

# A Tale of Coronary Artery Disease and Myocardial Infarction

Elizabeth G. Nabel, M.D., and Eugene Braunwald, M.D.

The remarkable facts, that the paroxysm, or indeed the disease itself, is excited more especially upon walking up hill, and after a meal; that thus excited, it is accompanied with a sensation, which threatens instant death if the motion is persisted in; and, that on stopping, the distress immediately abates, or altogether subsides; have . . . formed a constituent part of the character of Angina Pectoris.<sup>1</sup>

From Brigham and Women's Hospital and Harvard Medical School, Boston, MA. Address reprint requests to Dr. Nabel at Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at enabel@partners.org.

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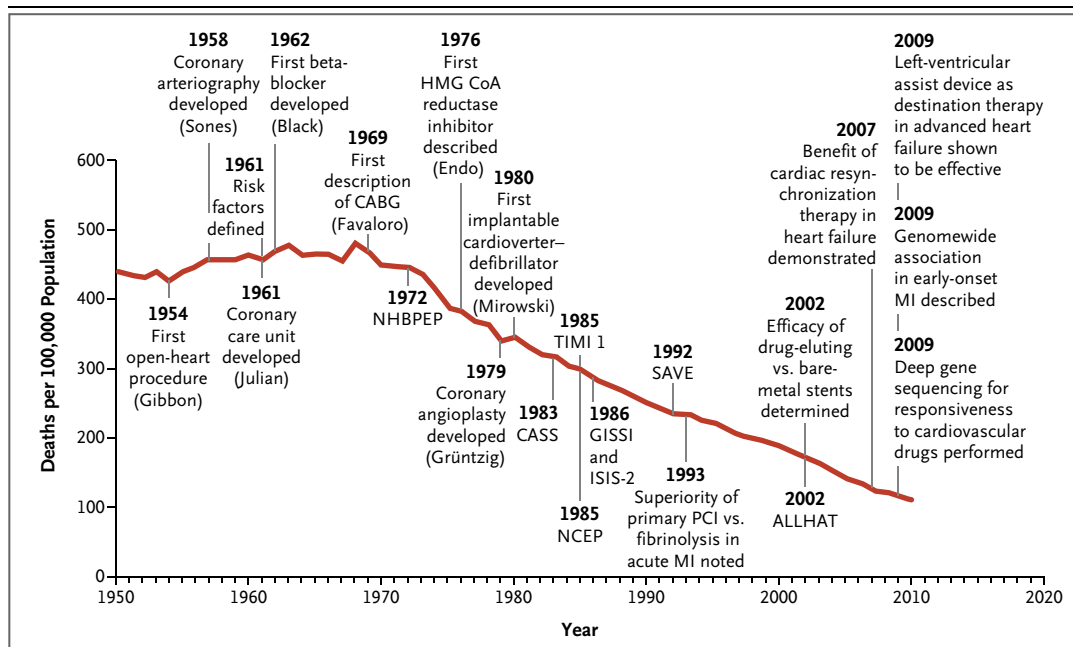
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“REMARKS ON ANGINA PECTORIS” BY JOHN WARREN, M.D., APPEARED IN 1812 as the first article in the first issue of *The New England Journal of Medicine and Surgery*.<sup>1</sup> Warren’s description of angina pectoris (derived from the Latin *angina*, “infection of the throat”; from the Greek *ἀγχόνη*, “strangling”; and from the Latin *pectus*, “chest”) is equally apt for physicians and medical students today. At the time, the pathogenesis was unknown, and treatment consisted of bloodletting, a tincture of opium, bed rest, or a combination thereof. In 1799, Caleb H. Parry speculated that Syncope Anginosa was related to coronary-artery ossification (i.e., calcification), occurring predominantly in men at about 50 years of age and rarely in women or children.<sup>2</sup>

Medical knowledge in the 18th and 19th centuries was grounded in clinical observation and anatomical dissection. Cardiovascular science emerged in the physiological era of the late 19th and early 20th centuries, first in Europe and subsequently in North America. To celebrate the 200th anniversary of the *New England Journal of Medicine*, our essay focuses on the themes of coronary artery disease and myocardial infarction to highlight the interplay between science and medicine, emphasizing how the remarkable advances in our understanding of the pathogenesis of heart disease have produced life-saving and life-extending therapies.

