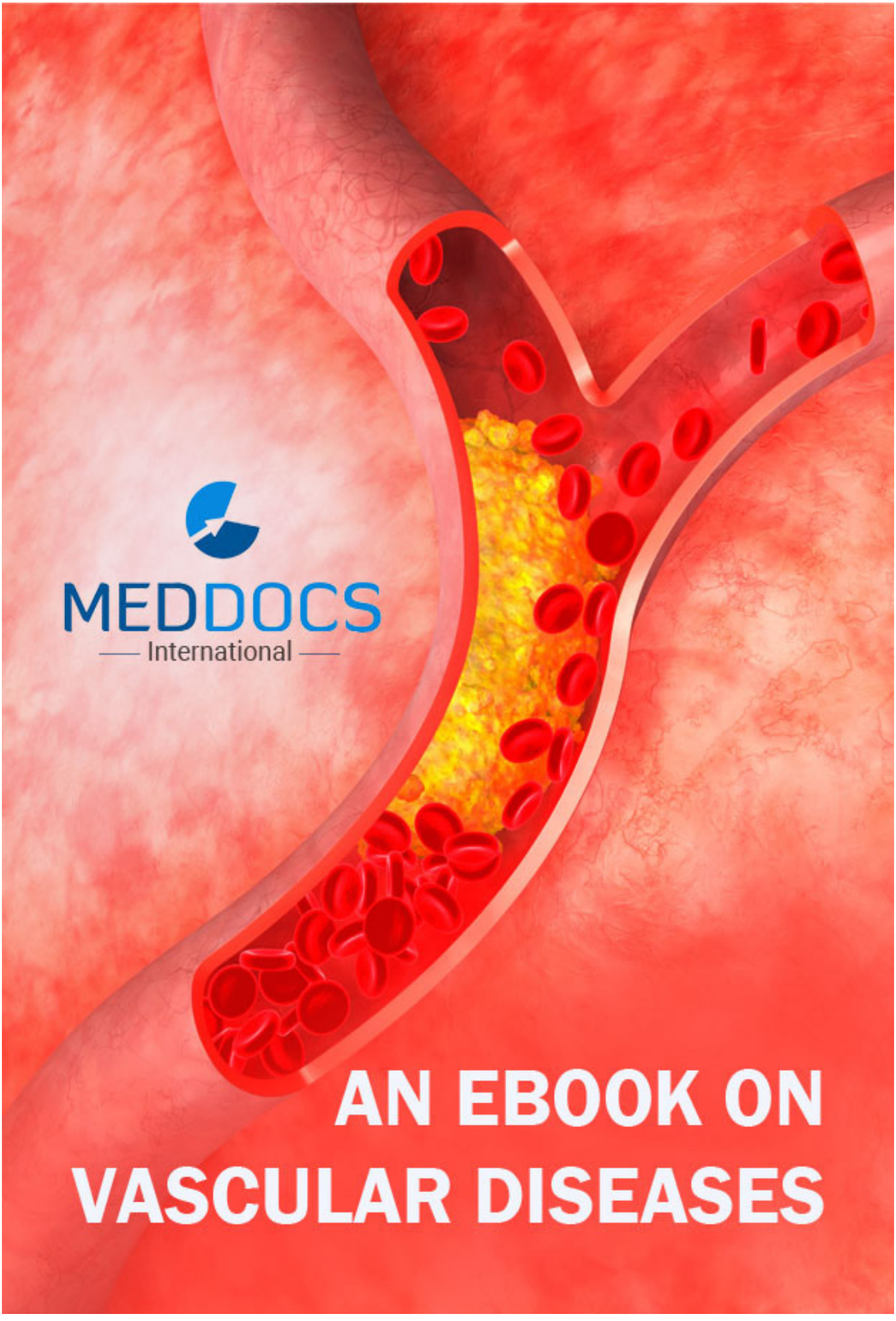

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AN EBOOK ON VASCULAR DISEASES

Hypertension in the 21st Century: Progress Report

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Introduction

A century ago, the life insurance industry provided convincing evidence for the relationship between blood pressure and mortality [1]. Despite some notable skeptics, Investigators had already begun searching for the cause of hypertension [2]. For more than half a century, the National Institutes of Health (NIH), other federal agencies, and professional societies have funded both basic and clinical/translational research that has contributed to an improved understanding of the pathophysiology of hypertension and to the development and implementation of approaches for hypertension prevention and control. Nevertheless, hypertension remains a major contributor to the global burden of disease [3]. In the US, hypertension accounts for more Cardiovascular Disease (CVD) deaths than any other modifiable risk factor [4]. The purpose of this report is to highlight 21st century advances in understanding the pathophysiology and management of hypertension.

