Contents

Note: We encourage health professionals to take the content of this Handbook into account whenever planning strategy for cardiovascular pharmacotherapy. However, the Handbook does not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions and verify the rules and regulations applicable to drugs at the time and place of prescription.

Epidemiology, definition, and classification of hypertension

Epidemiology

Elevation of blood pressure (BP) shows a close correlation with stroke and cardiovascular (CV), peripheral artery, and end-stage renal disease (ESRD). Considering the global burden of diseases, hypertension contributes the most to disability-adjusted life years and has major impact on mortality.[1] Systemic BP represents a continuum of risk whereby CV mortality rates increase with increased BP levels. In the year 2000, in adults aged ≤30 years, two-thirds of stroke cases, 50% of ischaemic heart disease (IHD) cases, and 75% of hypertensive disease cases were associated with a mean systolic BP (SBP) of >115mmHg, which represents the nadir of BP level versus risk. Hypertension is the root cause of approximately 7.1 million deaths worldwide. The prevalence of hypertension varies in different countries. Around 35–40% of the adult population suffer from hypertension, and the disease shows a strong positive correlation with age.[2]

In the long run, hypertension is a risk factor for:

- Cerebrovascular disease.
- IHD.
- Left ventricular hypertrophy (LVH).
- Heart failure (HF) with preserved, moderately reduced, and reduced ejection fraction.
- Peripheral vascular disease.
- Hypertensive renal disease.
- Hypertensive retinopathy.

Definition and classification of hypertension

Systemic hypertension is defined as persistently elevated BP (see Fig. 1.1.1), i.e. based on office readings of SBP and/or diastolic BP (DBP) of ≥140 and 90mmHg, respectively. Hypertension can be classified according to degrees of severity, as shown in Table 1.1.1.

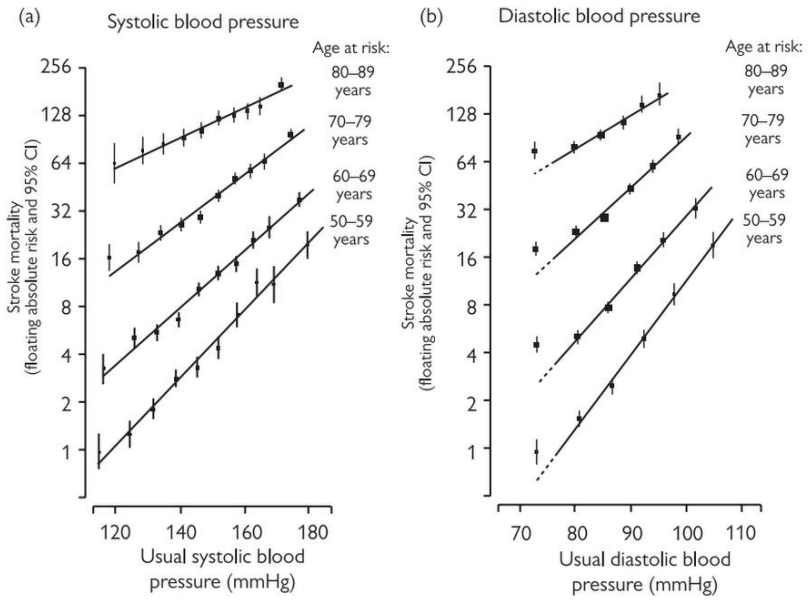

Fig. 1.1.1 Stroke mortality rate in each decade of age versus usual BP at the start of that decade. CI, confidence interval.

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Table 1.1.1 Definitions and classification of BP levels (mmHg)

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	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	≥140	and	≥90

The BP category is defined by the highest level of BP, whether systolic or diastolic. Isolated systolic hypertension should be graded 1, 2, or 3, according to systolic BP values in the ranges indicated.

