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Is the response to antihypertensive drugs heterogeneous? Rationale for personalized approach

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Arterial hypertension represents the most important cardiovascular risk factor with a direct responsibility for a large share of cardiovascular mortality and morbidity in the world. Despite the wide availability of antihypertensive therapies with documented effectiveness, blood pressure control still remains largely unsatisfactory in large segments of the population. Guidelines for the management of arterial hypertension suggest the preferential use of five classes of drugs—angiotensin-converting enzyme inhibitors, angiotensin II type I receptor inhibitors, calcium channel blockers, thiazide/thiazide-like diuretics, and beta-blockers—recommending the use of combination therapy, preferably in pre-established combinations, for the majority of hypertensive patients. The evidence of a non-negligible heterogeneity in the response to different antihypertensive drugs in different patients suggests the opportunity for personalization of treatment. The notable phenotypic heterogeneity of the population of hypertensive patients in terms of genetic structure, behavioural aspects, exposure to environmental factors, and disease history imposes the need to consider all the potential determinants of the response to a specific pharmacological treatment. The progressive digitalization of healthcare systems is making enormous quantities of data available for machine learning systems which will allow the development of management algorithms for truly personalized antihypertensive therapy in the near future.

Arterial hypertension represents the most important cardiovascular risk factor with a direct responsibility for a large share of cardiovascular mortality and morbidity in the world. According to estimates by the World Health Organization, arterial hypertension affects ~1.28 billion people in the 30–79 age group in the world, two-thirds of whom are in low-to-middle-income countries. In 2019, the global prevalence of arterial hypertension, standardized by age, in the 30–79 age group was 34% in men and 32% in women.[1] This epidemiological relevance translates into an enormous clinical and socioeconomic impact due to the considerable increase in the risk of cardio-cerebrovascular and renal diseases linked to increased blood pressure (BP) levels.[1] The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, which estimated the proportion of mortality, years of life lost, and years of life lived with disability attributable to 87 behavioural, environmental, occupational, and metabolic risk factors, highlighted how the predominant share of deaths in the world is attributable to systolic BP values ≥ 110–115 mmHg with an estimate of 10.8 million avoidable deaths every year and 235 million years of life lost or lived with disability every year.[2]

Unlike secondary forms of hypertension, which recognize specific pathophysiological determinants, primary hypertension—largely prevalent compared with the secondary form—is a clinical problem with a multifactorial

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aetiology supported by a complex network of nervous, cardiac, vascular, renal, and metabolic mechanisms under the influence of environmental and genetic factors.[1]

Alterations of the renin–angiotensin–aldosterone system, of the central and peripheral regulation of cardiac and vascular function, of the endothelin system, and of other vascular function control systems, including nitric oxide and natriuretic peptides, are frequently found in primary arterial hypertension and contribute, to varying degrees in different patients, to the increase in systemic vascular resistance which in turn represents the ultimate pathophysiological determinant of the increase in BP in almost all hypertensive patients.[1] Body weight, qualitative and quantitative composition of the diet, sodium and potassium intake, alcohol consumption, physical exercise, and air and noise pollution, together with educational, work, and socioeconomic aspects, represent the environmental factors that most influence BP values.[1]

The genetic architecture of arterial hypertension currently includes over 30 genes, with some rare variants that determine familial forms of hypertension or hypotension and ∼1500 single nucleotide polymorphisms associated with different BP phenotypes. Monogenic forms of hypertension mainly involve the renin–angiotensin–aldosterone system and the adrenal glucocorticoid axis together with a smaller proportion of cases of hypertension supported by neuroendocrine tumours of the sympathetic and parasympathetic nervous systems.[3] Single nucleotide polymorphisms globally explain ∼27% of the heritability of BP, estimated at 30–50%, with a rather modest share attributable to each single nucleotide.[3]

Due to the complex pathophysiology of arterial hypertension, the opportunity to use therapeutic approaches that can act simultaneously on its different pathophysiological determinants appears evident. The 2023 guidelines for the management of arterial hypertension developed by the European Society of Hypertension (ESH), in full continuity with the recommendations proposed by the 2018 edition, recommend, in fact, combination therapy with two antihypertensive drugs, preferably in pre-established association, as an initial therapeutic approach for the majority of hypertensive patients.[1] The preferential choice of combination therapy in the treatment of arterial hypertension is based on the evidence of the need to use two or more antihypertensive drugs to adequately control BP.[1] Although no clinical trial has ever compared the different efficacy of monotherapy and combination therapy, as initial therapeutic choices, in reducing cardiovascular outcomes, numerous arguments support the *ab initio* use of combination therapy: (i) the approach with a combination of drugs is invariably more effective than monotherapy in reducing BP as low doses of two drugs in combination are more effective than high doses of a single drug. Furthermore, the combination of drugs that act on different mechanisms involved in the rise in BP values reduces the variability of the BP response to treatment and allows for a faster BP response to be obtained than that which can be obtained with increasing doses of a single drug and it is safe and well tolerated with a modest risk of hypotensive episodes, even when prescribed to patients with grade 1 hypertension. (ii) Combination therapy allows BP control to be achieved more quickly, an aspect of non-negligible importance if one considers that the time necessary to reach the BP target significantly affects clinical outcomes, especially in patients at high cardiovascular risk. (iii) The use of combination therapy from the beginning allows to maintain BP control over time probably because it allows to overcome therapeutic inertia on the part of the doctor and improve therapeutic adherence on the part of the patient thanks to the simplification of the therapeutic scheme with the use of pre-established associations. The evidence deriving from controlled clinical studies demonstrates how the combination therapy with two antihypertensive drugs allows BP to be normalized in over 60% of hypertensive patients while the combination of three antihypertensive drugs allows BP control to be achieved in 90% of patients.[1]

