Coronary Heart Disease in the First 30 Years of the 21st Century: Challenges and Opportunities
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During the past 50 years, there has been an explosion of new knowledge regarding the biological mechanisms of cardiovascular disease. This knowledge and the emergence of new technology and new pharmacological, interventional, and surgical therapies, coupled with lifestyle changes in the American population, have contributed to a spectacular 60% decline in mortality from coronary heart disease (CHD) and stroke. Since 1965, there has been a dramatic and steady decline in CHD deaths. This marked decrease in the mortality rate for CHD can be attributed in part to enhanced survival in patients with an acute myocardial infarction (MI); highly effective secondary prevention measures in patients who have experienced an ischemic event; improved lifestyles in the population, with some progress in primary prevention of CHD; and advances in medical therapy and the emergence of coronary revascularization. With respect to the decline in CHD mortality from 1980 to 1990, 25% can be explained by primary prevention, 29% by secondary prevention, and 72% by the improvements in medical therapy and revascularization; only 3% is unexplained.

Improved Prognosis After Acute MI
Figure 1 depicts a significant decrease in the death rate and case fatality rate for acute MI among persons 45 to 64 years of age in the United States from 1970 through 1995. In Osler’s Textbook of Medicine published in 1892, only 2 pages were dedicated to a discussion of acute MI. This foremost educator of his era wrote, “A complete obliteration of one coronary artery, if produced suddenly, is usually fatal.” It was James B. Herrick (born in 1861) who changed our perception regarding this dire prognosis for patients with acute MI. In his historical article published in the Journal of the American Medical Association in 1912, Herrick stated:

“One may conclude, therefore, from a consideration of the clinical histories of numerous cases, from animal experiments, and from anatomic study that there is no inherent reason why this stoppage of a large branch of a coronary artery or even of a main trunk must of necessity cause sudden death. Rather, it may be concluded that while sudden death often does occur, yet at times it is postponed for several hours or even days, and in some instances, a complete, that is functionally complete, recovery ensues.”

If James B. Herrick were alive today, he would be amazed at how often such a “functionally complete” recovery actually does ensue: it is now the norm rather than the exception.

Prognosis after recovery from MI continues to improve, and much of the progress in recent years can be attributed to postinfarction therapeutic interventions. At the annual meeting of the European Society of Cardiology in Amsterdam in August 2000, Wallentin provided data regarding the effectiveness of 2 of these interventions, early statin therapy and coronary angioplasty, in >22,000 patients with acute MI from the Swedish National Registry of Cardiac Intensive Care. His group found that starting statins in the hospital after MI reduced 1-year mortality by 34%. Early coronary revascularization reduced mortality by 36%. The combination of starting statins in the hospital and coronary angioplasty reduced mortality by a remarkable 64%. Another recent study showed a 25% reduction in 1-year mortality when statins were started in the hospital for acute MI patients.

Improving Survival After Acute MI
We can still do better to improve survival after acute MI. More expansive and effective out-of-hospital defibrillation for potential sudden death victims and preventing delays to initial reperfusion therapy must be accomplished. More effective (ie, TIMI 3 flow) and earlier opening of an occluded infarct vessel and more potent adjunctive therapies in the acute phase of MI to salvage jeopardized myocardium and to prevent infarct vessel reocclusion need to be developed. Some have advocated out-of-hospital fibrinolysis only when a physician is present or out-of-hospital time is ≥60 minutes. In the future, out-of-hospital pharmacological reperfusion and antithrombotic therapy may become more feasible to administer in most patients with acute MI. Pharmacological therapy...
other than angiotensin-converting enzyme (ACE) inhibitors and β-blockers that is aimed at attenuating left ventricular remodeling and preventing congestive heart failure must be introducted. In the future, myogenesis therapy to repopulate myocytes in areas of damaged myocardium will certainly be forthcoming. Preliminary data from Dr R. Chiu’s laboratory at McGill University suggest that adult stem cells from the bone marrow injected into the damaged hearts of rats can differentiate into viable heart muscle cells. For patients with severely damaged myocardium, xenotransplantation with hearts from cloned pigs may become feasible. Better mechanical hearts than those previously tested could emerge as long-term alternatives to heart transplantation or more tolerable bridges to transplantation. Noninvasive imaging technologies performed in conjunction with exercise or pharmacological stress to identify high-risk postinfarction patients who may benefit from invasive strategies are being perfected. Also, additional secondary prevention measures to retard or reverse the underlying atherosclerotic process and to prevent the rupture of vulnerable plaques to enhance long-term survival are currently under investigation.

