5 major drug classes, thus expanding the choices available to the physician. The use of a three-drug combination is advised if two drugs at full doses do not achieve BP control, and mention is made that if adherence to treatment is adequate, this strategy may be effective in 90% or more of the overall population of hypertensive patients, with the additional advantage that in combination treatment drugs are used at lower doses, and thus drug-related side effects, as well as between-drug differences in treatment tolerability, are reduced. The use of single-pill combinations between the prescribed drugs is recommended whenever available because of the documented improvement of adherence to treatment with its simplification. Since the publication of the 2018 ESH guidelines, the availability of single-pill combinations between drugs from the 5 major classes has extended considerably, which makes the wide choice mentioned by the guidelines a realistic approach.

A true resistant hypertension (an uncontrolled office and ambulatory BP in patients adherent to a three-full dose drug treatment in whom secondary hypertension is ruled out) is regarded by guidelines as affecting possibly only about 5% of the patients. In this condition, the addition of spironolactone is advised but, considering the frequency of its side effects and contraindications, the use of other antihypertensive drugs is regarded as often necessary. In this context, mention is made of the importance of renal function for the selection of additional therapies, the thresholds for the use of spironolactone being an estimated glomerular filtration rate of ≥30 ml/min/m^2 and for use of renal denervation ≥40 ml/min/m^2. Based on novel evidence provided in the last 5 years in several ham-controlled trials (and in contrast with the 2018 European guidelines) in the 2023 guidelines renal denervation is recommended (II B class of recommendation and level of evidence) as an optional treatment in patients with true-resistant hypertension and in patients who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects or poor quality of life. The 2023 guidelines further recommend to consider new drugs, such as sodium-glucose transporter-2 inhibitors (SGLT2is) and the non-mineralocorticoid receptor antagonists finerenone because of their recently reported cardiac and renal protective effects. Of note, both drug classes have a BP-lowering potential that contributes to BP control in hypertensive patients. While SLGT2is are recommended as additional therapy for patients with chronic kidney disease (CKD) independently of the presence of diabetes, finerenone is recommended in patients with type 2 diabetes associated with CKD and particularly with albuminuria. Furthermore, together with SLGT2is, the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan is recommended for hypertensive patients with heart failure. While both drug classes are recommended with a IA class of recommendation and level of evidence for the treatment of heart failure with reduced ejection fraction, SGLT2is are recommended with IA and the ARNI with a IIB class of recommendation and level of evidence for heart failure with preserved ejection fraction. Nevertheless, in the latter condition, which frequently coexists with hypertension, all major antihypertensive drug classes will have to be considered, including a dihydropyridine calcium channel blocker, because treatment benefits are likely to importantly depend on BP reduction.

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