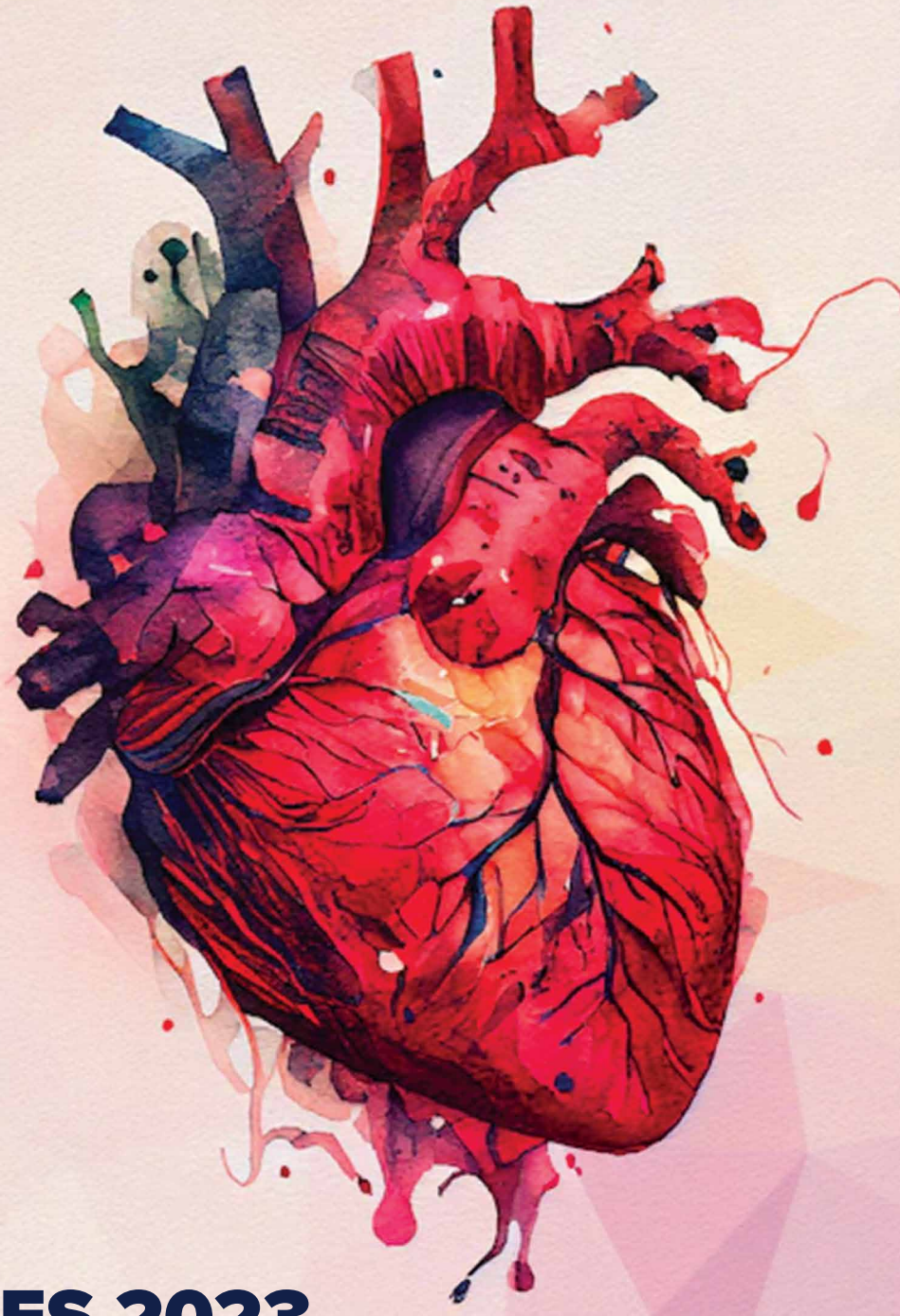
European Society of Hypertension



EXCERPTS FROM

# ESH GUIDELINES 2023

## ANTIHYPERTENSIVE DRUGS AND TREATMENT - BETA BLOCKERS

# 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 European Renal Association (ERA) and the International Society of Hypertension (ISH)

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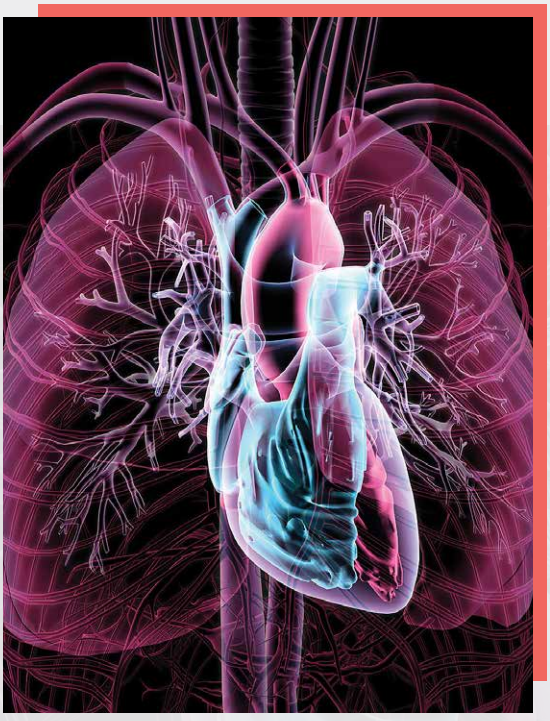