## THE EMERGENCE OF CORONARY ARTERY DISEASE

After Heberden’s clinical description of angina<sup>3</sup> in 1772, it took almost a century for pathologists to focus their attention on the coronary arteries and describe thrombotic occlusions in addition to “ossification.” However, for decades thereafter, these observations were not related to the symptoms of myocardial ischemia, which had become well known to physicians. Near the end of the 19th century, cardiovascular physiologists noted that occlusion of a coronary artery in the dog caused “quivering” of the ventricles and was rapidly fatal.<sup>4,5</sup> These three great branches of medical knowledge — clinical medicine, pathology, and physiology — advanced in separate yet parallel universes. In 1879, the pathologist Ludvig Hektoen concluded that myocardial infarction is caused by coronary thrombosis “secondary to sclerotic changes in the coronaries.”<sup>6</sup> In 1910, two Russian clinicians who were trained in pathology described five patients with the clinical picture of acute myocardial infarction, which was confirmed at postmortem examination.<sup>7</sup> Two years later,



**Figure 1. Decline in Deaths from Cardiovascular Disease in Relation to Scientific Advances.**

The timeline shows the steady decline in cardiovascular deaths over the late 20th and early 21st centuries, along with major advances in cardiovascular science and medicine. ALLHAT denotes Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, CASS Coronary Artery Surgery Study, GISSI Italian Group for the Study of Streptokinase in Myocardial Infarction, HMG-CoA 1-hydroxy-3-methylglutaryl coenzyme A, ISIS-2 Second International Study of Infarct Survival, MI myocardial infarction, NCEP National Cholesterol Education Program, NHBPEP National High Blood Pressure Education Program, PCI percutaneous coronary intervention, SAVE Survival and Ventricular Enlargement, and TIMI 1 Thrombolysis in Myocardial Infarction 1.

James B. Herrick emphasized total bed rest as the treatment for this condition<sup>8</sup> and by 1919 had used electrocardiography to diagnose it.<sup>9</sup> These approaches were the standard of care for patients with myocardial infarction until the mid-20th century.

#### CORONARY RISK FACTORS

Two seminal developments in the 1960s radically changed our understanding and management of acute myocardial infarction, which struck down and killed or greatly impaired apparently healthy men in their 40s or 50s, during their most productive years. One of the first acts of the National Heart Institute, later renamed the National Heart, Lung, and Blood Institute (NHLBI), was to establish the Framingham Heart Study in 1948, which involved the close collaboration of professionals from three disciplines: clinical cardiology, biostatistics, and epidemiology. Their goal was to understand how heart disease developed by studying the lifestyles of the residents of Framingham, Massachusetts. The first descrip-

tion of their findings, “Factors of Risk in the Development of Coronary Heart Disease,”<sup>10</sup> indicated that elevations in blood pressure and cholesterol levels were associated with an increased incidence of ischemic heart disease and acute myocardial infarction. The study also showed a high frequency of myocardial infarction among women, which often occurred later in life than it did in men. The identification of elevated blood pressure and cholesterol levels as risk factors and the institution by the NHLBI of national programs to educate clinicians and the public about the importance of controlling these risk factors have contributed to dramatic improvements in age-adjusted cardiac death rates (Fig. 1).<sup>11</sup> (See the timeline in the Supplementary Appendix, available with the full text of this article at NEJM.org.) With the identification of these coronary risk factors and others that followed, the veil that masked the underlying mechanisms in angina and myocardial infarction was lifted, and the concept that coronary heart disease and its complications could be prevented was introduced. Increasingly large multicenter clini-

cal trials subsequently showed that both primary and secondary prevention was possible when steps were taken to lower blood pressure and serum total cholesterol. Fortunately, drugs to reduce these risk factors safely became available as a result of a series of productive collaborations between industry and academic medicine.

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#### CORONARY CARE UNITS

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Until 1961, patients with acute myocardial infarction — if fortunate enough to survive until they reached a hospital — were placed in beds located throughout the hospital and far enough away from nurses' stations that their rest would not be disturbed. Patients were commonly found dead in their beds, presumably from a fatal tachyarrhythmia. Indeed, the risk of death occurring in the hospital was approximately 30%. The development of the coronary care unit,<sup>12</sup> which provided continuous monitoring of the electrocardiogram, closed-chest cardiac resuscitation, and external defibrillation, reduced in-hospital mortality by half among patients admitted with acute myocardial infarction.