Defining hypertension and hypertension control

Observational studies and subsequent clinical trials have demonstrated graded associations between higher systolic and diastolic blood pressures with increased CVD risk and overall mortality. In a meta-analysis of 61 prospective observational studies, the risk of CVD increased in a linear fashion from systolic blood pressure levels <115 mmHg to >180 mmHg and from diastolic blood pressure levels <75 mmHg to >105 mmHg [5,6]. Echoing earlier reports, the 7th report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure, published in 2003, defined hypertension as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg [7]. The goal of therapy was blood pressure <140/90 mmHg. Subsequently, results of randomized clinical trials also demonstrated a positive linear relationship between systolic blood pressure and risks of CVD and all cause mortality [8]. Lowest risks of CVD were observed among those with achieved systolic blood pressure of 120-124 mmHg. Influenced by these observations, in 2017 the American College of Cardiology (ACC/American Heart Association (AHA) recommended lower blood pressure thresholds for defining (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg) and treating (systolic blood pressure <130 mmHg and diastolic blood pressure <80 mmHg) hypertension [9].

A number of other professional societies in the US and other countries have also developed guidelines for defining and controlling hypertension. These guidelines generally include detailed recommendations for the evaluation and treatment of hypertensive individuals. In addition to drug therapy, up-to-date information about non-pharmacologic therapy (e.g. weight loss in the overweight and obese, nutrient consumption, physical activity, alcohol consumption) is summarized. In contrast to the more rigorous ACC/AHA guideline, in 2018, the European Society of Cardiology/European Society of Hypertension continues to define hypertension as blood pressure ≥140/90 mmHg and the initial target for blood pressure control as blood pressure <140/90 mmHg or lower if tolerated [10].

Scope of the problem

In the US adult population, hypertension awareness, treat-

ment, and control have been steadily improving since the 1960s. From 1999 through 2016, the percentage of US adults with hypertension did not change significantly, varying between 27.9 % and 29.6%, based on defining hypertension as systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg, or taking antihypertensive medications [11,12]. The prevalence of hypertension increases with age. In the US adult population, hypertension prevalence is higher and controlled hypertension is lower among non-Hispanic black and non-Hispanic Asian adults than among non-Hispanic white adults.

Among all US adults with hypertension, the prevalence of controlled hypertension increased from 31.6% in 1999-2000 to 53.1% in 2009-2010, but did not change significantly from 2009-2010 through 2015-2016 [11,12], Between 1999-2000 and 2013-2014, the percent of hypertensive adults treated with drugs increased from 59.1% to 74.7%, and in those individuals, hypertension control increased from 53.1% to 73.0%. Between 2013-2014 and 2015-2016, the percentage of individuals with controlled hypertension control tended to decrease from 53.9% to 48.3%, a statistically insignificant trend possibly related to an increased prevalence of obesity. Between 2000 and 2018, total hypertension-related CVD deaths in the US increased from 171,259 to 270,839, and overall age-adjusted mortality rates for hypertension-related CVD increased by 0.5%/year on average [13,14].

Based on the 2017 ACC/AHA definition of hypertension, from 1999 through 2016, the age-standardized prevalence of hypertension among US adults decreased from 48.4% to 45.4%, however the burden of hypertension increased from 87.0 million to 108.2 million adults [15]. The proportion of adults receiving antihypertensive drug therapy with controlled hypertension increased from 25.6% to 43.5%.

Measurement of blood pressure

For office blood pressure measurements, automated oscillometric devices have generally replaced column of mercury based auscultatory measures, in part due to toxicological issues with mercury. These devices should have a validated measurement protocol and should be calibrated periodically. Increasing evidence supports the use of automated blood pressure measurements [9].

Since its introduction in the 1960s, 24-hour automated ambulatory blood pressure monitoring (ABPM) devices have been refined, and ABPM has proven to be a useful strategy for detecting, confirming, and monitoring hypertension [16]. In contrast to office measurements, ABPM tracks blood pressure changes occurring in daily life over 24 hours. Home blood pressure monitoring with a manual device may be more practical than ABPM. Out-of-office blood pressures are generally lower than office measurements (Table 1). ABPM is a more robust predictor of target organ damage and CVD events than casual office measurements [17]. Additionally, nighttime blood pressure is a stronger predictor of target organ damage than daytime blood pressure [18].