# 01 Principles of Hypertension Pathophysiology

Hypertension is divided into a primary (formerly and still also currently referred to as ‘essential’) and secondary forms. Secondary hypertension originates from specific causes and can be detected in only a small fraction of hypertensive patients (see Section 6). Primary hypertension covers the remaining large fraction of the hypertensive population, and its origin depends on the complex interaction between a genetic background, a large number of environmental factors and the aging process. Both genetic and environmental factors operate through alterations of CV regulatory systems, leading to an increase of systemic vascular resistance, which is the hallmark hemodynamic abnormality responsible for BP elevation in almost all hypertensive patients. In the last few years, important new evidence has been obtained on the genetic background of hypertension, with more than 1000 genetic factors being identified, together with, in some instances, the biochemical and pathophysiological paths they work through. New environmental factors (e.g. air pollution and noise) have been added to those already documented by older research. Furthermore, new experimental and clinical studies have confirmed that alterations of several major CV control systems may contribute to chronic BP elevation. As shown in Fig. 3, primary hypertension may be accompanied by alterations of the renin–angiotensin–aldosterone system, central and peripheral autonomic cardiac and vascular regulation, the endothelin system and other systems controlling vascular function, including nitric oxide and natriuretic peptides. More recently, pressogenic effects (increased sodium sensitivity) of gut microbial dysbiosis have also been reported. In addition, the immune system is likely to play a pathophysiologic role, with effects that are possibly primarily mediated by inflammation, and involve not only BP regulation (and thus development of hypertension) but also the initiation and progression of HMOD. There is extensive experimental and clinical evidence that hypertension is associated with inflammation and immune cell.

# 02 Definition of Hypertension and BP Classification

## 3.1 Definition of hypertension:

According to the previous 2018 European and current international guidelines [32–34], hypertension is defined based on repeated office SBP values 140mmHg and/or DBP 90mmHg. However, there is a continuous relationship between BP and CV or renal morbid or fatal events starting from an office SBP >115mmHg and a DBP >75mmHg. Therefore, this definition is arbitrary and has mainly the pragmatic purpose of simplifying the diagnosis and decision on hypertension management. In this context, the above office threshold BP values correspond to the level of BP at which the benefits of intervention (lifestyle interventions or drug treatment) exceed those of inaction, as shown by outcome-based RCTs. Based on available evidence the definition of hypertension remains unchanged from the previous guidelines.

## 3.2 Classification of hypertension

The classification of office BP and definition of hypertension grades also remain the same from previous guidelines (Table 1).

In addition to grades of hypertension, which are based on BP values, we also distinguish stages of hypertension as follows:

**Stage 1:** Uncomplicated hypertension (i.e. without HMOD or established CVD, including CKD stage 1 and 2).

**Stage 2:** Presence of HMOD or CKD grade 3 or diabetes.

**Stage 3:** Established CVD or CKD stages 4 or 5.

**TABLE 1.:** Classification of office BP and definitions of hypertension grades

| Category | Systolic (mmHg) | | Diastolic (mmHg) |
|---|---|---|---|
| Optimal | <120 | and | <80 |
| Normal | 120 - 129 | and | 80 - 84 |
| High-normal | 130 - 139 | and/or | 85 - 89 |
| Grade 1 hypertension | 140 - 159 | and/or | 90 - 99 |
| Grade 2 hypertension | 160 - 179 | and/or | 100 - 109 |
| Grade 3 hypertension | ≥180 | and/or | ≥110 |
| Isolated systolic hypertension[a] | ≥140 | and | <90 |
| Isolated diastolic hypertension[a] | <140 | and | ≥90 |

The BP category is defined by the highest level of BP, whether systolic or diastolic.
[a]Isolated systolic or diastolic hypertension is graded 1, 2 or 3 according to SBP and DBP values in the ranges indicated. The same classification is used for adolescents ≥16 years old (Section 15.1).