Reduction of prehospital deaths must be accomplished to make further major inroads with respect to reducing mortality in patients with acute MI. Such deaths comprise >50% of the deaths of patients with acute MI who die in the first 30 days. Prevention of the “no reflow” phenomenon from occurring after reperfusion using better adjunctive therapy is another goal for clinical researchers in the field of acute MI research. Angiographic no reflow, which is defined as TIMI 2 flow or less, predicts long-term mortality after acute infarction. No reflow is associated with subsequent left ventricular remodeling, heart failure, and premature death. Measures to improve outcome with reperfusion are continuing to be reported (Figure 2). As shown in a recent study, as shown in a recent study, the cumulative incidence of death, reinfarction, or stroke was reduced by 34% in patients who received a glycoprotein IIb/IIIa platelet antagonist and underwent coronary stenting compared with those who received thrombolytic therapy with tissue plasminogen activator alone. In the group that received a coronary stent plus abciximab, the median size of the final infarct was 14.3% of the left ventricle, as compared with a median of 19.4% in the thrombolytic therapy alone group. Other pharmacological adjunctive therapies such as adenosine infusion are undergoing clinical trials at the present time.

Although the proportion of acute MI patients developing heart failure during hospitalization has declined substantially since 1975, the 1-year discharge mortality rate for MI survivors with congestive heart failure has not changed in the 20-year period between 1975 and 1995, even after controlling for additional prognostic characteristics. The authors of the study that reported this data concluded that long-term prognosis did not improve over this 20-year period because MI survivors with heart failure in the 1990s are increasingly older and have more comorbidities than postinfarction patients who developed heart failure in the 1970s. The 1-year follow-up of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-III study showed that the 1-year mortality rate in patients who received thrombolytic therapy had increased compared with the mortality rate of patients followed-up in the GUSTO-I trial. They found it “disturbing” that, in light of the more intensive pharmacological interventional after MI with aspirin, statins, β-blockers, and ACE-inhibitors, a 35% increase in late deaths was observed compared with the mortality reported in the 1996 GUSTO-I trial. These data highlight the need for substantially improved postinfarction treatment strategies in the upcoming years to diminish the incidence of heart failure and late cardiac deaths in the MI population that is becoming more elderly and represents a higher-risk group because of significant comorbidities.

Some elderly patients with acute MI are not benefiting from the advances in therapy already implemented in everyday clinical practice. Berger et al. found that less than half of elderly patients considered ideal candidates for reperfusion therapy received primary angioplasty or thrombolysis within 6 hours of hospital arrival. Similarly, the percentage of eligible elderly patients receiving ACE inhibitors for heart failure is suboptimal. Thus, not only must we continue to make new discoveries that improve the survival and quality of life for MI patients, but we also need to implement proven diagnostic and therapeutic strategies better in this patient population.
the number of young individuals with CHD in the United States and worldwide. This is because diabetes increases the risk of CHD 2- to 4-fold. Presently, 10.2 million Americans have diabetes; it is estimated that 5.4 million have undiagnosed diabetes. Two-thirds of these patients will die of heart or blood vessel disease. The risk of diabetes for Mexican-Americans and non-Hispanic blacks is twice that for non-Hispanic whites. For people in their 40s, the incidence of diabetes increased 40% from 1990 to 1998. For people in their 30s, it rose nearly 70%. In 1999 alone, the incidence of diabetes rose an astounding 6% compared with the previous year. By 2025, the number of adults with diabetes will rise to 300 million worldwide compared with 135 million 5 years ago. Diabetes is estimated to increase by 42% in developed countries, but a 170% increase is expected in developing countries, with India and China showing the greatest increase. Today, children as young as 8 years old are being diagnosed with type 2 diabetes. As noted by Dr Richard Kahn, type 2 diabetes was virtually unheard of in children just a decade ago, and now as many as 300 000 children have it. A consensus panel of the American Academy of Pediatrics and American Diabetes Association issued recommendations concerning the prevalence of diabetes among children. The panel noted that type 2 diabetes is an “emerging epidemic” among children. This disorder used to be called “adult-onset diabetes” because of its tendency to emerge in middle age or later. Because of its increased prevalence in children and young adults, it is now simply called “type 2 diabetes” to distinguish it from juvenile diabetes, which is now known as “type 1 diabetes.”