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#### PHYSIOLOGY, CARDIAC CATHETERIZATION, ANGIOPLASTY, AND SURGERY

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The publication of *De Motu Cordis* in 1628, William Harvey's seminal description of the circulation and the function of the heart,<sup>13</sup> set the stage for the physiological era several centuries later. The 19th-century French physiologist Claude Bernard catheterized animals and measured the pressures in the great vessels and cardiac chambers.<sup>14</sup> This experiment led to the first human cardiac catheterization, performed by Werner Forssman — on himself — in 1929,<sup>15</sup> which in turn led to the exploration of cardiac hemodynamics by André Frédéric Cournand and Dickinson W. Richards.<sup>16</sup> All three of these investigators were awarded the Nobel Prize in Physiology or Medicine in 1956.

Cardiac catheterization paved the way for the development of coronary arteriography in 1958.<sup>17</sup> When combined with left ventriculography, the use of this imaging technique allowed clinicians to elucidate the natural history of coronary artery disease. Coronary arteriography and left ventriculography became the standard diagnostic

tool for defining pump function and vessel anatomy and provided the foundation for surgical treatment by means of coronary revascularization. The development and refinement of the technique of open-heart surgery required close collaborations among surgeons, engineers, cardiologists, anesthesiologists, and hematologists.<sup>18</sup> The field of invasive cardiology soon emerged, built on the pioneering work of Dotter and Judkins, although Andreas Grüntzig is considered the father of percutaneous interventional cardiology (Fig. 2).<sup>19</sup> The initial technique of balloon angioplasty was followed by the insertion of bare-metal stents, and today, drug-eluting stents are used to prevent coronary restenosis.<sup>20</sup> Once again, cross-disciplinary collaborations, this time among engineers, cardiologists, radiologists, and pathologists, forged remarkable advances in terms of improved vascular devices and techniques. Obstructions in the heart and circulation can now be successfully opened, and abnormal openings successfully closed, in the catheterization laboratory.

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#### MODERN THERAPY

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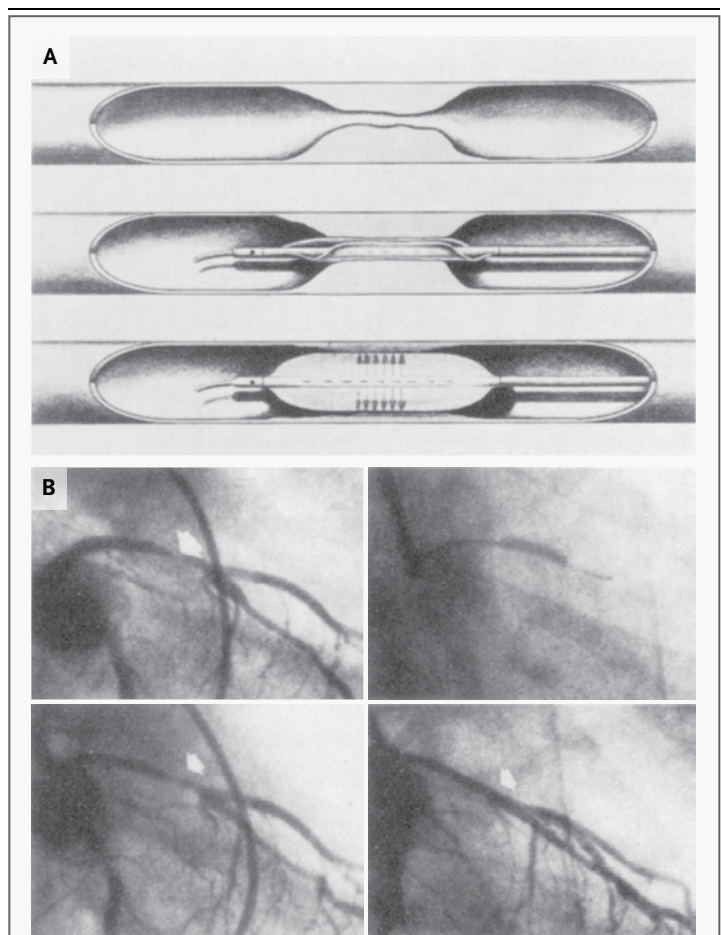
By the 1970s, in-hospital mortality from acute myocardial infarction was approximately 15%, and in the first year after hospital discharge, roughly 10% of patients died from left ventricular failure associated with large infarctions. Studies in laboratory animals suggested that infarct size could be reduced by rectifying the imbalance between myocardial oxygen supply and demand.<sup>21</sup> In 1976, cardiologists were able to open acutely occluded coronary arteries by intracoronary infusion of the fibrinolytic agent streptokinase.<sup>22</sup> The Italian Group for the Study of Streptokinase in Myocardial Infarction (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) (GISSI) trial, one of the first cardiac "mega-trials" (involving more than 10,000 patients), showed that intravenous streptokinase reduced early mortality in patients with acute myocardial infarction.<sup>23</sup> The Second International Study of Infarct Survival (ISIS-2) showed that the addition of aspirin (an antiplatelet drug) led to further reductions in mortality.<sup>24</sup> Coronary angioplasty and stenting,<sup>25</sup> together with newer, more potent platelet inhibitors (e.g., P2Y<sub>12</sub> and glycoprotein IIb/IIIa platelet-receptor blockers), further reduced in-hospital mortality to about 7%. The efficacy of