Table 1: Corresponding values of office and out of office blood pressures [9].

Office	HBPM	Day ABPM	Night ABPM	24-hour ABPM
120/80	120//80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

Source: reference [9]

Home Blood Pressure Monitoring (HBPM); Ambulatory Blood Pressure Monitoring (ABPM)

Out-of-office blood pressures have led to the identification and clinical significance of white coat hypertension (elevated office blood pressure and normal ABPM) and masked hypertension (normal office blood pressure and elevated ABPM) [9]. Masked hypertension reportedly occurs in 10% to 30% of patients and is associated with CVD risk similar to those with sustained hypertension. The prevalence of white coat hypertension ranges from 13% to 35% and increases with age. White coat hypertension appears to be associated with a minimally increased risk of CVD. In patients with sustained hypertension, blood pressures are elevated in both office and out-of-office settings.

Discovery

As one approach to highlighting outstanding research accomplishments over the past two decades, Table 2 lists recipients of the American Heart Association Council on Hypertension annual award for outstanding research. The purpose of this award is to recognize scientists who have had a major impact in the field of hypertension and "whose research has contributed to improved treatment and greater understanding of high blood pressure." Although not the exclusive arbiter of meritorious research, the spectrum of discoveries recognized by this award provides new information about the pathophysiology of hypertension and hypertension-related cardiovascular disease and the application of this understanding to the treatment of hypertension. In several instances, identification of mechanisms contributing to blood pressure control and vascular disease has led to the development of novel therapeutic agents.

Table 2: American Heart Association Council of Hypertension awards for outstanding research.

Year	Recipient	Discovery
2000	Haralambos Gavras, MD	(1) Demonstrated in experimental animals and human hypertensives, the capacity of angiotensin II receptor blockers and ACE inhibitors to lower blood pressure. (2) Helped elucidate pathogenic mechanisms, hemodynamic responses, and hormonal patterns in hypertension, ischemic heart disease, and heart failure and the role of blocking the renin-angiotensin system in treating these abnormalities.
	Hans R. Brunner, MD	(1) Observed that angiotensin II is a risk factor for cardiovascular complications in hypertensive patients. (2) Investigated the role of angiotensin II antagonists and ACE inhibitors in experimental animals and humans with hypertension.
	Jay Cohn, MD	(1) Demonstrated benefits of vasodilator therapy in patients with left ventricular failure. (2) Explored the role of neurohumoral factors in congestive heart failure and demonstrated a direct relationship between mortality and plasma norepinephrine.