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BP measurement and diagnosis of hypertension

Estimation of the true BP burden for individual patients remains an almost unaffordable exercise. Absolute BP levels can vary considerably, depending on the time, point, and method of measurement (beat-to-beat, circadian, seasonal). Therefore, obtaining an accurate diagnosis of hypertension is a difficult task, even though several simple or more sophisticated tools and methods for BP assessment are available. All national and international guidelines ask for additional information in any individual patient beyond the level of BP for confirmation of diagnosis and determining non-pharmacological or drug treatment of hypertension. Concomitant risk factors, presence or absence of end-organ damage, and/or pre-existing CV or renal disease contribute to this decision.[2]

Currently, we employ the following methodologies to measure BP and diagnose hypertension:

1. Invasive beat-to-beat measurement.
2. Non-invasive beat-to-beat measurement.
3. Office BP measurement—conventional.
4. Office BP measurement—automated.
5. Office BP measurement—automated and unattended.
6. Home BP monitoring.
7. Ambulatory BP monitoring (ABPM).
8. BP measurement during stress testing.

Invasive beat-to-beat measurement

This kind of BP assessment represents the gold standard. Due to its invasive nature, it is not suitable for routine use in the management of hypertension. It is considered an important tool for research on hypertension in experimental setups.

Non-invasive beat-to-beat measurement

Devices placed on a fingertip can perform non-invasive beat-to-beat measurement. They measure BP oscillometrically. For routine use, the advantages of beat-to-beat measurements are outweighed by the fact that hydrostatic pressure at the level of the site of measurement, compared to the reference which is the level of the heart, distorts the result. Today, these tools are restricted to research applications.

Office BP measurement—conventional

Nearly all evidence from epidemiologic studies that identified BP as an independent risk factor was gathered by conventional office BP measurement. The same holds true for almost all studies showing the beneficial effects of pharmacologic treatment of hypertension on morbidity and mortality. BP assessment by means of office BP measurement is based on the strongest evidence, but it lacks informative value and reproducibility in individual patients. In particular, BP variability and white-coat effects cannot be excluded.

High-quality standards for conventional office readings improve the result. The state-of-the-art measurement is defined by averaging three readings

in an interval of 3–5min, which markedly improves the diagnosis, prognosis, and control of hypertension. According to recommendations of the European Society of Cardiology (ESC)/European Society of Hypertension (ESH), in most countries, the diagnosis of hypertension is based on conventional office BP readings with an average BP of >140mmHg systolic and/or >90mmHg diastolic.[2] By contrast, to confirm the presence or absence of hypertension, the scientific societies of Austria, Great Britain,[3] and Canada[4] have integrated the use of out-of-office BP measurements in their recommendations.

Office BP measurement—automated

Automated office BP measurements represent an improvement on the technique of taking conventional office BP readings by means of automated devices. The devices used measure BP oscillometrically, with cuffs attached to the upper arm. By taking an average of multiple readings, these devices reduce, according to some evidence, errors in measurement and increase the positive/negative predictive values.

Office BP measurement—automated and unattended

The main goal of this method is to avoid anxiety or white-coat effects during the assessment of BP. Patients should sit alone in a quiet room without talking for at least 5min. BP is taken by an automated oscillometric device, with the cuff attached to the upper arm. The device automatically calculates the average of three readings taken at intervals of at least 1min. This method of BP assessment gained publicity when it was used in the recent SBP intervention trial (SPRINT).[5] Despite its advantage of minimizing the white-coat effect, the scientific community discusses the fact that this method gives lower BP values in individual patients, compared to conventional office readings. Consequently, conclusions derived from studies using different methods of BP assessment are not transferable with respect to achieved BP levels and targets for treatment.

Home BP monitoring

Home BP monitoring has a long-standing tradition. It is a variant of the out-of-office BP assessment, which avoids the white-coat effect and facilitates long-term follow-up. Furthermore, this method empowers patients, as they actively participate in the management of their disease. It has been shown that this method improves control of hypertension due to better compliance and adherence to pharmacological therapy, as well as implementation of a healthier lifestyle. According to current recommendations, patients should use automated devices that measure BP oscillometrically, with the cuff attached to the upper arm.