these treatments, including ventricular defibrillation, depends on a short interval between the onset of symptoms and the patient's arrival at the hospital. Considerable progress has been achieved since the 1970s through massive public and professional education programs led by partnerships among the NHLBI, the American Heart Association, and the American College of Cardiology. It was also in this era that randomized, controlled clinical trials became the paradigm for the advancement of clinical cardiovascular therapeutics.

Based on studies in animals showing the benefits of angiotensin-converting-enzyme inhibitors in experimentally induced myocardial infarction, the Survival and Ventricular Enlargement (SAVE) trial showed that long-term administration of these inhibitors reduced mortality among patients with left ventricular dysfunction after infarction.<sup>26</sup> The use of beta-adrenergic blockers and aldosterone blockers in these patients further reduced mortality. Despite these notable advances, however, life-threatening heart failure still occurs late in patients with extensive ventricular scarring as a consequence of large infarcts. Implantable defibrillators,<sup>27</sup> cardiac resynchronization therapy with pacemakers,<sup>28</sup> and left ventricular assist devices<sup>29</sup> have improved the prognosis for such patients. Cardiomyocytes from patients with severe heart failure have been found to be deficient in sarcoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA2a). In a pilot study, an adeno-associated virus has been used to deliver the gene for SERCA2a by intracoronary infusion, with seemingly beneficial results.<sup>30</sup>

#### UNSTABLE ANGINA AND NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

In the late 1930s, alert clinicians called attention to what we now refer to as unstable angina and non-ST-segment elevation acute coronary syndrome. Patients with this disorder have severe anginal pain, usually at rest, often with biochemical evidence of some myonecrosis and severe, multivessel, obstructive coronary artery disease. These patients now outnumber those with ST-segment elevation myocardial infarction by about 3 to 1 and account for about 1 million hospital admissions yearly in the United States. Patients with non-ST-segment elevation acute coronary syndrome have improvement with prompt coro-



**Figure 2. Percutaneous Coronary Angiography and Intervention in the Treatment of Arterial Stenosis.**

Panel A shows the technique of percutaneous transluminal coronary angioplasty, as pioneered by Andreas Grüntzig in 1979, and the catheter used in the procedure. To treat stenosis of the coronary artery (top image), the catheter is introduced over a guidewire, passed across the lesion (middle image), and then inflated, dilating the artery (bottom image). Panel B shows severe stenosis of a left anterior descending artery as revealed on coronary angiography (arrow in upper left image). After angioplasty was performed (upper right and lower left images), repeat coronary angiography 4 weeks later showed improved patency of the artery (arrow in lower right image). (Reprinted from Grüntzig et al.<sup>19</sup>)

nary revascularization and require inhibition of the two clotting-system pathways with aspirin and a platelet P2Y<sub>12</sub>-receptor antagonist (e.g., clopidogrel), together with an anticoagulant (low-molecular-weight heparin). Their course after hospital discharge is improved by an intensive reduction in low-density lipoprotein (LDL) cholesterol levels<sup>31</sup> and administration of an anticoagulant.<sup>32</sup> The latter advance is reported in this issue of the *New England Journal of Medicine*,<sup>32</sup> high-

lighting that after 200 years, the clinical problems of coronary artery disease and myocardial infarction are still being actively investigated and reported in the *Journal*.