2001	Victor J. Dzau, MD	(1) Purified renin and developed monoclonal antibodies that enabled direct assay of renin. (2) Cloned the angiotensin II type 2 receptor gene and found that the angiotensin II type 2 receptor is antagonistic to the angiotensin II type 1 receptor. (3) Elucidated the importance of renin- angiotensin as a mediator of tissue function and pathology. (4) Demonstrated the efficacy of NO synthetase II gene therapy for prevention of experimental vascular stenosis.
2002	Gerald F. Dibona, MD	(1) Described the role of the renal nerves in control of renal function (renin secretion, sodium excretion, and renal blood flow). (2) Demonstrated that increased neural activity to the kidneys limits their ability to excrete sodium
	John E. Hall, PhD	(1) Defined the causative role of pressure-natriuresis in the development of hypertension
2003	M. Judah Folkman, MD	(1) Grew endothelial cells in vitro. (2) Discovered the mechanism of angiogenesis that led to clinical trials of angiogenesis inhibitors. (3) Described the use of silicone rubber implantable polymer for the sustained release of drugs.
2004	Jorge H. Capdevila, PhD	(1) Discovered biological pathway of arachidonic acid and its products (EETs) involved in the regulation of arterial pressure.
	David G. Harrison, MD	(1) Demonstrated how hypercholesterolemia and atherosclerosis alter endothelium-dependent vasodilatation. (2) Characterized NADPH oxidase as a source of radicals in hypertension. (3) Discovered that the adaptive immune system plays a role in the genesis of experimental hypertension.
2005	Kenneth E. Bernstein, MD	(1) Cloned the angiotensin-converting enzyme gene and demonstrated its tissue specific expressions and activities. (2) Cloned the angiotensin II type 1 receptor.
	Barry M. Brenner, MD	(1) Demonstrated that inhibition of renin- angiotensin provides renal protection in hypertension, diabetes mellitus, and a variety of primary renal diseases.
2006	William B. Campbell, PhD	(1) Described a role for endothelium-derived factors in the regulation of vasomotor function and aldosterone. (2) Discovered a new class of endothelium-derived eicosanoids (epoxyeicosatetranoic acids)
	Theodore W. Kurtz, MD	(1) Identified molecular gene variants contributing to cardiovascular and metabolic phenotypes in experimental models of hypertension
2007	Friedrich C. Luft, MD	(1) Discoveries on the physiology of renal sodium handling in hypertension, the pathophysiology of hypertension-mediated target organ injury, and the genetics of hypertension.
2008	Mordecai P. Blaustein, MD	(1) Discovered and described physiological significance of plasma membrane sodium-calcium exchanger and endogenous ouabain
	John W. Funder, MD, PhD	(1) Characterized mineralocorticoid receptor in kidney and other tissues. (2) Characterized blood pressure-independent effects of aldosterone to produce inflammation and fibrosis. (3) Demonstrated role of 11 hydroxysteroid dehydrogenase in converting cortisol/corticosterone to inactive metabolites.
	Juan Carlos Romero, MD	(1) Described interaction of prostaglandins with intrarenal renin- angiotensin system. (2) Described roles of prostaglandins and NO in regulation of renal hemodynamics. (3) Developed innovation approaches for imaging the kidney.
2009	Carlos M. Ferrario, MD	(1) Determined mechanism of action of angiotensin in brain. (2) Identified new pathways leading to formation of angiotensin (1-7). (3) Described mechanism of action of angiotensin-converting enzyme and angiotensin receptor antagonists. (4) Described the role of angiotensin II in the pathogenesis of atherosclerosis.
	Curt D. Sigmund, PhD	(1) Described molecular biology and genetics of renin- angiotensin. (2) Helped to define the importance of renin- angiotensin in blood pressure regulation and hypertension. (3) Described the regulation of vascular function and blood pressure by peroxisome proliferator-activated receptor-Ý.
2010	John Oates, MD	(1) Studied the antihypertensive effect of aldomet. (2) Determined that sudden coronary death is reduced when a K+ sparing diuretic is compared with a thiazide; (3) Analyzed the metabolism and physiological effects of prostaglandins; (4) Determined that low dose aspirin is an antiplatelet agent.
	Paul Vanhoutte, MD, PhD	(1) Determined mechanisms relating to vascular endothelium-dependent contraction.
2011	Ernesto Schriffrin, MD, PhD	(1) Identified mechanisms involved in remodeling of small resistance arteries in experimental and human hypertension. (2) Demonstrated that antihypertensive therapy causes regression if vascular remodeling in hypertensive patients.
	Christopher Wilcox, MD., PhD	(1) Described the contributions of thromboxane-prostanoids and neuronal nitric oxide on tuboglomerular feedback and renal vascular function. (2) Clarified the role of oxidative stress, NADPH, and asymmetric dimethylarginine in hypertensive kidney disease.
2012	Robert Carey,MD	(1) Described roles of the renin-angiotensin system and the peripheral dopaminergic system on control of kidney function and blood pressure. (2) Identified the importance of the angiotensin A2 receptor, bradykinin, nitric oxide, and cGMP.
	Gabriel Navar, PhD	(1) Demonstrated that renal blood flow and glomerular filtration rate are regulated by a macula densa-tuboglomerular u feedback mechanism. (2) Demonstrated that intrarenal paracrine mechanisms mediate and modulate pressure natriuresis.