Diabetes and Cardiovascular Outcomes

Diabetes adversely affects cardiovascular outcomes. Diabetics with no clinical evidence of CHD have the same risk for future cardiac death as nondiabetics with a prior infarction. The absolute risk of CHD death at any concentration of cholesterol is 3 to 5 times higher in the presence of diabetes. Diabetes increases the risk of cardiac events and mortality in patients with established CHD. The cardiovascular mortality rate has more than doubled in men and more than quadrupled in women who have diabetes compared with nondiabetics. Diabetics have increased mortality and morbidity after thrombolysis for an acute MI, and they have a worse prognosis with unstable angina and a worse outcome after percutaneous coronary intervention. Figure 4 shows the MI rate in nondiabetics with or without a prior infarction compared with the rate in diabetics with or without a prior infarction. Note that diabetics with or without a prior infarction have a markedly higher risk of a new infarction than do nondiabetics. What is impressive is the observation that 45% of diabetics with a previous infarction will experience a recurrent infarction.

The 2-year prognosis of diabetics who are hospitalized with unstable angina or non-Q-wave MI is significantly worse than nondiabetics. From the prospectively collected data from 6 different countries participating in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry, diabetes independently predicted mortality (relative risk, 1.57), cardiovascular death, new MI, stroke, and new
congestive heart failure. Diabetic patients with no previous cardiovascular disease had the same long-term morbidity and mortality as did non-diabetic patients with established cardiovascular disease after hospitalization for an acute coronary syndrome.35

Diabetics do worse with primary angioplasty than do non-diabetics.36 In one survey, the mortality rate after primary angioplasty, both in-hospital and at 1 year, was ∼2-fold higher for diabetics than for the entire group of patients evaluated (Figure 5). Diabetics in the Bypass Angioplasty Revascularization Investigation (BARI) registry who underwent multivessel coronary angioplasty had a significantly higher all-cause mortality and cardiac mortality at 5 years after revascularization than did patients who were randomized to coronary bypass surgery.37 Cardiac mortality was 23% for diabetics undergoing angioplasty compared with 8% for those undergoing bypass surgery. Recent data have shown that glycoprotein IIb/IIIa platelet receptor antagonists can improve outcomes and reduce subsequent ischemic cardiac events in diabetic patients undergoing percutaneous coronary intervention.38

Great efforts are being made to reduce cardiovascular morbidity and mortality in diabetics with improved medical therapy, and studies like those reported from the Heart Outcomes Prevention Evaluation (HOPE) trial are encouraging.39 In this trial, cardiovascular death was reduced by 37% and total mortality by 24% in diabetics randomized to ramipril therapy compared with placebo. Lowering LDL cholesterol with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) in diabetics with preexisting CHD yields a significant benefit with respect to reduction of subsequent CHD events.40

**Pathophysiology of Type 2 Diabetes and CHD**

Certain concepts have emerged regarding how the pathophysiology of type 2 diabetes leads to cardiovascular disease.41 Saltiel42 outlines the metabolic staging of type 2 diabetes, providing a basis for understanding the mechanism by which this disorder promotes atherosclerosis. As shown in Figure 6, type 2 diabetes begins with peripheral insulin resistance contributed to mainly by obesity. Hyperinsulinemia, a consequence of this insulin resistance, can be detected long before impaired glucose tolerance occurs. Insulin resistance is a common state and is also associated with aging, a sedentary lifestyle, and a genetic predisposition.43 Impaired insulin action and hyperinsulinemia lead to a variety of other abnormalities, including elevated triglycerides, low levels of HDL cholesterol, enhanced secretion of VLDL, disorders of coagulation, increased vascular resistance, central obesity, hypertension, and atherosclerosis. Eventually, pancreatic β-cells can no longer compensate for the insulin-resistant state. This leads to decreased insulin secretion and glucose intolerance. Finally, full-blown β-cell failure and loss of insulin secretion occur, yielding the late diabetes syndrome.

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**Figure 4.** The MI rate in nondiabetics with or without a prior infarction compared with the rate in diabetics with or without a prior infarction. Note that diabetics with or without a prior infarction have a markedly higher risk of a new infarction than do nondiabetics. Data obtained from Reference 31.