#### CORONARY ATHEROSCLEROSIS

The ability to access vascular and cardiac tissue rapidly led to the development of animal models of vascular disease, as well as clinical studies in humans. Two lines of investigation in the 1970s and 1980s forged the field of vascular biology: the observations that thrombotic occlusion of a ruptured or eroded atherosclerotic plaque led to acute myocardial infarction<sup>33</sup> and that nitric oxide was a physiological dilator of blood vessels, a discovery for which Furchgott, Ignarro, and Murad received the 1998 Nobel Prize in Physiology or Medicine (Fig. 3A).<sup>34,36-38</sup> This pioneering work transformed our understanding of the cellular interactions in both normal and diseased blood vessels and influenced the direction of subsequent research. Investigators shifted their attention from animal preparations of intact vessels to molecular and cellular regulation and, ultimately, to the genes that encode the growth factors, enzymes, other proteins, and RNAs responsible for the development of normal or diseased vessels.

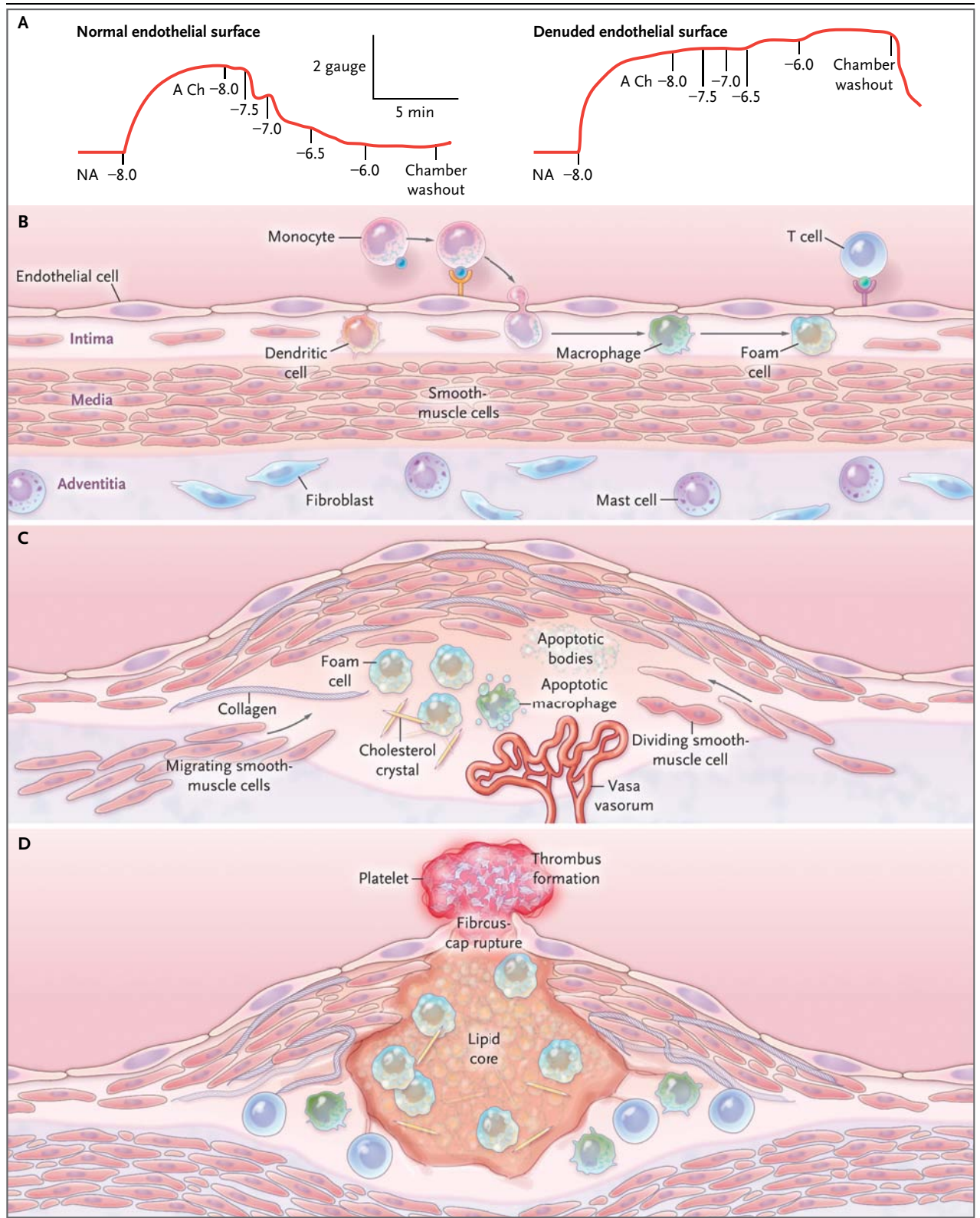
On the basis of these and other studies, we now understand that atherosclerosis is a chronic inflammation of arteries, which develops over decades in response to the biologic effects of risk factors (Fig. 3B).<sup>34,39,40</sup> Atherogenesis begins as a qualitative change to intact endothelial cells; when subjected to oxidative, hemodynamic, or biochemical stimuli (from smoking, hypertension, or dyslipidemia) and inflammatory factors, they change their permeability to promote the entry and retention of blood-borne monocytes and cholesterol-containing LDL particles. Inflammation and biochemical modifications ensue, causing endothelial and smooth-muscle cells to proliferate, produce extracellular matrix molecules, and form a fibrous cap over the developing atheromatous plaque. Plaques lead to clinical symptoms by producing flow-limiting stenoses (causing stable angina) or by provoking thrombi that interrupt blood flow on either a temporary basis (causing unstable angina) or a permanent one (causing myocardial infarction). Physical disruption (rupture) of the plaque ex-