Ambulatory BP monitoring (ABPM)

This method of BP assessment represents the gold standard of non-invasive measurement. It allows the recording of a large number of readings (every 15s during daytime, every 30s during night-time). The burden of BP in individual patients can be estimated reliably, with good reproducibility and close correlations with target organ damage (cross-sectional) or prognosis (longitudinal). The most important parameters calculated, based on 24h

ABPM, are the 24h mean BP, as well as the daytime and night-time means. Additionally, the circadian pattern of BP and its physiological or pathological variations are shown (normal dipping profile against abnormal non-dipping, extreme dipping, or inverse dipping). This method allows the calculation of early-morning surges of BP or BP variability. Furthermore, night-time BP readings are important to predict future events, if monitored in individuals without pharmacological therapy. However, BP values acquired by ABPM are not a substitute to office BP readings; they complement each other.

Regression to the mean causes a gap between office and ambulatory BP readings. The larger the gap, the higher office the BP values, and vice versa. On the other hand, if the office BP reading is low, the ambulatory BP reading might be higher than the office measurements. Ambulatory and home BP values show a closer correlation but are not interchangeable. Indeed, these technologies are complementary, and not competing.

An overview of BP levels corresponding to a correct diagnosis of hypertension and derived from different methods of measurement is provided in Table 1.1.2.

BP measurement during stress testing

The rise in BP during stress testing is considered physiological, but it can also contribute to the diagnosis or prognosis of hypertension and related issues. The maximum rise in BP during exercise should not exceed 10 ± 2mmHg per metabolic equivalent (MET). At peak exercise, SBP rises physiologically up to <210mmHg (male) or <190mmHg (female), and DBP up to <110mmHg (both sexes). Compared to baseline, the rise in SBP at peak exercise should not exceed 50–60mmHg (male) or 40–50mmHg (female). In higher age groups, these differences might also be more pronounced. Submaximal exercise, however, can yield more information on the prognosis of hypertension.

Several algorithms provide proposals to confirm the diagnosis of hypertension using out-of-office BP measurements. The very reasonable Canadian algorithm is shown in Fig. 1.1.2.

Table 1.1.2 Diagnosis of hypertension adjusted for the method of BP measurement used

Method	Hypertension (mmHg)
Office measurement—conventional	≥140/90
Office measurement—automatic, unattended	≥135/85
Home BP measurement	≥135/85
Ambulatory BP monitoring—24h mean	≥130/80
Ambulatory BP monitoring—daytime mean	≥135/85
Ambulatory BP monitoring—night-time mean	≥120/70