2013	Murray Esler, PhD	(1) Demonstrated activation of cardiac sympathetic outflow in patients with heart failure. (2) Demonstrated activation of renal sympathetic outflow in essential hypertension.
2014	Thomas Coffman, MD	(1) Developed and applied methods to quantify sympathetic nervous system activity in specific regions of the body in human subjects. (2) Established the principle that sympathetic activity does not change uniformly in disease.
	Toshiro Fujita, MD, PhD	(1) Developed and applied methods to quantify sympathetic nervous system activity in specific regions of the body in human subjects. (2) Established the principle that sympathetic activity does not change uniformly in disease.
2015	Constantino Iadecola, MD	(1) Disclosed the role for hypertension and its modulation of cerebral micro vessel function on neuronal and cognitive function.
	Pedro Jose, MD, PhD	(1) Disclosed the role of dopamine in hypertension and it's signaling mechanisms and receptors in blood vessels and the kidney.
2016	Suzanne Oparil, MD	(1) Studied pathophysiology and treatment of hypertension with special emphasis on understanding sexual dimorphism in the development of hypertensive vascular disease.
	R. Ariel Gomez, MD	(1) Elucidated the embryonic origin, identity, regulation, fate and physiological functions of the renin cell, both in the kidney and in extra renal tissue.
2017	Allyn Mark, MD	(1) Described a neurogenic component to salt-sensitive hypertension. (2) Evaluated the role of leptin resistance tn obesity-related hypertension. (3) Measured the contribution sympathetic nerves to human hypertension.
	Richard Roman, PhD	(1) Described the role of the renal medullary circulation in pressure natriuresis. (2) Described the contribution of P-450 eicosanoids to the control of vascular junction.
2018	Paul Whelton, MD, MSc	(1) Contributed to blood-pressure-related cardiovascular/renal disease, epidemiology, prevention, clinical trials, and policy. (2) Committed to global health,
	R. Clinton Webb, PhD	(1) Contributed to the understanding of mechanisms controlling vascular function in normal and hypertensive states.
2019	Rhian M. Touyz, MBBCh, PhD	(1) Contributed to the knowledge molecular mechanisms, cell signaling pathways, and vascular biology of hypertension.
2020	Giuseppe Mancia, MD, PhD	(1) Contributed to the understanding and clinical applications in the pathophysiology, evaluation and treatment of human hypertension.

Genetics

Goals of genetic investigation are to further identify individuals at risk for hypertension and cardiovascular disease and to develop personalized strategies for prevention and treatment.

Although specific genetic variants have been identified in rare Mendelian forms of hypertension, these variants are not applicable to the vast majority (>98%) of patients with hypertension. Animal models have identified a number of genetic loci and genes associated with hypertension. Clinically, results of candidate gene studies and genome-wide association studies have identified more than 25 rare mutations that influence blood pressure and more than 1,000 common polymorphic haplotypes associated with blood pressure [19]. A number are involved in pathways that regulate arterial pressure. These polymorphisms collectively explain 27% of the estimated heritability of blood pressure, although they account for only approximately 5.7% of systolic blood pressure variability.

Based on adoption, twin, and family studies, heritability of blood pressure levels and hypertension ranges from 30% to 60% [20]. Genome sequences alone do not account for nutritional, environmental and lifestyle factors that also contribute to common complex diseases such as hypertension. One hypothesis to account for the "missing heritability" in hypertension is that epigenetic modifications of DNA contribute to the heritability of blood pressure [20]. Epigenetic processes change gene expression without changing DNA sequence, and epigenetic changes are the consequence of the interplay between DNA and environmental factors [21].

Earlier studies of epigenetic associations of human hypertension have focused on gene-specific modifications [22]. With the introduction of the Infinium Human Methylation 450K array, the focus of cardiovascular epigenetics has shifted from candidate gene regions to epigenome-wide studies. In a study of 17,010 individuals of European, African American, and Hispanic ancestry, results of a recent genome-wide DNA methylation (an epigenetic marker) meta-analysis indicate that there is an association of DNA methylation with blood pressure that is likely independent of previously known genetic variants [23].

Increasing animal and clinical evidence suggests specific genetic associations and epigenetic changes that are also predictive of CVD [24]. Both global and candidate gene methylation patterns have been linked to cardiovascular outcomes. However, the results are somewhat conflicting, and the clinical advantage to identifying a genetic predisposition to hypertension and cardiovascular disease remains to be clarified. In a recent study involving 277,005 individuals without previous CVD, healthy lifestyles were strongly associated with blood pressure and incident CVD, regardless of the underlying blood pressure genetic risk [25].

Conclusion

Based on the number of citations in PubMed, hypertension has been an active topic of investigation over the past 2 decades [26]. Between 1999 and 2018, 90,308 hypertension-related articles have been published worldwide, and during that period, the number of articles increased by 43.5%. The number of collaborations among countries has also increased. Over the past two decades, there have been improvements in hypertension awareness, treatment, and control. Nevertheless, prevention and control of hypertension remain a compelling clinical and public health challenge. Since 1999, US death rates attributed to hypertension as the underlying cause of death have steadi-

ly increased. The ultimate goal of future research should be to develop and implement new strategies to more effectively prevent and treat hypertension and its related cardiovascular consequences. This will require active involvement and collaboration among basic scientists, clinical/translational scientists, community partners, medical care providers, and hypertensive patients.

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