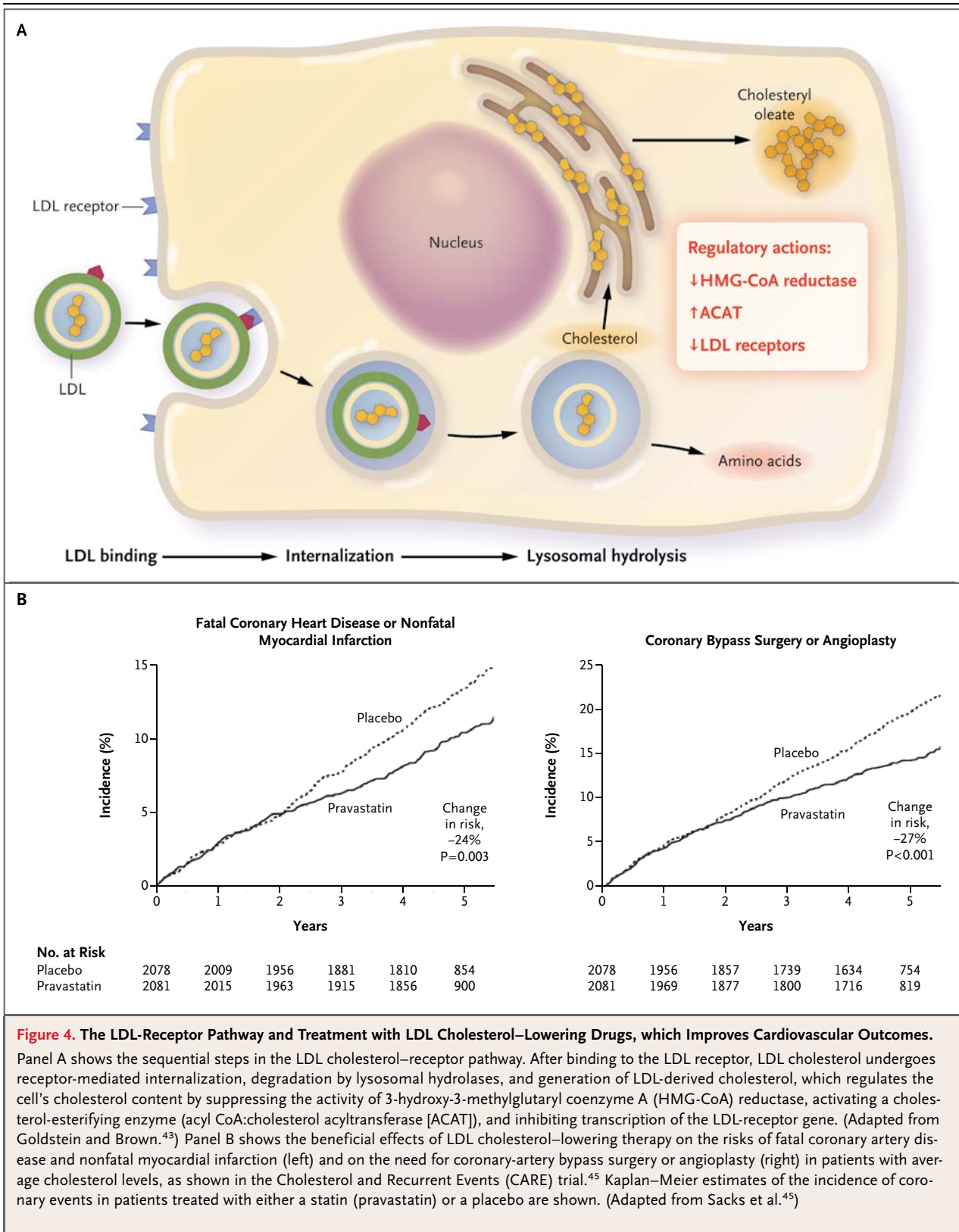
#### Figure 3 (facing page). Discoveries in Vascular Biology Pertaining to Atherosclerosis.

