# A compendium on hypertension: new advances and future impact

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The population burden of hypertension was initially highlighted over 45 years ago (1) and since then almost 10,000 papers in Pubmed have been published with key words 'hypertension and burden'. With hypertension the major cause of morbidity and mortality worldwide (2,3), the personal, societal and health burden of high blood pressure remains a reality. Exacerbating this situation are declining trends in blood pressure control in patients with hypertension (4,5) and the potential impact on hypertension and cardiovascular risk of COVID-19 (6,7). Accordingly, it is not surprising that there have been many national and international 'Calls to Action' to address hypertension as a health priority including the recent 2020 USA Surgeon General's call to control hypertension (8-10).

The evidence that normalization of blood pressure is accompanied by beneficial clinical outcomes is unequivocal. This was already evident in the 1960s, when data from the pioneering Framingham Heart Study clearly showed that elevation in blood pressure was tightly linked to an increased risk of illness and death from cardiovascular disease (11). More recently findings from the Systolic Blood Pressure Intervention Trial (SPRINT) revealed that more intensive lowering of blood pressure to levels below previously recommended values was associated with significantly reduced rates of cardiovascular events and risk of death (12). Numerous clinical trials have demonstrated efficacy of the different classes of antihypertensive drugs (13).

Why then does hypertension remain sub-optimally controlled and how do we explain that in 2021 the 'silent killer' still remains the major cause of morbidity and mortality worldwide? This 'Hypertension Paradox' of more uncontrolled hypertension despite improved therapies, defined by Chobanian in the 2009 Shattuk lecture (14) is

multifactorial and likely relates, at least in part, to gaps in knowledge about the causes, mechanisms and complex interplay between modifiable and non-modifiable risk factors. Nonetheless there has been major progress in the field to address the gaps and to advance knowledge so that hopefully it will not be too long before the burden of hypertension is reduced. The present Compendium on Hypertension is a collection of state-of-the art reviews by experts in the field including a wide range of topics spanning population health to molecular mechanisms to artificial intelligence and focuses on new concepts, recent advances and future impact. It is a follow-up of the 2015 and 2019 Hypertension Compendia in Circulation Research, with the aim of providing new topics and advancements in the field to complement and build upon those previously published (15,16).

For many years, hypertension has been considered a clinical problem primarily in high income countries. However more recently it has emerged that over 30% of adults in low- and middle- income countries (LMIC) are hypertensive, contributing to the global ‘pandemic’ of hypertension. Unless effective measures are put into place the trajectory of increasing blood pressure will continue. Schutte and colleagues discuss the reasons behind the growing trend in LMICs and suggest some novel solutions in a region-specific context (17). In addition, they introduce some of the global initiatives in place to address the issue, including the WHO HEARTS Technical Package. Managing hypertension in different regions involves diverse strategies.

Fundamental to best clinical practice is evidence-based medicine, lessons learned from clinical trials and user-friendly and appropriate guidelines. Carey et al present a comprehensive update on modern evidence-based hypertension guidelines (18). They

contextualize the findings of relevant observational studies, randomized clinical trials and meta-analyses that have been published between January, 2018 and March, 2021. In particular they highlight practical topics including blood pressure measurement, patient evaluation for secondary hypertension, and cardiovascular disease risk assessment. Additionally, important issues related to management are presented including blood pressure thresholds for drug treatment, lifestyle and pharmacologic management, treatment blood pressure goals, management of hypertension in older adults, diabetes mellitus, chronic kidney disease, resistant hypertension, and optimization of care using patient, provider and health system strategies. This inclusive review should help to increase hypertension awareness, and improve treatment and control, which are essential for prevention of cardiovascular disease.

To effectively treat hypertension in a disease- and a targeted-specific manner it is essential to understand the molecular mechanisms and pathophysiological processes that underlie blood pressure elevation. However, this is complicated because hypertension is a multifactorial disorder involving multiple interlinked physiological systems and organs, numerous cell types, myriad sub-cellular processes and innumerable signaling pathways and networks. This complexity was already appreciated in the 1940s when Dr Page developed the Mosaic Theory of Hypertension (19) advocating that hypertension is the result of many factors that interact to raise blood pressure and cause end-organ damage. The original mosaic comprised genetic, environmental, anatomical, adaptive, endocrine, humoral and hemodynamic factors. With new discoveries it became clear that other factors are also important including sodium homeostasis, oxidative stress and inflammation, and the microbiome. The complexity

continues to expand and many novel systems and factors have recently been discovered that further define the ‘mosaic’ as discussed by Harrison and colleagues (20). In this issue, they appraise the interdependency between the various elements and nodes of the mosaic and provide a provocative discussion on the interpretation of data in the context of experimental models.

