Brief Review

Building on a Legacy of Hypertension Research
Charting Our Future Together

George A. Mensah, Zorina S. Galis, Lawrence J. Fine, Melissa E. Garcia, Daniel F. Levy, Gary H. Gibbons

In partnership with other public and private funders of biomedical research, the National Heart, Lung, and Blood Institute (NHLBI) has pursued its mission to provide global leadership in research that advances the prevention, treatment, and control of hypertension over the last half century. Since its founding in 1948, NHLBI has fostered investigator- and institute-initiated research in hypertension that encompassed studies in basic, translational, clinical, and population science research. In fact, 60% of the overall National Institutes of Health investment in hypertension research, by dollar amount of funding or by number of grants, comes through the NHLBI, followed by the National Institute of Digestive Disorders and Kidney (15%).

These many research advances have ushered in a wide spectrum of safe and effective interventions for the prevention, detection, evaluation, treatment, and control of hypertension. In spite of these remarkable achievements, hypertension continues to play a major role in mortality disparities because of its high prevalence and earlier age of onset in non-Hispanic blacks compared with other race/ethnic groups. Hypertension explains ≈50% of the excess cardiovascular risk among non-Hispanic blacks compared with non-Hispanic whites. These persisting challenges compel a continued commitment to identify effective strategies for the prevention of hypertension-related morbidity, mortality, and disparities.

In this endeavor, the NHLBI remains committed to the full spectrum of hypertension research from molecular, genomic, cellular, and pathophysiological origins to the role of important social and environmental determinants and conditions under which people live and work. We support continued exploration of these social determinants and conditions, especially obesity, sedentary lifestyle, sleep-disordered breathing, and dietary factors, such as higher sodium intake and lower potassium intake.

Key mechanistic insights and connections remain incompletely understood and constitute ripe opportunities for future hypertension research. For instance, future improvements will critically depend on answering fundamental enduring questions about the relations of hypertension and associated target organ damage, chronic kidney disease, cognitive impairment, and small-vessel cerebral ischemic disease. To translate the latest fundamental discoveries to real-world health impact, the NHLBI seeks to identify and enable the most meritorious research with the firm understanding that all the various types of research are needed to inform each other and is, thus, committed to a balanced overall research portfolio.

In this article, we highlight a few NHLBI-supported advances from basic and early translational research, clinical trials, and population science encompassing hypertension research over the prior 50 years and the foundational insights they provide for future research. We also address the NHLBI enduring principles and propose how collectively we can seize unprecedented opportunities to address the challenges we face today by setting the agenda for hypertension research over the coming decade.

Building on Our Past Legacy and Present Strengths

Basic and Early Translational Science Contributions

An analysis of the most impactful publications in the field of hypertension, which examined the top 100 most-cited hypertension-related reports, showed that the majority (68%) of the most-cited basic studies and 21% of the most-cited clinical publications relied on National Institutes of Health support. Many of these fundamental discoveries have helped advance our understanding of molecular pathways involved in the control of blood pressure regulation, including central, renal, and vascular control, and the development of hypertension in various experimental models and in humans. The resulting new fundamental knowledge also provided a rational basis for the development of new therapeutics responsible for numerous advancements in clinical care of hypertension. In fact, when examining the type of reports that had been the most cited by hypertension-related patents, we found all of them to be basic science studies. An exemplar of such NHLBI-supported basic science is related to the discovery and characterization of G-protein–coupled receptors, rewarded with a Nobel Prize in Chemistry in 2012. These molecules are the targets of many current antihypertensive and other cardiovascular...
agents and constitute the largest family of molecules targeted by today’s most successful therapeutics, including β-blockers, angiotensin receptor blockers, opioid agonists, and histamine receptor blockers. Likewise, most of the targets for the new antihypertensive drugs being currently developed and tested by pharmaceutical companies reflect the basic science insights of NHLBI investigators into novel pathways of hypertension. In addition, through a variety of translational programs and initiatives, NHLBI also supports the direct involvement of our investigators in the development of new biomedical products.

Although the well-known translation paradigm depicts bench discoveries being translated into clinical interventions, the new and sometimes unexpected results obtained in clinical trials many times demand an enhanced, or even different, fundamental understanding of the underlying mechanisms and, thus, offer great bedside-to-bench opportunities for fresh perspectives to help initiate basic research. A recent example of the virtuous circle connecting experimental and real-world recent findings in hypertension was offered by the concurrence of not only the results but also the timing of findings obtained from basic and epidemiological research studies funded by the NHLBI in an effort to clarify the relationship between arterial stiffening and hypertension. Several concurrent basic research studies confirmed that arterial stiffening preceded overt hypertension in different experimental models, including the elastin-deficient mice, obese mice, or stroke-prone Dahl salt–sensitive hypertensive rats. The same temporal sequence, that is, arterial stiffening preceding hypertension, was reported in FHS (the Framingham Heart Study). The clinical finding reinforced the importance of pursuing experimental studies needed to prove the causal relationship and to elucidate the specific cellular and molecular mechanisms by which arterial stiffening leads to hypertension. Indeed, the ensuing experimental studies identified several molecular pathways by which inflammation, fibrosis, autophagy, or redox stress drive arterial stiffening are leading to hypertension. These findings indicate that monitoring and control of arterial stiffening could prevent hypertension and, thus, could inform the potential development and clinical testing of new generations of diagnostics and therapeutic interventions.