In Panel A, endothelium-derived nitric oxide was found to relax arterial smooth muscle. A rabbit aortic strip was suspended in a muscle chamber, attached to a strain gauge, and exposed to increasing molar concentrations of acetylcholine (A Ch). This led to release of nitric oxide by endothelial cells that acted on smooth-muscle cells to cause vasodilation (left). The strip was then denuded of endothelial cells by mechanical rubbing, and A Ch was applied in equivalent molar doses. In the absence of endothelial cells, nitric oxide was not released, leading to vasoconstriction by smooth-muscle cells (right). (Adapted from Furchgott and Zawadzki.<sup>34</sup>) Panels B through D show the stages in the development of atherosclerosis. The initial steps include adhesion of blood leukocytes to a monolayer of activated endothelial cells, migration of bound leukocytes into the intima, and maturation of monocytes into macrophages and their uptake of lipid, yielding foam cells (Panel B). Lesions progress as smooth-muscle cells migrate from the media to the intima, the resident intimal and media-derived cells proliferate, and extracellular matrix macromolecules are synthesized. Lipid, cholesterol crystals, and microvessels accumulate in the central region of the plaque, forming a necrotic core (Panel C). Thrombosis complicates physical disruption of the atherosclerotic plaque. Fracture of the cap exposes blood coagulant components to tissue factors in the plaque, triggering occlusive thrombus formation that limits blood flow (Panel D). NA denotes noradrenaline. (Adapted from Libby et al.<sup>35</sup>)

poses procoagulant material within the core of the plaque to coagulation proteins and platelets, triggering thrombosis.<sup>41</sup>

Evidence of the causative role of LDL cholesterol in atherosclerosis is threefold: first, genetic mutations that impair receptor-mediated removal of LDL cholesterol from plasma cause fulminant atherosclerosis; second, animals with low LDL-cholesterol levels have no atherosclerosis, whereas increasing these levels experimentally leads to disease; and third, human populations with low LDL-cholesterol levels have minimal atherosclerosis, and the process increases in proportion to the level of LDL cholesterol in the blood.<sup>42,43</sup> A remarkable victory for patients with coronary artery disease came when the LDL-cholesterol pathway was delineated<sup>43,44</sup> (Fig. 4A) and the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), discovered by Akira Endo,<sup>46</sup> was developed to lower LDL-cholesterol levels. Brown and Goldstein's discovery of the LDL-receptor pathway,<sup>44</sup> for which they were awarded the 1985 Nobel





Prize in Physiology or Medicine, provided a genetic cause for myocardial infarction in persons with familial hypercholesterolemia and introduced three general concepts to cell biology: receptor-mediated endocytosis, receptor recycling, and feedback regulation of receptors. This last concept is the mechanism by which statins selectively lower LDL-cholesterol levels in plasma, reducing the risk of myocardial infarction and prolonging life, as shown in multiple, definitive clinical trials (Fig. 4B).<sup>45,47</sup>