The importance of the vascular system and kidneys in the pathophysiology of hypertension has long been recognized, with ongoing debate whether hypertension is primarily a disorder of the vascular system or the kidneys (21-23). More recently other systems have been suggested to be central players including the immune system (24). What is clear is that all physiological systems are interlinked and that perturbed cross-talk between systems contributes to development of hypertension. In this issue Boutouyrie et al provide an update on arterial stiffness in the pathophysiology of hypertension (25). They highlight the notion that structural stiffness predicts outcomes in models that adjust for conventional risk factors and propose that arterial stiffness measurement should be a keystone in hypertension management and cardiovascular prevention. Some new insights on mechanisms that contribute to arterial stiffness during the course of aging and hypertension are discussed and the potential impact of antihypertensive therapy on reversing vascular remodeling and improving cardiovascular health is suggested.

Expanding on new concepts in pathophysiological systems, Sequeira-Lopez and Gomez introduce the notion that renin producing cells play an important role in regulating intrarenal arteries and kidney function (26). In this comprehensive review they discuss molecular mechanisms that control the fate of renin producing cells, highlight their pleiotropic nature and discuss how these unique cells have evolved to adapt to

homeostatic threats and stresses. During development renin producing cells are progenitors involved in the morphogenesis of the renal arterial tree whereas in adulthood they are involved in blood pressure regulation, fluid electrolyte balance and tissue perfusion. Many of these processes involve the renin-angiotensin system, salt and inflammation, which influence the immune system in hypertension. Madhur et al advance these concepts and discuss how chronic overactivation of immune cells, especially T cells, influences tissue damage and development of hypertension (27). They suggest that factors that impact the gut microbiome are central to the immune responses contributing to blood pressure elevation. Molecular mechanisms that activate T cells and how they infiltrate tissues to produce cytokines causing renal and vascular dysfunction and target organ damage in hypertension are discussed. Supporting the notion that the microbiome is important in immune activation and hypertension, Avery et al remind us that the gastrointestinal tract houses the largest compartment of immune cells in the body and represents the intersection of the environment and the host (28). In this issue they provide an up-to-date appraisal of the role of the microbiome in the pathophysiology of hypertension and discuss pharmacological and lifestyle-centred strategies targeting the microbiome as an emerging potential therapy in cardiovascular medicine.

Hypertension is closely associated with other co-morbidities especially overweight and obesity. Together, these co-morbidities add to the growing global burden of cardiovascular and metabolic disease. A common factor underlying these co-morbidities is adipose tissue, which is a highly dynamic organ that undergoes expansion and remodeling and produces adipokines, vasoactive peptides and inflammatory mediators that influence cardiovascular function. Koenen et al address the abnormal remodeling of

specific adipose tissue depots during obesity and how this contributes to the development of hypertension, endothelial dysfunction and vascular stiffness (29). They also delineate the local and systemic roles of adipose tissue-derived secreted factors and increased systemic inflammation in obesity, and highlight their detrimental impact on cardiovascular health. New insights on the vasoprotective effects of brown adipose tissue (BAT) and the injurious vascular effects of white adipose tissue (WAT) in different adipose depots are described, providing new insights into potential beneficial effects of BAT.

Advances in molecular biology, proteomics, cell biology, imaging, systems biology, big data and experimental medicine approaches have enabled discovery of new mechanisms of disease in hypertension. Highlighted in the present compendium are some of these exciting new paradigms. Cicalese et al develop the concept that hypertension results from chronic physiological maladaptation against stressors including circulating or local neurohormonal factors, mechanical stress, intracellular accumulation of toxic molecules and dysfunctional organelles (30). They discuss the role of endoplasmic reticulum stress, oxidative stress, metabolic mitochondrial stress, DNA damage, stress-induced senescence and pro-inflammatory processes. Highlighted in this review are some common adaptive signaling mechanisms against these stresses including unfolded protein responses, antioxidant response element signaling, autophagy, mitophagy and mitochondrial fission/fusion, signaling effector stimulator of interferon genes-mediated responses and activation of pattern recognition receptors. Recent advancements in stress-adaptive signaling mechanisms as well as potential therapeutic targets are discussed. Griendling et al further develop the concept that oxidative stress is

fundamental to many of the cell stressors in hypertension and discuss new advances in mechanisms of oxidative stress, redox signaling and clinical implications (31). They emphasise the importance of endoplasmic reticular stress and mitochondrial oxidative stress and discuss the emerging field of oxidative redox proteomics in hypertension.