# 03 What is new and what has changed in the 2023 european society of Hypertension arterial hypertension guidelines?

1. Modified and simplified criteria for evidence grading recommendations
2. Pathophysiological background of primary hypertension
3. Clinical BP measurements by different methods and in different settings and clinical conditions
4. Thorough description of office, ambulatory and home BP measurements and value in different demographic and clinical conditions
5. Upgrading of out-of-office BP measurements in hypertension management
6. New HMOD measurements and their clinical value in hypertension work-up
7. New CV risk factors and update on CV 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 RAS blockers, CCBs and Thiazide/Thiazide-like diuretics, and their various combinations for BP-lowering treatment. Inclusion of BBs 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 HFrEF and HFpEF
18. New diagnostic approaches to diagnosis and treatment in hypertensive patients with AF
19. Update on treatment in CKD, 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. Detailed recommendations on patients' follow-up strategies, including assessment and minimization 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)

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**Beta-blockers**

RCTs and meta-analyses have demonstrated that when compared with placebo, first-generation and second-generation BBs like propranolol, atenolol and metoprolol significantly reduce the risk of stroke, HF and major CV events in hypertensive patients. When compared with other BP-lowering drugs, BBs were almost equivalent in preventing major CV events, except for a less effective prevention of stroke. It is possible that this difference on stroke data between BBs and other antihypertensive drug classes originates from small differences in achieved BP, including central SBP, to which cerebrovascular events may be, especially sensitive. BBs are also associated with increased risk of new-onset diabetes in predisposed individuals (mostly those with the metabolic syndrome). They also exhibit a less favorable side-effect profile than that of RAS blockers, with a higher rate of treatment discontinuation when assessed in real-life conditions. In previous guidelines, BBs were included among the five major antihypertensive drug classes. However, in the

general treatment algorithm, they were recommended only when there is a specific indication, e.g. in patients with HF, angina, post-MI, AF or in younger hypertensive women of child-bearing potential or planning pregnancy. BBs do not constitute an homogeneous class but show several pharmacological differences, among which beta1-selectivity and an additional direct vasodilating property are of special interest. Third-generation BBs, such as nebivolol or carvedilol, exhibit direct vasodilating properties. Studies not only with nebivolol but also with bisoprolol, i.e. BBs with higher beta-1 selectivity and limited to nebivolol an added vasodilatation via increased release of nitric oxide, reported a more favorable side effect profile than other BBs, including fewer adverse effects on sexual function. RCTs with carvedilol, bisoprolol, metoprolol and nebivolol showed improved outcomes in patients with HFrEF. However, there are no outcome trials with vasodilating BBs in hypertensive patients, and the same applies to bisoprolol. There are also some recent large realworld studies with vasodilator BBs conducted in the USA, with inconsistent results. In one study, there was no statistically significant difference in CV outcomes between 118 133 patients receiving either nebivolol or carvedilol and 267 891 patients receiving atenolol. In other three studies, use of nebivolol led to greater CV protection compared with use of atenolol or metoprolol.

A recent pragmatic review scrutinized the use of BBs in medical treatments. It was seen that, in addition to their compelling use as GDMT in specific diseases, BBs exhibit favorable effects in about **50 clinical conditions** including (i) various cardiac diseases less or not related to hypertension, (ii) other vascular conditions and (iii) non-CV diseases.

Finally, increased resting heart rate (>80 bpm) is common in hypertension, in which it reflects an increased sympathetic activity. A progressive increase in resting heart rate is accompanied by a progressive increase in the risk of AF, HF and mortality both in the general population and in hypertensive patients. Although in hypertension, the advantage of reducing heart rate is limited to post hoc analysis of RCTs , the available evidence makes treated hypertensive patients with an increased heart rate a clinical phenotype supporting the use of BBs.

**TABLE 16.:** Selected diseases and conditions for the use of BBs in patients with hypertension.

| Selected indications with guideline directed medical therapy for BBs |
|---|
| Chronic coronary syndromes, antiischemic therapy |
| Postmyocardial infarction: arrhythmias, angina, known incomplete re-vascularization, HF |
| Acute coronary syndrome |
| HFrEF and HFpEF if coronary disease (ischemia), arrhythmias and tachycardia |
| Atrial fibrillation: prevention, rhythm control, heart rate control |
| Women with child-bearing potential/planning pregnancy |
| Hypertension disorders in pregnancy |
| Selected other conditions in which therapy with BBs can be favourable |
| Hypertension with elevated resting heart rate >80 bpm |
| Emergency, urgency and parenteral administration |
| Perioperative hypertension |
| Major noncardiac surgery |
| Excessive pressor response to exercise and stress |
| Hyperkinetic heart syndrome |
| Postural orthostatic tachycardia syndrome |
| Orthostatic hypertension |
| OSA |
| Peripheral arterial disease with claudication |
| COPD |
| Portal hypertension, cirrhosis-related esophageal varices and recurrent variceal bleeding |
| Glaucoma |
| Thyrotoxicosis, hyperthyroidism |
| Hyperparathyroidism in uremia |
| Migraine headache |
| Essential tremor |
| Performance anxiety and anxiety disorders |
| Psychiatric disorders (posttraumatic stress) |