Introduction to a Compendium on Hypertension

Giuseppe Mancia

Hypertension is by far the most common disease that affects human beings, its high prevalence involving both sexes and extending to either industrialized and developing countries. Compared with normotensives, individuals with a high blood pressure stand a much greater chance of having during their life a stroke, coronary heart disease, heart or renal failure, and peripheral artery disease, with a substantially higher risk also of developing atrial fibrillation, deterioration of cognitive function, and dementia. The high prevalence and the multifold important contribution of hypertension to cardiovascular and renal risk account for its position as the top contributor to the burden of disease worldwide.

Despite extensive research the cause or causes of hypertension in a given patient remain in most instances as unclear today as they were decades ago. Yet, the data that have been obtained by basic and clinical studies have provided considerable knowledge of the factors that may be potentially involved as well as of the molecular, humoral, neural, and structural mechanisms through which a blood pressure increase may occur. The aim of this compendium, the first devoted to hypertension by Circulation Research, is to offer clinicians and investigators a critical review of this knowledge, covering a large spectrum of data, that is, from genetic and molecular to integrated pathophysiology, epidemiology, diagnosis, and treatment.

Rahimi et al open the series with a survey of the epidemiology of hypertension. Evidence of the progressive increase in the risk of cardiovascular or renal diseases with the increasing blood pressure values is reviewed together with issues of great current interest such as the hypertension-related risk in different ethnicities, the debated existence of a J-curve phenomenon, the relative importance of systolic versus diastolic blood pressure, and the independent contribution of pulse pressure to the risk. Dominiczak et al next deal with the genetic aspects of hypertension, which now extend far beyond the rare forms that were identified as having a monogenic cause years ago. They describe the genes or gene combinations associated with blood pressure control and hypertension that have emerged from genome-wide association studies and include in their description the expanding area of the functional pathways through which a given genetic variant may lead to blood pressure alterations.

Several articles then provide an update of the alterations of systems majorly involved in cardiovascular modulation that may be linked to initiation and maintenance of a blood pressure increase. Danser et al review the alterations of the renin–angiotensin–aldosterone system, emphasizing the multiple consequences that this may have at both renal and extrarenal sites in the absence and during the chronic blockade of renin secretion, angiotensin II formation, and angiotensin receptor stimulation that can be therapeutically achieved in the clinical setting. Grassi et al review the evidence that sympathetic hyperactivity may promote hypertension or work as an amplifier of the pressor influence of other factors. Special attention is given to (1) the complex relationships that the sympathetic nervous system entertains with metabolic factors in obese patients and (2) the particularly pronounced sympathetic overdrive that may occur in hypertensive patients resistant to drug treatment, a pathophysiological trait that provides a rationale for the adoption, yet not conclusively validated, of invasive sympathodeactivating interventions. Hall et al review thoroughly the multiple mechanisms that may trigger a blood pressure increase when weight undergoes an excessive gain, that is, sympathetic activation but also impairment of pressure natriuresis, renin–angiotensin stimulation, mineralocorticoid receptor abnormalities, and even interference with kidney functions by the compression exerted by renal fat. Finally, Laurent and Boutouyrie provide a comprehensive update of a field in which information has made substantial progress, that is, the large artery stiffening and the small artery remodeling that characterize hypertension as well as the functional consequences this may have for the progression of this condition, the development of its clinical complications, and the response to antihypertensive treatment. Harrison et al offer an exciting insight into the complex cellular mechanisms that may account for the stimulating new evidence that inflammation contributes to the development of cardiovascular damage and perhaps also favors appearance and progression of a blood pressure elevation. This justifies research on future treatment approaches completely different from those validated in the past and used today.

The new diagnostic approaches to hypertension is addressed by Mancia and Verdecchia who review the growing evidence in favor of measuring blood pressure by ambulatory monitoring, which carries the inestimable advantage that many values are collected throughout the day and night in a real-life setting. The authors, however, also emphasize that, despite some favorable evidence, ultimate proof that adoption

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of this approach substantially improves prediction of cardiovascular and renal risk in untreated and treated hypertensive patients is still not available. This means that the time-honored approach based on office blood pressure (which is supported by a huge amount of epidemiological and intervention type of evidence) remains for the time being of cardinal importance.

The last 3 articles of the compendium address therapeutic issues. O’Donnell et al\(^1\) first discuss the persistent controversy generated by dietary salt data, that is, whether drastic reductions in salt intake should be imposed on all hypertensive patients (and perhaps also on the general population) to prevent new onset hypertension and cardiovascular disease. Randomized clinical trials showing blood pressure reductions with a reduction of sodium intake are reviewed, but mention is made that long-term data are rare and direct evidence that chronic low sodium diets effectively protect against cardiac and vascular events is absent or scientifically weak. Emphasis is further given to the interesting studies that have recently shown that the relationship between sodium intake and events may be U-shaped, namely the cardiovascular risk may have a nadir somewhere around a sodium intake of 3 to 5 g/d and an increase below. Zanchetti et al\(^1\) describe the results of a recent large meta-analysis which offers future guideline new elements to decide when to recommend antihypertensive drug treatment and how low to take blood pressure to maximize cardiovascular protection. Based on a large number of randomized trials, antihypertensive drug treatment seems to (1) offer cardiovascular protection also in grade 1 low-to-moderate risk patients and (2) reduce cerebrovascular events progressively from blood pressures >140/90 to <130/80 mm Hg. A further finding is that, although the treatment-induced reduction of absolute cardiovascular risk increases progressively with the increase of baseline risk level, so does, to a much greater extent, the residual risk and thus the rate of treatment failures. This implies that only early therapeutic interventions can successfully normalize the risk, challenging the belief that treatment is highly cost-effective, and should thus be implemented, only when cardiovascular risk is elevated. Finally, Oparil and Schmieder\(^1\) provide an overview of the antihypertensive drugs under current investigation as well as of the 2 main nonpharmacological interventions (renal denervation and baroreceptor stimulation) that have come to attention in the past few years, mentioning in each case available evidence, potential, and limitations.

A single compendium cannot deal with the extremely large number of topics that characterizes a complex multifaceted condition such as hypertension. The topics addressed, however, help developing a clear idea not only of what has been to date obtained by previous studies but also of the unmet needs on which future research should focus. As mentioned in the initial article of the compendium,\(^4\) perhaps the most important unmet need is to substantially improve the low rate of blood pressure control in the hypertension population of virtually all countries. This means to fight against the major causes of this phenomenon, namely the deficiencies of healthcare systems in the field of preventive medicine, the failure of physicians to take action when blood pressure is uncontrolled (therapeutic inertia), and, above all, the low adherence of patients to the prescribed treatment regimens. Only if this is achieved, hypertension will have a chance to step down from the undesired privilege of being the first cause of death worldwide.\(^1\)

**Disclosures**

None.

**References**


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