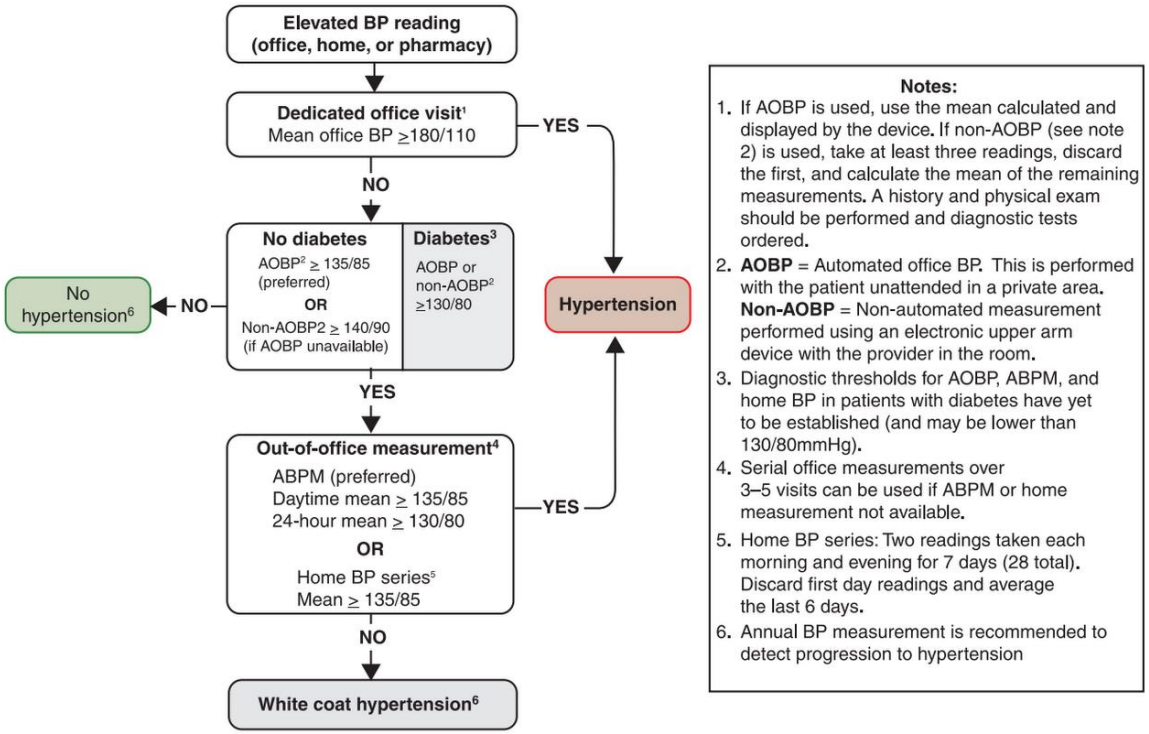

Fig. 1.1.2 Hypertension diagnostic algorithm, Canadian Society of Hypertension. ABPM, ambulatory blood pressure monitoring; AOBP, automated office blood pressure; BP, blood pressure.

Reproduced from Leung AA, Daskalopoulou SS, Dasgupta K, *et al*. Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. *Can J Cardiol* 2017;**33**:557–76, with permission from Elsevier.

Risk assessment and clinical evaluation

In >90% of cases, hypertension has no identifiable secondary/treatable causes. Essential (idiopathic, primary) hypertension is caused by polygenetic and environmental predisposing risk factors like sedentary lifestyle, obesity, and high alcohol consumption. High BP contributes mostly to the prognosis of cerebrovascular and CV diseases, but it is rarely an isolated condition. In many cases, CV and cerebrovascular risk factors and/or target organ damage accompany the diagnosis of hypertension. Hypertension impacts particularly on the prognosis of pre-existing CV and renal diseases.

Target BP and individualized hypertensive drug therapy for patients with hypertension depend on risk factors (see Fig. 1.1.3) and target organ damage. The higher the risk, the greater the benefit gained from BP-lowering therapy.

- *Risk factors*: male sex; age (men >55 years, women >65 years); smoking; dyslipidaemia [cholesterol >190, low-density lipoprotein (LDL) >115, high-density lipoprotein (HDL) <40/46 (men/women), triglycerides (TGs) >150mg/dL]; impaired glucose tolerance; abdominal obesity >88/102 (men/women); family history of premature CV disease <55/<65 years (men/women); sedentary lifestyle.
- *Target organ damage*: electrocardiographic (ECG) or echocardiographic evidence of LVH, carotid wall thickening, pulse wave velocity (carotid–femoral) >10m/s, pulse pressure >60mmHg, ankle–brachial index (ABI) <0.9; glomerular filtration rate (GFR) <60mL/min; microalbuminuria >30mg/24h.

Clinical assessment

The aims of clinical assessment include:

- Determining the duration of hypertension, previous levels of high BP, atherosclerotic risk factors, and concomitant CV or renal diseases that may affect the prognosis and guide treatment.
- Identifying potential secondary causes of hypertension (obstructive sleep apnoea syndrome, acute/chronic kidney disease, potential endocrine causes of hypertension, coarctation of the aorta, concomitant drug treatment).
- Detecting the presence/absence of organ damage.

Medical history

- Contributing lifestyle factors (salt intake, obesity, amount of physical exercise, alcohol consumption, sedentary lifestyle, dietary and smoking habits).
- Suggestion of secondary hypertension (hypertension in young age with sudden onset or worsening, especially in the absence of a family history of hypertension, organ damage disproportionate to the duration of hypertension, presentation as malignant hypertension, resistant hypertension—requiring ≤3 drugs).
- Family history of hypertension, kidney disease, and other CV risk factors.
- Concomitant drug treatment [e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptives, corticosteroids, mineralocorticoids, ciclosporin, amphetamines, erythropoietin, liquorice).