The great majority of new NHLBI-supported research is the result of investigator-initiated applications. In addition, NHLBI has a tradition of engaging the investigator community in thinking about important emerging research topics, opportunities, and gaps using many different formats and avenues. For instance, the NHLBI convened a group of multidisciplinary experts to consider the role of epigenetics in hypertension and then partnered with the American Heart Association’s Council on Hypertension to form the International Consortium for Blood Pressure Genome-Wide Association Studies, thereby permitting meta-analysis of GWAS results in a larger sample size. The number of reported blood pressure genes recently

**Contribution From the Population Sciences**

A prominent example of the contributions of observational studies to the understanding of hypertension as a risk factor for cardiovascular disease comes from the FHS, which was begun by the US Public Health Service in 1948 and was soon thereafter transferred to the newly established National Heart Institute. Nearly 60 years ago, FHS investigators reported a strong association between blood pressure and risk of coronary heart disease after only 4 years of follow-up. Additional follow-up of FHS participants allowed Kannel et al. to publish one of the most important papers in the field of preventive cardiology. This landmark publication is widely credited for coining the term risk factor, and it identified hypertension as one of the initial risk factors for coronary heart disease. They reported that definite hypertension increased the risk of coronary heart disease by nearly 3-fold in men and 6-fold in women. In 1970, FHS researchers provided conclusive evidence of hypertension as a risk factor for stroke, observing that hypertension increased the risk of ischemic stroke by >3-fold and that only 15% of strokes were unaccompanied by hypertension. Similarly, in 1972, FHS researchers established hypertension as a risk factor for heart failure, noting that hypertension preceded heart failure in 75% of the cases, and 6X more heart failure cases developed in hypertensive than in normotensive people.

The FHS was also instrumental in documenting the association of hypertension with target organ damage, with particular attention to left ventricular hypertrophy on the ECG and later on the echocardiogram. With the advent of echocardiography, researchers had a tool that could provide more detailed anatomic assessment of cardiac structure and function and the effects of hypertension on the heart. FHS investigators used the echocardiogram to calculate left ventricular mass and to develop new criteria for left ventricular hypertrophy. This approach was then applied to FHS participants, providing evidence that each 50 g/m increase in left ventricular mass corresponded to a 49% increase in risk of cardiovascular disease in men and a 57% increase in risk in women after adjusting for established risk factors, including blood pressure, which contributed to left ventricular hypertrophy.

In addition to the FHS, other epidemiological studies undertaken by NHLBI remain at the cutting edge of epidemiological research into hypertension. Several NHLBI-funded cohort studies, including the FHS, ARIC (Atherosclerosis Research in Communities), and CHS (Cardiovascular Health Study), joined forces with the Age, Gene/Environment Susceptibility study from Iceland (with support from the National Institute on Aging) and the Rotterdam Study to form the CHARGE consortium (Cohorts for Heart and Aging Research in Genomic Epidemiology). CHARGE conducted one of the first genome-wide association studies (GWAS) of blood pressure and identified 8 genomic loci associated with systolic blood pressure, diastolic blood pressure, or hypertension. The list of blood pressure loci increased to 30 when the CHARGE consortium teamed up with another international team to form the International Consortium for Blood Pressure Genome-Wide Association Studies, thereby permitting meta-analysis of GWAS results in a larger sample size.
increased several fold with the recent publication of 3 studies in which data from NHLBI-supported cohort studies figured prominently.35

FHS investigators recently published results of transcriptome-wide association studies of blood pressure and hypertension using whole blood RNA from >7000 individuals and identified 34 differentially expressed genes (mRNAs) that will explain 5% to 9% of interindividual blood pressure variability.36 FHS investigators further implemented a systems biology approach and identified key driver genes and gene networks underlying hypertension.37 One novel blood pressure gene to emerge from this approach was SH2B3, which was previously reported to be associated with blood pressure in GWAS.33 The FHS investigators joined forces with researchers from Vanderbilt University, who studied a Sh2b3 (also known as lnk) knockout mouse model38 that revealed a causal role for Sh2b3 in hypertension and its associated renal/vascular dysfunction. Moreover, many of the genes predicted from the FHS systems analysis to be regulated by SH2B3 in human gene networks were perturbed in the Sh2b3−/− mice. This body of work illustrates the potential power of integrating systems biology in humans with mouse models to validate population-based findings and to discover promising therapeutic targets for the treatment of hypertension.

