

A HALF-CENTURY OF PROGRESS IN HEALTH: THE NATIONAL ACADEMY OF MEDICINE AT 50

## Conquering Atherosclerotic Cardiovascular Disease — 50 Years of Progress

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One of the most important biomedical success stories of the past half-century in the United States has been a 50% reduction in cardiovascular mortality. This progress reflects the

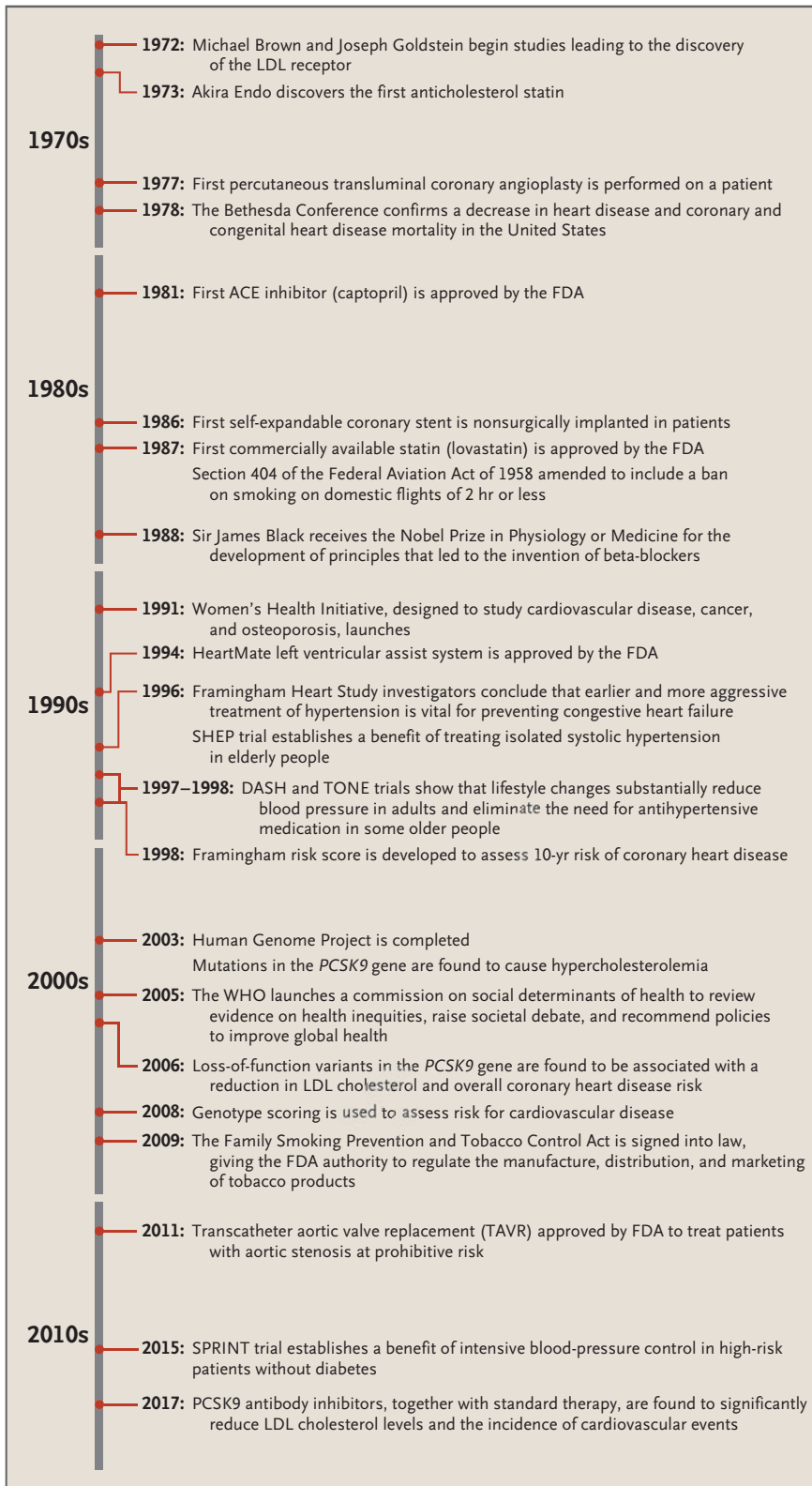
power of a system that facilitates the cross-disciplinary interchange of scientific ideas and catalyzes the integration of basic science, translational research, technological innovation, evidence-based public policy, and public health practice.