However, statin therapy does not eliminate cardiovascular risk.<sup>48,49</sup> Levels of high-density lipoprotein (HDL) cholesterol correlate inversely with cardiovascular risk, but despite considerable improvements in our understanding of HDL cholesterol and its metabolism, none of the pharmacologic agents that raise HDL cholesterol that have been tested so far have had a significant effect on cardiovascular morbidity and mortality. Ongoing clinical trials of agents that raise HDL-cholesterol levels and that have other antiinflammatory and antiatherosclerotic effects are currently under way.<sup>50</sup>

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GENOMICS, CELL-BASED THERAPIES,  
AND MOLECULAR TARGETING —  
THE NEXT FRONTIERS

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Several active areas of investigation hold promise for future advances in cardiovascular science and medicine, including genetics and genomics, molecular targeting, pharmacogenomics, and stem-cell biology and regenerative medicine.

Genetic investigations have led to discoveries of the heritable components of cardiovascular risk factors and coronary artery disease, including studies of families with inherited genetic mutations<sup>51</sup> and genomewide association studies across populations.<sup>52</sup> Multiple chromosomal loci associated with coronary artery disease harbor protein-coding genes known to be important in variations in lipid levels. In addition, associations of single-nucleotide polymorphisms with chemokines suggest that an inflammation pathway may regulate the process of coronary atherosclerosis.<sup>52</sup> To date, the major contribution of these genomewide association studies has been new insights into biologic pathways that were often unsuspected and that underlie the development of cardiovascular disease. These

insights have in turn led to hypothesis-driven research in which molecular, genetic, biochemical, and cellular techniques are used to investigate pathways. Knowledge of molecular pathways is essential to the development of therapeutics, defined conceptually as “molecular targeting.”

Pharmacogenomics applies our understanding of genetic variability in patients' responsiveness to a drug in order to inform clinical decisions about dosing and selection. The anti-coagulant warfarin is a case in point. Genetic variation in *CYP2C9* and *VKORC1*, the two genes that encode the liver proteins required for warfarin metabolism, explains up to 40% of the differences observed among patients in their responses to the same dose of warfarin. The Food and Drug Administration has used this information to revise warfarin labeling in order to allow for genotype-specific dose ranges.<sup>53</sup> In patients with gene variants in the cytochrome P-450 enzyme, *CYP2C19*, the antiplatelet drug clopidogrel is less efficacious and the risk of coronary artery disease is increased.<sup>54</sup> Deep sequencing of the genes related to drug absorption, distribution, metabolism, and excretion may identify specific variants that contribute to the heterogeneity of patients' responsiveness to cardiovascular drugs.

Cell-based therapies ranging from autologous noncardiac cells (e.g., bone marrow, skeletal muscle, fat, and endothelial progenitors) to allogeneic mesenchymal cells and putative resident cardiac progenitors have been studied in preclinical animal models and in early trials in humans, with mixed, yet promising, results.<sup>55-57</sup> A subset of progenitors is mobilized in vivo by paracrine signals in cases of cardiac injury, suggesting that the delivery of such signals to the heart or vasculature may stimulate regenerative tissue.<sup>58</sup>

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GLOBAL CARDIOVASCULAR DISEASE

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Cardiovascular disease, including heart disease and stroke, is the leading cause of death worldwide, including low-income and middle-income countries.<sup>59</sup> Several factors account for the increasing burden of cardiovascular diseases, including a longer average life span, tobacco use, decreased physical activity, and increased con-



sumption of unhealthful foods.<sup>60</sup> New collaborations are under way to address cardiovascular and other noncommunicable diseases by building capacity in health care delivery, research, and training and developing low-cost interventions.<sup>61,62</sup>

## CONCLUSIONS

From John Warren's description of angina pectoris in 1812 as a strangling of the chest vaguely related to ossification of the coronary arteries to our current understanding of the genetic and

molecular basis of coronary artery disease, the pathways of discovery, innovation, and therapeutic advancement in cardiovascular science and medicine over the past two centuries have been truly remarkable. We are now poised to take advantage of scientific opportunities, fueled by the results of rich epidemiologic studies of populations and large, randomized clinical trials evaluating science-based therapeutics, and thus further refine the cardiovascular care of patients around the globe.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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