**Figure 5.** Mortality rates after primary angioplasty, both in-hospital and at 1 year, are ∼2-fold higher in diabetics than in the entire group of MI patients evaluated. Data obtained from Reference 36.

**Figure 6.** Schematic diagram demonstrating the mechanism of type 2 diabetes (see text for detailed explanation). Reprinted with permission from Reference 42, J Clin Invest. 2000;106:163–164.
Atherosclerosis may develop in young adults who have the early diabetic state of insulin resistance before an increased fasting blood glucose level is detected. McGill et al. quantified the extent of atherosclerosis in the aorta and right coronary artery of persons aged 15 to 34 years who died of external causes. An association between atherosclerotic lesions and elevated glycohemoglobin levels obtained from postmortem blood was observed. The thickness of the panniculus adiposus and body mass index were associated with more extensive fatty streaks in the right coronary artery and aorta. These data and data from other similar studies are indeed disturbing. Because hyperinsulinemia can occur a decade before an elevation of fasting blood glucose, the atherosclerotic process may be well underway before such patients come to the attention of a physician.

The Obesity Epidemic

Epidemiology of Obesity

As depicted in Figure 6, obesity is the major driving force in the development of type 2 diabetes. In the United States, the age-adjusted prevalence of obesity increased by ~30% from 1980 to 1994. Obesity is estimated to account for ~325,000 deaths annually in the United States. Overweight means having a body mass index ≥25 kg/m². Obesity is defined as having a body mass index ≥30 kg/m² (30 pounds overweight). Obesity increased from a prevalence of 14.5% in the US population during the period of 1976 to 1980 to 22.5% from 1994 to 1998. Table 1 shows the marked increase in the prevalence of obesity and weight in US adults from 1991 to 1998. In 1998, 54% of Americans were considered overweight, and 23% were considered obese, with 1 in 10 children being obese. From 1963 to 1990, there was a 42% increase in the prevalence of obesity in children. Over a period of 14 years from 1980 to 1994, the prevalence of obesity in children doubled from 6.5% to 11.4% in children aged 6 to 11 years.

Of great importance is that 60% of overweight children 5 to 10 years of age already have one associated biochemical or clinical cardiovascular risk factor, such as hyperlipidemia, hypertension, or hyperinsulinemia, and 25% have ≥2 risk factors that are observed to lead to CHD in adults. According to Koplan and Dietz, almost 80% of obese adults have diabetes, high blood cholesterol levels, high blood pressure, coronary artery disease, gallbladder disease, or osteoarthritis, and almost 40% have ≥2 of these comorbidities. These figures are indeed frightening, because obesity is associated with an almost 3-fold higher risk of cardiovascular disease mortality and a 2-fold risk of all-cause mortality.

Causes of Increased Obesity

The causes of obesity are related to genetic factors, physical activity, and poor nutrition. The latter is particularly characterized by the increased ingestion of “fast foods” in this country, which are high in both fat and total calories. Genetic factors can be magnified by lifestyle changes with respect to the propensity for developing type 2 diabetes. Japanese Americans have a higher prevalence of type 2 diabetes than do people in Japan. This has been shown to be a consequence of the development of central obesity due to a diet higher in animal fat and decreased physical activity, leading to insulin resistance in the Japanese living in the United States. This occurs in the face of a genetic background of reduced β-cell reserve in all Japanese.

In addition to poor nutrition and genetic factors, physical inactivity plays a major part in the increased incidence of obesity and type 2 diabetes. In the United States, 50% of youth aged 12 to 21 years are not vigorously active on a regular basis. Twenty-five percent of Americans are sedentary, and only 15% of US adults engage in regular physical activity, which is defined as exercising 3 times a week for at least 20 minutes. Inactivity by itself is a risk factor that increases CHD risk. The benefits of physical activity and exercise are shown in Table 2. Benefits include diminished cardiovascular mortality and development of CHD, a lowered blood pressure in hypertensive patients, an increase in insulin sensitivity, prevention of obesity, an elevation of HDL cholesterol, a favorable effect on the fibrinolytic system, enhanced endothelial function, and enhanced parasympathetic activity.