Hypertension may be a syndrome, rather than a single disorder, in that a variety of body systems malfunctions would lead to a hypertensive response, and we would need to be able to identify and be able to treat the cause rather than the symptom. In that regard, prevention of hypertension would even be more effective than lifelong pharmacological therapy, although presently prevention strategies are even more challenging to implement widely. For example, data from the Nurses’ Health study suggested that optimal dietary and lifestyle habits could prevent the development of hypertension among younger women.39 The importance of hypertension prevention was highlighted by recent findings from FHS investigators noting that although the treatment of hypertension reduces the risk of cardiovascular disorders, there is still a substantial residual risk of 50% even for treated individuals who have treated blood pressures <140/90 mm Hg.40

Clinical Trials
NHLBI clinical trials substantially contributed to the scientific foundation underlying the clinical and public health strategy that has led to the effective treatment of hypertension. NHLBI clinical trials have been built on the remarkable and pioneering clinical trials have been built on the remarkable and pioneering clinical trials conducted by the Veterans Administration Cooperative Study Group on Antihypertensive Agents.41 NHLBI then followed with a much larger trial, HDFP (Hypertension Detection and Follow-Up Program), which found that total mortality was reduced by more aggressive treatment.42 After these early trials, there was an increased recognition of the importance of systolic hypertension, particularly in older individuals. As a result, NHLBI started SHEP (Systolic Hypertension in the Elderly Program) in 1984. SHEP reported that treatment with chlorthalidone substantially reduced the rate of fatal and nonfatal stroke.43 By the time that SHEP was completed, newer classes of antihypertensives were in common use in the United States. Because there were few trials comparing these newer drugs with chlorthalidone, NHLBI started ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) to determine whether these new antihypertensives were superior to a generic thiazide-type diuretic, chlorthalidone. The most important result of ALLHAT was that the heart failure rate was significantly lower in the chlorthalidone arm compared with either the lisinopril or amlodipine arms.44

After ALLHAT, the most important scientific question returned to the issue of what should be the systolic target for treatment of hypertension. The ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) began in 1998, focused on optimal treatment goals for systolic blood pressure. ACCORD studied high-risk participants with type 2 diabetes mellitus and compared intensive treatment to a systolic goal of <120 mg Hg to a standard goal of <140 mg Hg. The intensive strategy compared with the standard strategy did not reduce the composite cardiovascular outcome; however, the interpretation of the results is complicated by low event rate in the control arm.45 Although the ACCORD study was still ongoing, in 2007, NHLBI, in partnership with the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke, decided to test a similar strategy in a high-risk group of participants without diabetes mellitus in SPRINT (Systolic Blood Pressure Intervention Trial). The blood pressure intervention in SPRINT was terminated early because of a clear indication that more intensive lowering of blood pressure (to systolic blood pressure <120 mm Hg) can significantly lower cardiovascular events and mortality compared with the standard treatment.46 The final results showed a significant lower rate of cardiovascular events and total mortality, although the rates of some adverse events were higher in the intensive-treatment group. Although the blood pressure intervention was stopped, the cohort continues to be followed for cognitive/dementia and renal outcomes.47 In addition to challenging the widely accepted blood pressure treatment targets, this study should also inspire the scientific community to identify the molecular mechanisms that may be responsible for the significant cardiovascular health benefits and secondary effects of a lowered blood pressure goal from 140 to 120 mm Hg. It would be important to investigate whether the clinical research strategy used in SPRINT can be implemented in routine clinical practice to achieve similar benefits.

NHLBI has also funded trials to study nonpharmacological strategies to lower blood pressure. One prominent example is the Dietary Approaches to Stop Hypertension eating plan, which combines healthy food choices with a focus on reduced dietary sodium. This NHLBI-funded study showed that this combined diet is as effective as an antihypertensive medication in lowering systolic blood pressure in individuals with hypertension.48 Together, these NHLBI trials over more than 4 decades have substantially influenced the treatment of hypertension.