During the first half of the 20th century, advances in science and public health led to a dramatic decline in infectious diseases. This achievement provided a backdrop for the gradual emergence of cardiovascular disease as the new leading cause of death in the United States. As the death toll from cardiovascular disease climbed to a peak in the mid-

1960s, findings from clinical and epidemiologic research began to elucidate sex-specific differences in its natural history. After launching in 1948, the Framingham Heart Study — the first large-scale, multigenerational study of cardiovascular risk in the United States — led to the identification of major risk factors for cardiovascular disease, including smoking, high cholesterol, hypertension, physical inactivity, and diabetes. The rapid translation of these findings into public policy and public health campaigns resulted in a substantial reduction in exposure to tobacco smoke and in hypertension treatments that

accelerated the decrease in deaths from cardiovascular disease. Support from public and private investments and initiatives, such as the Dietary Reference Intakes series published by the Institute of Medicine, now called the National Academy of Medicine (NAM), have bolstered this progress by serving a foundational role in federal and state food and nutrition programs and policies. This process of translating discovery science into public health benefits established a model of primary prevention of cardiovascular disease based on risk stratification — a cornerstone of biomedical research and public health practice.

Biomedical progress against infectious diseases was driven by the paradigm of Koch's postulates, which established that identifying a disease's causative agent



### Key Milestones in the Past 50 Years of Progress against Atherosclerotic Cardiovascular Disease.

ACE denotes angiotensin-converting enzyme, DASH Dietary Approaches to Stop Hypertension, FDA Food and Drug Administration, LDL low-density lipoprotein, PCSK9 proprotein convertase subtilisin–kexin type 9, SHEP Systolic Hypertension in the Elderly Program, SPRINT Systolic Blood Pressure Intervention Trial, TONE Trial of Nonpharmacologic Interventions in the Elderly, and WHO World Health Organization.

is an important prerequisite for developing therapeutic interventions. Yet the causative factors involved in chronic, age-related disorders such as cardiovascular disease remained poorly understood. It's in this context that key mechanistic insights were gained through the lens of molecular genetics. Early insights were gleaned from the study of familial clusters of dyslipidemias and people with extreme phenotypes, such as children with myocardial infarctions. The characterization of heritable forms of early-onset cardiovascular disease enabled Michael Brown, Joseph Goldstein, and others to elucidate the causal role of low-density lipoprotein (LDL) cholesterol metabolism in the development of atherosclerosis (see timeline). Their Nobel Prize–winning work characterizing the LDL receptor and Akira Endo's identification of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase as an amenable drug target were an important chapter in the cardiovascular disease success story.

The gradual bench-to-bedside translation of these findings involved a robust portfolio of large-scale, randomized clinical trials, something the field of cardiology widely embraced, years before

other scientific fields did so. The results of these trials collectively provided definitive evidence that reducing LDL cholesterol levels prevents myocardial infarctions, thereby closing the causal loop of Koch's postulates for the LDL cholesterol hypothesis.<sup>1</sup> This milestone, which led to the development of multiple effective cholesterol-lowering drugs, illustrates the power of collaboration between public and private entities to link discovery science with clinical practice. This group of molecular-genetics studies, basic biochemical investigations, cohort studies (e.g., the Dallas Heart Study), and clinical trials also collectively identified the *PCSK9* gene as another molecular mediator of LDL cholesterol metabolism and determined that *PCSK9* inhibition significantly reduces rates of myocardial infarctions and strokes.<sup>2</sup>

Although cardiovascular disease is often conceptualized as affecting the elderly, it has become increasingly clear that the antecedents of atherosclerosis begin in utero and evolve throughout the lifespan, depending on genetic predisposition and, to a larger extent, behavioral factors and exposures. Ongoing progress in molecular genetics has led to the creation of polygenic risk scores that capture the collective effects of many heritable inputs that portend a high-risk trajectory for cardiovascular disease. Combining this increased understanding of risk with the long history of research on the advantages of controlling hypertension and the development of drugs for this purpose permits preemption and prevention of disease.