Fang et al examine the role of nuclear receptors as ligand-activated transcription factors that act as sensors to make cell adaptations by mediating changes in gene expression (32). They focus on PPARs, a family of orphan receptors, and particularly on PPARγ, the isoform implicated as an important regulator of blood pressure. PPARγ, influences blood pressure by modulating renal, vascular and immune function. Impaired PPARγ function promotes hypertension as indicated in genetic studies where PPARγ mutations cause hypertension. They provide clinical trial evidence that PPARγ activators have beneficial effects on blood pressure and suggest that future research should focus on developing these agents as safe potential therapeutic vasoprotective and antihypertensive agents.

Drug-induced hypertension is an unappreciated cause of secondary hypertension (33). Many commonly used drugs such as non-steroidal anti-inflammatory agents, pseudoephedrine-containing decongestants, cyclosporine and others have long been known to increase blood pressure (33). More recently it has become evident that anti-cancer drugs, especially vascular endothelial growth factor (VEGF) inhibitors, cause an elevation in blood pressure. Of significance, over 80% of cancer patients treated with anti-angiogenesis drugs demonstrate an increase in blood pressure and ~ 40% become hypertensive. Emerging evidence indicates that this phenomenon extends beyond VEGF

inhibitors. Accordingly, while new chemotherapies prolong cancer survival this may be at an increased risk of hypertension and associated cardiovascular morbidities. Van Dorst et al highlight the implications of this upward trend and the potential impact on cardiovascular health in cancer survivors (34). They also delineate the growing number of anti-neoplastic drugs that cause hypertension and elucidate potential underlying mechanisms. This paper highlights hypertension at the interface of cardiovascular medicine and oncology (cardio-oncology), emphasising the need for collaborative clinical care between cardiologists, hypertension specialists, and oncologists. It also underlines the importance of mechanistic research and clinical trials to provide evidence-based information so that anti-cancer effects of novel chemotherapies are maximized while minimizing cardiovascular risk.

Emerging new factors that will likely influence the future impact of hypertension is Coronavirus Disease 2019 (COVID-19). Hypertension is both a risk factor and consequence of COVID-19 with recent studies indicating that young patients with hypertension and obesity are especially at increased risk of severe COVID-19 disease (35-37). Processes linking cardiovascular disease to COVID-19 are elusive, although it has been suggested that the renin-angiotensin system, and especially angiotensin converting enzyme (ACE)2, the receptor via which SARS-CoV-2 enters cells, may be important. Kreutz et al update us with the epidemiological and clinical data linking hypertension and COVID-19, and critically discuss the notion that inhibitors of the renin-angiotensin system could have adverse effects in COVID-19 patients (38). The authors review current data on the role of hypertension and its management in COVID-19 patients, and also how COVID-19 affects hypertension management.

Despite the many effective antihypertensive drugs currently available worldwide, hypertension control remains sub-optimal. To address this there have been numerous efforts made to develop novel and alternative approaches for the management of hypertension, including device-based technologies. In this issue, Mahfoud and colleagues discuss interventional therapies, based in large part on targeting the sympathetic nervous system (39). The newer technologies that have emerged are aimed at modulating the peripheral nervous system, including renal denervation, baroreflex activation therapy, endovascular baroreflex amplification therapy, carotid body ablation and pacemaker-mediated programmable hypertension control. Of these, renal denervation is the most advanced in development, with encouraging results from new clinical trials. This approach shows great promise.

Exciting new strategies to improve diagnosis and management of hypertension are discussed by Padmanabhan et al (40). They highlight the potential utility of artificial intelligence and machine learning. This is a very exciting area that will certainly impact the way clinicians manage patients with hypertension. The authors discuss the challenges and opportunities in advancing these technologies and development of algorithms, and highlight the importance of validation of these approaches.

Together this collection of outstanding reviews provides the reader with new insights in the field of experimental and clinical hypertension research. These articles will allow readers to have a fresh look at hypertension, from genetics to mechanisms to diagnosis and management, demonstrating that the science of hypertension and related cardiovascular disease is in constant evolution, and that we are headed to discovery of novel approaches that will contribute to improve outcomes for hypertensive patients. We

hope that they will also stimulate new basic, clinical, epidemiological and health services research, and further progress in the management of high blood pressure.


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## Conflicts to declare

There are no conflicts to declare.

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