A new large investigator-initiated NHLBI-funded clinical trial that is currently beginning to enroll is CHAP (Chronic Hypertension and Pregnancy). CHAP is a randomized, open-label trial that evaluates the effectiveness and safety of treating mild chronic hypertension in pregnancy (unique identifier:
Clinical randomized trials will continue to play an important role in the NHLBI portfolio. Trials will span the range from early intervention development, to large-scale testing of major efficacy questions, to implementation trials. Progressively greater understanding of genetics and other omics will allow us to more successfully identify patients who will respond to therapeutic interventions and to better understand the mechanisms of action of interventions. We are gradually learning how to more efficiently conduct trials and to recruit more rapidly large number of trial participants. This should ensure that our study populations will reflect the diversity of our nation. Electronic health records and increased patient access to them should permit efficiencies in the design and conduct of trials and permit longer term follow up. Trials, particularly implementation trials, will be more easily done in all parts of our healthcare system and in a larger number of our communities. Advances in portable electronic sensors should also allow us to collect data more quickly and more comprehensively and better define the dynamic interactions between the environment and the individual and their biology. As successful as our past investments in trials have been, the future should be even more productive.

**Implementation Research in Hypertension**

In spite of the remarkable advances that have been made in basic, clinical, and population science research, more than half of American men, Hispanics, non-Hispanic Blacks, and non-Hispanic Asians still have uncontrolled hypertension.49 This is particularly challenging because we know that hypertension control rates of 80% and higher are achievable, especially in integrated health systems that use systemic implementation strategies including performance feedback in managing hypertension.50–52 For example, using these strategies, the Kaiser Permanente Southern California healthcare system was able to improve hypertension control in a multiethnic population from 54% to 86% from 2004 to 2012.52 What could we learn from these examples that could be adopted and adapted for sustained implementation in other healthcare settings and in populations without a similar level of health insurance coverage or degree of integrated healthcare delivery? What system-level changes and behavioral interventions at the level of patients and practitioners would lead to greater hypertension control? How do we best identify and support rigorous implementation research studies that help pave the way for increased uptake and sustained adoption of evidence-based prevention, treatment, and control of hypertension? Strategic partnerships are needed to identify and address gaps in research evidence and gaps in implementation of evidence-based guidelines and recommendations for the prevention, treatment, and control of hypertension.

**A Vision for the Future of Hypertension Research**

The NHLBI remains committed to our collective effort to create a future for hypertension research built on the legacy of remarkable successes of our funded investigators and guided by our enduring principles. Important among the enduring principles are the commitment to continue valuing investigator-initiated fundamental discovery science; maintaining a balanced, cross-disciplinary portfolio of basic, translational, clinical, and population science research; training a diverse new generation of leaders in science; supporting implementation science that empowers patients and enables partners to improve the health of the nation; and innovating an evidence-based effort to eliminate health inequities in the United States and around the world. As the NHLBI prepares to build on this legacy of research in the next decade, the Institute looks to its investigator community to identify mission-oriented strategic priorities and help chart this future together.9

What if we could unravel the molecular basis of resilience that enables some individuals to maintain normotension in the face of environmental drivers and conditions that lead to hypertension in others? Such insights are beginning to emerge and could inspire the future generation about clinical interventions to prevent or treat hypertension.53 What if we could leverage advances in transomics and precision medicine to refine precision treatments for hypertension? What if we could effectively integrate information from genomics, phenotyping, and biomarkers to understand the molecular pathways of hypertension to predict individual risk of hypertension, tailor the treatments, and preempt end-organ complications?

The research endeavors needed for a deeper understanding of an individual’s hypertension could unmask the basis for distinct individual clinical phenotypes and, thus, seem prime for the new National Institutes of Health Precision Medicine initiative. Many data sets and other resources are already available to investigators through existing NHLBI clinical data repositories, such as the Biological Specimen and Data Repositories Information Coordinating Center,54,55 and more are being planned through new programs, such as TransOMics for Precision Medicine Program.56 The opportunity to tackle compelling questions and critical challenges in hypertension research has never been greater! We look forward to charting this future together.9

**Disclosures**

None.

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Correction to: Building on a Legacy of Hypertension Research: Charting Our Future Together

In the article by Mensah et al, “Building on a Legacy of Hypertension Research: Charting Our Future Together,” which published online on November 14, 2016, and appeared in the January 2017 issue of the journal (Hypertension. 2017;69:5–10. DOI: 10.1161/HYPERTENSIONAHA.116.06582), a correction is needed.

On p 7, Clinical Trials, right column, “120 to 140 mm Hg” in the sentence “In addition to challenging the widely accepted blood pressure treatment targets, this study should also inspire the scientific community to identify the molecular mechanisms that may be responsible for the significant cardiovascular health benefits and secondary effects of a lowered blood pressure goal from 120 to 140 mm Hg.” has been changed to read, “In addition to challenging the widely accepted blood pressure treatment targets, this study should also inspire the scientific community to identify the molecular mechanisms that may be responsible for the significant cardiovascular health benefits and secondary effects of a lowered blood pressure goal from 140 to 120 mm Hg.”

The authors apologize for this error.

This correction has been made to the current online version of the article, which is available at http://hyper.ahajournals.org/content/69/1/5.