The 2018 European Society of Cardiology (ESC)/ESH guidelines proposed five classes of antihypertensive drugs as the first line of treatment in hypertensive patients: angiotensin-converting enzyme inhibitors (ACE-I), angiotensin type I receptor inhibitors (ARB), calcium channel blockers (CCBs), thiazide/thiazide-like diuretics, and beta-blockers (BBs)—suggesting a prominent position for ACE-I and ARB as the common basis of any antihypertensive treatment and restricting the use of BBs to specific clinical conditions or situations. The selection of these five classes of drugs was based on their documented hypotensive efficacy in monotherapy, on the evidence deriving from randomized controlled trials of reduction in mortality and morbidity and on their ease of handling. The 2023 guidelines have taken up and expanded these indications, broadening the indications for the preferential use of BBs and confirming the subordinate position of drugs with less evidence deriving from randomized clinical trials or with lower tolerability (alpha-blockers, centrally acting antihypertensive, and antialdosterone), whose use must in any case be considered in association with reference drugs in specific conditions or in case of inadequate control of BP values.[1]

Despite the wide availability of antihypertensive therapies with documented effectiveness, BP control still remains largely unsatisfactory in large segments of the population, so much so that it led the World Health Organization to publish a document raising awareness on the devastating impact of this condition on collective health globally.[4] On average, adequate BP control is achieved in 20% of men and 25% of women.[5] Furthermore, a recent analysis of data from the National Health and Nutrition Examination Survey (NHANES) has provided worrying evidence of how the percentage of patients with arterial hypertension not adequately controlled by therapy is progressively increasing.[6] The determinants of this therapeutic failure are probably multiple and diversified in the various geographical areas, with a certain degree of therapeutic inertia on the part of the doctor and non-optimal therapeutic adherence on the part of the patient still playing an important role. Although guidelines recommend the use of combination therapy, many hypertensive patients continue to be treated with monotherapies whose effectiveness in normalizing BP generally does not

exceed 20%.[1] Furthermore, the variability of BP, the extent of which may be greater than the hypotensive effect of a drug, can create problems in assessing the real extent of the response to antihypertensive treatment and in deciding whether and how to titrate therapy.

Over the last few years, increasing attention has been paid to the possibility of maximizing the therapeutic yield of antihypertensive therapy by trying to select a specific class of drugs for each patient rather than setting up an empirical treatment based on the random choice of using a pool of antihypertensive agents of which clinical trials have demonstrated the effectiveness and ease of handling. The recently published Precision Hypertension Care (PHYSIC) study has produced some interesting evidence on this fascinating topic.[7] The study, randomized, double-blind, repeated crossover, was conducted in 280 patients, aged between 40 and 75 years (average age 64 years, 46% women, average clinical BP 154/89 mmHg) with grade I hypertension in the previous 5 years, untreated or receiving monotherapy, and at low risk of cardiovascular events, patients for whom the guidelines recommend starting treatment with monotherapy.[1] The study design involved the assignment of each participant to four treatment periods with the ACE-I lisinopril (20 mg/day), the ARB candesartan (16 mg/day), the CCB amlodipine (10 mg/day), and the diuretic hydrochlorothiazide (25 mg/day) after a wash-out period with placebo lasting 2 weeks at the end of which systolic BP values had to be between 140 and 179 mmHg and diastolic BP values $\leq$ 109 mmHg.

Patients received each monotherapy treatment in random order, and two treatments were randomly selected for each patient to be repeated for a total of seven to nine treatment periods separated by a 1-week placebo wash-out period. Furthermore, the use of half doses was envisaged for the first 2 weeks of each treatment and, therefore, the full dose for the remaining weeks. The purpose of such a structured study design was to evaluate not only differences in the antihypertensive response to the four treatments between the different patients but also any variations over time in the response to a specific treatment in the individual patient in order to precisely quantify the consistency of the response to treatment and the extent of the therapeutic benefit obtainable with a personalization of the therapy. Specifically, the hypothesis that individualized drug therapy could improve BP outcomes was tested by comparing two models: one that assumed that the variation in treatment effects was similar for individual patients and another that assumed that such variation in the treatment effect differed in individual patients. The latter model fit well with the data set, suggesting that treatment responses varied between patients within a treatment group to a greater extent than between treatment groups. The study highlighted significant differences in the BP response of patients to the different treatments, particularly for the choices of lisinopril vs. hydrochlorothiazide, lisinopril vs. amlodipine, candesartan vs. hydrochlorothiazide, and candesartan vs. amlodipine, while no relevant differences were observed for the choices of lisinopril vs. candesartan and hydrochlorothiazide vs. amlodipine. The net additional benefit in terms of systolic BP reduction was estimated at 4.4 mmHg.

