Cardiovascular Science in the Service of National Strength

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On October 31, 1940, President Franklin Delano Roosevelt dedicated the new Bethesda, Maryland, campus of the National Institutes of Health. As cardiovascular disease was emerging as the biggest threat to the nation's health, and as threats of war loomed from Europe, Roosevelt declared, "Total defense . . . which the nation seeks, involves a great deal more than building airplanes, ships, guns, and bombs. We cannot be a strong nation unless we are a healthy nation. And so we must recruit not only men and materials but also knowledge and science in the service of national strength."[1]

Nearly 61 years after Roosevelt's dedication, the US government announced the Million Hearts initiative with a goal of preventing 1 million myocardial infarctions and strokes over 5 years "by implementing proven, effective, inexpensive interventions."[2] Centers for Disease Control and Prevention director Thomas Frieden and Centers for Medicare & Medicaid Services administrator Donald Berwick seek to implement the ABCS, namely, aspirin prophylaxis, reduction of blood pressure levels, reduction of cholesterol levels, and cessation of smoking. For each of these interventions, the research enterprise can take credit for discovering the problem and rigorously demonstrating, often through large-scale randomized trials, the value of clinical and public health interventions.

The profound influence of cardiovascular research has been remarkable. Between 1960 and 2000, life expectancy in the United States increased by 7 years, with 70% of the increase attributable to fewer cardiovascular deaths.[3] Improved cardiovascular health can be attributed to "high-technology" medicine, including cardiac surgery, acute revascularization, and defibrillators; "low-technology" medicine, including clinical and community management of blood pressure and cholesterol levels; and behavioral changes, in particular marked reductions in cigarette smoking. For each intervention, researchers played critical roles. Echoing Roosevelt, knowledge and science served admirably to improve national health.

Yet all is not well. Cardiovascular disease remains the leading cause of death in the United States and in most of the world. In the United States, the nature of cardiovascular disease is changing, as the population becomes older, more obese, and more urban with substantial changes in nutrition, work, physical activity, and transportation. The incidence and prevalence of acute ST-segment elevation myocardial infarction and rheumatic heart disease are decreasing while they are increasing for heart failure, degenerative aortic stenosis, peripheral arterial disease, and atrial fibrillation, conditions for which there is much to learn. Clinical cardiology has been criticized, as a recent magazine headline declared that "Cardiac care is a money-making machine that too often favors profit over science."[4] Nearly 90% of professional society recommendations are based on suboptimal evidence.[5] Even though some cardiovascular research has been successful, much more needs to be accomplished.

What is next for cardiovascular research? Several areas are likely to be of major importance.

Biology

The elucidation of the human genome has generated new ideas about pathways of cardiovascular disease. Numerous groups have shown links between the 9p21.3 variant and cardiovascular diseases, perhaps through inflammatory signaling pathways.[6] Other discoveries suggest important roles for microRNA, intestinal microflora, and epigenetic modifications. Each discovery offers myriad novel therapeutic targets. Meanwhile, stem cell technology offers more efficient ways to develop candidate therapies.

New Treatment Models

Current medical management of atherosclerotic disease is based on use of aspirin, β-blockers, inhibitors of the renin-angiotensin axis, and statins. The link between inflammation and cardiovascular risk opens the possibility of benefit from use of potent anti-inflammatory agents, such as methotrexate. Despite disappointments, research groups continue to pursue increasing high-density lipoprotein cholesterol levels as a treatment strategy; others may consider exploiting the PCSK9 variant as an alternate approach to lowering low-density lipoprotein cholesterol levels.

Diagnostic Tests and Imaging

Among all services covered by Medicare, utilization is increasing most rapidly for diagnostic tests and imaging. In

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most cases, cardiovascular tests are adopted in the absence of randomized trial evidence of benefit. Previous experiences, especially in cancer screening, have shown that it is incorrect to assume that a test that predicts clinical events will necessarily prevent them. Leaders in cardiovascular imaging have called for a major shift in the evaluation of novel modalities; there are now at least 3 ongoing major randomized trials of computed tomographic coronary angiography, one of the latest rapidly increasing diagnostic technologies.

New Device Technologies

Cardiovascular medicine has been at the vortex of an explosion of devices and procedures, including stents, implantable defibrillators, biventricular pacemakers, percutaneous aortic valve replacements, cardiac transplants, and repairs of complex congenital lesions. Cardiovascular technologies will likely continue to evolve and in some cases, like sudden death prevention, supersede medical strategies. The major challenge for researchers is to determine how best to assess the clinical value of rapidly changing technologies. Many major devices and procedures have been subjected to large-scale randomized trials, but these trials are increasingly difficult and expensive to conduct, especially within the United States.

Comparative Effectiveness

Many cardiovascular disease management models and technologies are adopted or promoted despite absence of high-quality evidence. Yet there are major unanswered clinical questions. For instance, does screening for coronary disease with calcium scoring prevent major clinical events? Can routine electrocardiography prevent sudden death among young athletes? Is there benefit from using measures of myocardial ischemia to select patients for coronary angiography? Does routine ablation of atrial fibrillation improve long-term clinical outcome? Is there benefit from stenting tight renal artery stenosis in patients with severe hypertension? For some of these issues (myocardial ischemia, ablation of atrial fibrillation, and renal artery stenting), planned or ongoing comparative effectiveness trials promise to provide insights.

Health Services Research, Implementation Science, and Public Health

Cardiovascular medicine may be the "poster child" for the need of implementation science. After publication of a definitive randomized trial, it took 25 years for β-blockers to be routinely prescribed for survivors of myocardial infarction.[7] Less than 50% of statin users are adherent over the long-term.[8] Many patients with hypertension are unaware of their condition or have inadequately controlled blood pressure.[9] Implementation of evidence-based strategies is a legitimate subject for rigorous research. Some researchers have tested novel approaches, like involving barber shops in the management of hypertension.[10] Yet there is considerable controversy about the nation's approach to health services research.

There is also increasing recognition of the need for rigorous public health implementation science. This includes applying findings of behavioral and social science research to prevention; exploring the effects of social networks; evaluating the roles of the food, transportation, and urban design industries; and appreciating that public policy needs to be informed by solid research.

Research Management

Government and industry sponsors spend billions of dollars every year on cardiovascular research, but it is unclear how best to allocate those funds. Many argue that it makes little sense for basic scientists to spend huge amounts of time writing grants. Efforts are under way to restructure translational research, although it is unclear how best to combine public and private resources. The clinical research enterprise is in jeopardy, as clinical trials have become increasingly expensive, complicated, slow, and bureaucratic. Added to these challenges, government and private support for cardiovascular research is shrinking. The most important duty now is to determine how to sustain and transform the national commitment to cardiovascular research during difficult economic times. Otherwise, the cardiovascular research and clinical community will not be able to answer President Roosevelt's call for total defense.

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