Advances in vascular biology

have further informed the LDL cholesterol hypothesis by defining critical interactions between the immune system and vascular cells that create a complex molecular environment during atherosclerotic plaque progression. The multiple molecular networks activated by oxidized lipids, proinflammatory cytokines, and prothrombotic factors can induce important changes in the plaque (e.g., rupture or erosion) that trigger acute coronary syndromes.<sup>3</sup> A key component of the cardiovascular disease success story has involved the progressive development of treatments for acute coronary syndromes, including fibrinolytic and antiplatelet agents and percutaneous coronary intervention; diagnostic tools that permit direct imaging of the vasculature, such as intravascular ultrasound technology; interventions that alter the vasculature, such as coronary bypass surgery and stents; and therapeutics that selectively modulate the prothrombotic and proinflammatory plaque milieu.


The trajectory of cardiovascular disease is shaped by the interaction between polygenic factors and environmental influences. Longitudinal studies have provided evidence that during childhood and early adulthood, exposure to neighborhood-level factors such as social deprivation and racial segregation, limited access to a healthy diet, lack of opportunities for regular exercise, and suboptimal health care can affect the trajectory of cardiovascular disease over the life course. The influence of social determinants of health and the exacerbation of health inequities have prevented further progress against cardio-

vascular disease.<sup>4</sup> Addressing inequities will be an important next step in efforts to alleviate the burdens of cardiovascular disease. This step will require a collective approach involving academic researchers, clinicians, and many other partners that engages the community to test strategies for achieving optimal uptake and continued sustainability of proven interventions.

As biomedicine enters the age of precision health, we anticipate that genomic science will continue to expand our understanding of the biologic systems and molecular networks that mediate the development and clinical manifestation of cardiovascular disease. New methods of immune phenotyping and "multi-omic" characterization of the epigenome, transcriptome, metabolome, and microbiome will probably accelerate the discovery of biomarkers and the identification of new targets for therapeutic intervention. We also expect that investigators will advance our understanding of the ways in which the social determinants of health "get under the skin" to modulate the epigenome and other biologic systems to promote resilience or accelerate disease development. We look forward to the development of biomarkers, personal sensor technology, and artificial-intelligence apps that will continuously monitor biologic systems, permit real-time implementation of personalized dietary recommendations, and reinforce the importance of healthy lifestyle habits for the prevention of cardiovascular disease.

We envision that the next chapter of this story will involve building on advances in genomics,

systems biology, and data sciences to better predict cardiovascular disease onset in early adulthood. In contrast to the current focus on slowing the progression of advanced plaques after middle age, future therapeutic options should be targeted at earlier stages of the disease process, with the intent of preempting the progression of cardiovascular disease. Recent proof-of-concept studies have demonstrated the feasibility of *in vivo* genetic engineering with nanoparticle-delivery technology to introduce PCSK9 mutations with salutary effects within the liver that cause sustained reductions in LDL cholesterol levels. The next

 **An audio interview with Dr. Gibbons is available at NEJM.org**

50 years of efforts to conquer cardiovascular disease will probably leverage new tools and technologies, from biologics and small-molecule drugs to preventive strategies including genome editing. This endeavor will require a multilevel, systems-based approach to preempt disease at its earliest stages and exert a long-term, cumulative benefit throughout the lifespan.

The past half-century of progress in alleviating the burdens of cardiovascular disease gives us great optimism as we look ahead to emerging opportunities to further enhance cardiovascular health. Achieving this goal will require disciplined and continuous re-investment in discovery science, translational research, and development leading to interventions that benefit public health. This cycle enriches our understanding of the causal factors of disease — both molecular mediators and social factors — as powerful targets of action for improving patient care and public health. There will be a persistent need for advances in the science of health delivery to develop innovative strategies that propel people to adopt healthier lifestyle habits, prompt communities to make structural investments to support healthier neighborhoods, and promote the effective adoption of evidence-based solutions in various real-world contexts. As the NAM pursues scientific advances during the next five decades, the success story won't be complete until cardiovascular dis-

ease no longer represents an important cause of morbidity or death.

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## Reform of Payment for Primary Care — From Evolution to Revolution

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Reforming payment for primary care has been on policymakers' agendas for well over a decade. The impetus derives from primary care's foundational role in a high-value health system and from troubling declines in the financial viability of primary care practices. Recent sur-

veys found that 20 to 40% of respondents from primary care practices were considering sale, permanent closure, or consolidation, with safety-net practices appearing especially vulnerable. Moreover, primary care's share of total U.S. health expenditures continues to decrease. In this con-

text, questions about how best to pay for primary care, how much to pay, and how rapidly change needs to be implemented have reemerged as urgent considerations.

Fee for service (FFS) persists as the predominant method of paying for primary care in the