The finding of a substantial heterogeneity in the individual response to the different treatments used in the PHYSYC study suggests the possibility of obtaining additional advantages with a personalization of the treatment, but in the current state of knowledge, this eventuality still appears rather theoretical, especially due to the difficulties in making personalized choices. Following the approach used in the PHYSIC study, one could hypothesize testing the patient's individual response to a series of short periods of treatment before defining long-term therapy with one or more drugs, but this approach appears quite laborious. Furthermore, a recent *post hoc* analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation (ADVANCE) studies has demonstrated that the BP variations observed in the short term before or after the initiation of antihypertensive therapy are not associated with long-term response to treatment.[8]

Theoretically, it would be simpler to identify phenotypic characteristics that can predict a satisfactory response to a drug or a combination of drugs. Indeed, beyond the long-known modest sensitivity of black hypertensive patients to treatment with ACE-I,[9] the limited availability to date of phenotypic indicators of response to a drug makes this approach difficult to pursue. In the past, it was thought to use the measurement of plasma renin activity to predict the response to antihypertensive treatment, but this approach was then abandoned due to the lack of specificity. The phenotypic characterization could also be useful for the preventive evaluation of the response to a more or less intensive antihypertensive treatment. A recent exploratory analysis of the results of the SPRINT study, carried out according to a data-driven approach, demonstrated a different response to intensive antihypertensive treatment in relation to the prevalent phenotype with evidence of advantage in hypertensive patients with or without additional risk factors but not in obese hypertensive patients, while in hypertensive patients with renal failure, intensive treatment was associated with an increased risk of adverse events.[10]

The results of the PHYSYC study are configured as a proof-of-concept of the possibility of achieving an accurate personalization of antihypertensive treatment in the near future and undoubtedly represent an interesting stimulus to the search for new biomarkers that can accurately predict the BP response to a specific antihypertensive drug. It is conceivable that an important impetus to studies on the personalized approach to the treatment of hypertension may derive in the near future from the identification of new biomarkers of resistant hypertension, from studies of the genomics of hypertension, from the development of mathematical models, and from artificial intelligence.

Indeed, hypertensive patients differ considerably in terms of genetic makeup, behavioural aspects, exposure to environmental factors, and disease history, all factors that can significantly influence the response to a given antihypertensive therapy. The true personalization of pharmacological therapies should, therefore, be based

on 'virtual patient' models implemented at the level of abstraction required for a specific pathology.[11,12] The progressive digitalization of healthcare systems is making enormous quantities of data available for machine learning systems which will allow the derivation of management algorithms for truly personalized antihypertensive therapy in the near future.

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References

1. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A *et al*. 2023 ESH guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). *J Hypertens* 2023;**41**:1874–2071.
2. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;**396**:1223–1249.
3. Padmanabhan S, Dominiczak AF. Genomics of hypertension: the road to precision medicine. *Nat Rev Cardiol* 2021;**18**:235–250.
4. WHO Global report on hypertension. The race against a silent killer. 2023 https://www.who.int/publications/i/item/9789240081062
5. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. *J Hypertens* 2005;**23**:2101–2107.
6. Egan BM, Li J, Sutherland SE, Rakotz MK, Wozniak GD. Hypertension control in the United States 2009–2018: factors underlying falling control rates during 2015 to 2018 across age- and race-ethnicity groups. *Hypertens* 2021;**78**:578–587.
7. Sundström J, Lind L, Nowrouzi S, Hagström E, Held C, Lytsy P *et al*. Heterogeneity in blood pressure response to 4 antihypertensive drugs: a randomized clinical trial. *JAMA* 2023;**329**:1160–1169.
8. Wang N, Harris K, Woodward M, Harrap S, Mancia G, Poulter N *et al*. Clinical utility of short-term blood pressure measure to inform long-term blood pressure management. *Hypertens* 2023;**80**:608–617.
9. Peck RN, Smart LR, Beier R, Liwa AC, Grosskurth H, Fitzgerald DW *et al*. Difference in blood pressure response to ACE-inhibitor monotherapy between black and white adults with arterial hypertension: a meta-analysis of 13 clinical trials. *BMC Nephrol* 2013;**14**:201.
10. Yang DY, Nie ZQ, Liao LZ, Zhang S-Z, Zhou H-M, Sun X-T *et al*. Phenomapping of subgroups in hypertensive patients using unsupervised data-driven cluster analysis: an exploratory study of the SPRINT trial. *Eur J Prev Cardiol* 2019;**26**:1693–1706.
11. Hu Y, Huerta J, Cordella N, Mishuris RG, Paschalidis IC. Personalized hypertension treatment recommendations by a data-driven model. *BMC Med Inform Decis Mak* 2023;**23**:44.
12. Kutumova E, Kiselev I, Sharipov R, Lifshits G, Kolpakov F. Mathematical modeling of antihypertensive therapy. *Front Physiol* 2022;**13**:1070115.