Definition of Hypertension and Establishment of Treatment Targets

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Hypertension is the most frequent chronic and non-communicable disease all over the world, with about 1.5 billion affected individuals worldwide. Its impact is currently growing, particularly in low-income countries. Even in high-income countries, hypertension remains largely underdiagnosed and undertreated, with consequent low rates of blood pressure (BP) control.

hypertension | antihypertensive therapy | Epidemiology | Blood pressure | Prognosis

1. Introduction

Because of its high prevalence and important clinical impact, hypertension remains a leading contributor to the risk of cardiovascular disease and death [1][2][3][4]. In 2015, about 1.5 billion adults worldwide had a measured office blood pressure (BP) higher than 140 mmHg systolic or 90 mmHg diastolic [5]. According to a recent study, the number of subjects aged 30–79 years with a prior diagnosis of hypertension doubled from 331 million women and 317 million men in 1990 to 626 million women and 652 million men in 2019, despite a stable age-standardized prevalence worldwide [6]. It has been estimated that a systolic BP ≥140 mmHg explains about 70% of the burden of morbidity and mortality worldwide [7][8][9].

Despite such impressive growth, the proportion of treated hypertensive subjects with normal BP (‘controlled hypertension’) remains very low worldwide. It has been estimated that such a proportion approaches 23% in women and 18% in men [6]. Notably, despite an improvement in diagnosis, treatment, and control of hypertension in most developed and high-income countries, important disparities around the world remain. About two-thirds of patients with hypertension actually live in low-income countries [1][10]. Over the past 20 years, there have been no improvements in hypertension awareness, treatment, and control in several countries in sub-Saharan Africa and Oceania [6][11][12][13].

Thus, a first basic consideration is that, although the prevalence and clinical impact of arterial hypertension is consistently growing worldwide, its control remains disappointing, particularly in low-income countries.

A second consideration is that, despite the huge number of observational studies and randomized controlled trials completed over the past four decades, the last few years have been characterized by an impressive paucity of innovative studies. In a comprehensive review, Dzau noted that research on new antihypertensive drugs and therapeutic targets is slowing dramatically [14]. In addition, there has been no recent attempt to develop clinical

applications based on the several genomic polymorphisms associated with hypertension [14]. It should be considered that the time lag between initial discovery and the marketing of a new antihypertensive drug may exceed 10 years, with a consequent final cost greater than two billion US dollars [15][16]. Within this framework, industry is directing most efforts to maximize the utilization of old and effective antihypertensive drugs (e.g., development of new combinations, new dosages, etc.) and to redirect these toward hypertension through the use of BP-lowering drugs, initially developed for different diseases (e.g., gliflozines, drugs for heart failure, etc.) [16].

2. Digital/Health Technology for Diagnosis and Monitoring

Owing to the refinement of digital/health technology, the marketing of electronic devices for remote BP measurement and transmission is growing. Theoretically, these devices have the potential to improve the diagnosis of hypertension and the achievement of an adequate BP control at the population level. Just to create a parallel with diabetes, Dzau noted in his review that the number of apps for diabetes management was about 1800 in 2016, with an impressive increase in digital diabetes marketing [14]. There is no reason why this growth should not apply to the hypertension field in the near future, although the growth of devices and apps for hypertension seems to be much less explosive than that of the management of diabetes [14].

Unfortunately, not all BP measurement devices on the market have been appropriately validated according to existing guidelines [17][18] and some of those show some limitations and shortcomings [14]. Particular attention is being devoted to cuff-less continuous BP monitoring systems as alternative to current cuff-based systems, although their validity and reliability are still under research [14][19][20][21]. It is believed that some steps are critical to make a new system reliable:

1. The system should be easily wearable, cheap, and non-intrusive. Systems included in normal smartwatches would be ideal;
2. The system should be validated for accuracy at independent academic or hospital centers. It should allow continuous or almost-continuous BP detection over prolonged periods of time of months or even years;
3. The system should be connectable to an easy-to-use protected digital repository, with software allowing easy BP retrieval over variable periods of time for calculation of appropriate statistical measures (BP averages, variability, etc.) and attached graphics;
4. The system should be easily accessible to doctors, thereby enabling rapid check and response for patients and the suggestion of changes in drug treatment or other measures;
5. Clinical research should urgently identify BP measures retrievable from the system which are more appropriate for the prediction of organ damage and, hopefully, prognosis. In other words, research should identify which BP measurements obtained by the system are more important for clinical decisions.

It is hoped that the application of artificial intelligence to these databases, which are expected to include many different types of biological data for each patient, may help doctors and patients in identifying better strategies for hypertension control, possibly in combination with strategies promoting a healthier diet, better physical activity, and

a more intelligent use of drugs. The growing use of ‘tele-medicine’ during the current COVID pandemic should be extended to the management of hypertension. However, there still a long way to go.

3. Definition of Hypertension and Establishment of Treatment Targets

Whereas the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) define hypertension by office BP levels ≥140 mmHg systolic or 90 mmHg diastolic, [22] the American Heart Association (AHA), the American College of Cardiology (ACC) and other scientific societies have endorsed a more ‘aggressive’ definition based on office BP values ≥130 mmHg systolic or 80 mmHg diastolic [23]. In addition, the International Society of Hypertension (ISH) adopted the 140/90 mmHg definition [24].

Of note, the more aggressive diagnostic targets endorsed by the US guidelines [23] do no imply that all subjects with office BP in the range of 130–139/80–89 mmHg require drug treatment. Instead, the AHA/ACC guidelines suggest to apply more appropriate life-style measures (weight control, smoking cessation, low-sodium diet, etc.) for these subjects, and to reserve drug treatment for cases of inefficacy of non-pharmacologic measures.

Notably, all guidelines share the recommendation that drug treatment should be started immediately for:

a. Patients with office BP ≥ 160/100 mmHg regardless of other considerations [22][23][24];
b. Patients with BP ≥ 140/90 mmHg in the presence of ischemic heart disease, cerebrovascular disease, or heart failure [22][23][24].

All guidelines suggest that drug treatment should be initiated, regardless of other considerations, in patients with BP persistently ≥ 140/90 mmHg in case of inefficacy of life-style measures [22][23][24].

In the case of a BP between 130/80 and 140/90 mmHg, the AHA/AHA guidelines recommend drug treatment in patients with overt cardiovascular disease (i.e., secondary prevention), as well as in patients without overt cardiovascular disease (i.e., primary prevention) if their 10-year risk of cardiovascular disease is ≥10% according to the ASCVD calculator [23].

Available guidelines provide different recommendations in terms of BP targets and definitions of BP control. The ISH and the ESC/ESH guidelines recommend a uniform BP target (<140/90 mmHg), and individualized targets based on age, tolerability, and comorbidities. Conversely, the AHA/ACC guidelines recommend an identical BP target (<130/80 mmHg) in all patients, regardless of age and comorbidities. The potential advantages and disadvantages of these different approaches have been discussed in detail [25][26][27].

Interestingly, the recent 2021 ESC Guidelines on Cardiovascular Prevention [28] introduce the concept that BP targets lower that 130/80 mmHg are always acceptable when a treatment is well tolerated. Such a statement

contrasts with prior ESC/ESH guidelines which state that, for safety reasons, systolic BP should not be targeted below 120 mmHg in people younger than 65 years, or below 130 mmHg in older subjects [22].

In summary, hypertension guidelines seem to be oriented towards individualized BP targets according to the general principle that the lowest well-tolerated BP target should be a reasonable target, with the main goal to prevent the most closely BP-related adverse complication of hypertension, which include stroke and heart failure [29].

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