As caregivers, cardiologists have a professional obligation to promote increased, regular physical activity in the population. The importance of physician counseling cannot be overemphasized. It is as important as counseling for better nutrition. Data suggest that only one third of patients are counseled by physicians regarding beginning or continuing an exercise program. Merely counseling obese women to engage in a program of reducing caloric intake to ~1200 kcal/day, to eat a low-fat diet, and to incorporate increased lifestyle activity resulted in health benefits (ie, weight loss...
healthcare costs will increase 41% by 2010 and 54% by 2025. The major driving force for these increased costs will be the growth in the aging of the population. Certainly, costs will rise as a function of the increased prevalence of new cases of CHD contributed to by physical inactivity, obesity, and type 2 diabetes. Contributing to these rising costs will certainly be expensive new technology and new pharmaceuticals for the evaluation and management of the populations of patients with CHD and heart failure.

The Future

The next 30 years presents us with formidable challenges in the continuing battle to reduce the case fatality rate for CHD, the overall prevalence of CHD, and the prevalence of congestive heart failure in the population. Further advances in basic science research and breakthroughs in clinical care for patients with or at risk for CHD will surely emerge. This progress will have enormous impact in reducing death and morbidity from CHD and preventing its occurrence in the first place. A greater emphasis will need to be placed on the primary prevention of CHD, including educating the public on the need to adhere to a heart-healthy diet, incorporating regular physical activity as part of daily life, and preventing the initiation of smoking in our youth. We must ensure that the quality of cardiovascular care becomes more uniform throughout the United States. The issue of whether more cardiologists should be trained in our fellowship programs to meet the needs of the expected increased number of patients with cardiovascular disease. Only 6 years ago, we thought we were training too many cardiology fellows. As the knowledge base in cardiovascular disease continues to grow exponentially, new approaches to disseminating scientific and medical information must be undertaken using innovative electronic online learning technology.

In conclusion, certain predictions can be made with respect to the future.

1. Despite a decrease in mortality rate, the prevalence of CHD and congestive heart failure will increase, as will the costs of health care.
2. An increasing elderly population and the epidemic of type 2 diabetes fueled by physical inactivity and obesity will contribute to the increasing prevalence of CHD in the next 30 years.
3. New technology will be introduced that will be accurate for the preclinical or subclinical detection of coronary atherosclerosis and vulnerable plaques. This will have an impact on the further reduction in coronary events in patients who have atherosclerosis, with or without diabetes.
4. Genetic screening for future risks of diabetes and CHD as an outgrowth of the Human Genome Project and earlier primary prevention measures will hopefully emerge to identify and treat those at high risk for premature CHD.
5. Novel therapeutic interventions for chronic CHD, such as therapeutic angiogenesis and myogenesis (cell therapy), will be introduced that will further decrease

Impact on Increasing Prevalence of CHD on Costs of Health Care

The increasing prevalence of cardiovascular disease being fueled by the epidemics of obesity and type 2 diabetes and the aging of our population will greatly impact the costs of health care. The US healthcare system is the most expensive in the world, with 14% of gross domestic product going to health care in 1998. Expenditures for health care in 1998 totaled ≈$1 trillion. The estimated cost of cardiovascular disease and stroke in 2000 was $326.6 billion (Figure 7). As to cost projections for the future, Steinwachs et al predict that

Figure 7. Estimated direct and indirect costs of cardiovascular diseases (CVD) and stroke in the United States in the year 2000. Reprinted with permission from Reference 20, 2000 Heart and Stroke Statistical Update. Copyright 1999 American Heart Association.
mortality and morbidity from CHD for those patients in whom we cannot prevent the ravages of atherosclerosis.

6. Gene therapy, organogenesis for developing living tissue products, artificial mechanical hearts, xenotransplantation using pig hearts, and products emanating from the new field of nanotechnology will become part of our therapeutic armamentarium.

Although future research and development will bring us new medical discoveries based on progress in technology, we must not forget that less costly, low-tech interventions have already proven effective in preventing CHD and its complications.

I would like to end with a quote from Dr Claude Lenfant’s editorial, “Conquering Cardiovascular Disease: Progress and Promise”: “Although the potential for the fields of molecular biology and genetics to improve identification of persons and populations at risk, to predict the evolution of a disease in a specific patient, and to optimize pharmacological intervention is exciting and worthy of pursuit, physicians must not lose sight of perhaps more mundane but clearly effective approaches such as lowering blood pressure, reducing obesity and physical inactivity, and applying other proven therapeutic strategies (eg, β-blockers, aspirin) in a timely fashion. The real challenge of the new millennium may indeed be to strike an appropriate balance between the pursuit of exciting new knowledge and the full application of strategies that are already known to be extremely effective, but are considerably underused.”

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