

VASCULAR DISEASE: ONGOING NATIONAL INSTITUTE OF HEALTH RESEARCH & RESOURCES

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Vascular disease is the leading cause of death around the world. A growing epidemic of cardio- and cerebrovascular disease is now projected to kill many more millions and create further disability due to stroke, heart and renal failure, peripheral vascular disease and the other consequences of atherosclerosis and hypertension. This epidemic threatens the economic health of developed and developing countries as well as the health of its peoples. The situation is not at all hopeless because the largest component of the burden of illness due to vascular disease is preventable. However, lack of action will lead to irreversible consequences. The United States National Institutes of Health (NIH) is the major funding body for medical research and is committed to developing the knowledge to combat this global health problem.

The toll in life and quality of life in the United States due to atherosclerotic-hypertensive vascular disease is enormous. Heart disease is the second leading cause of death, and 8% of the total health expenditures is devoted to treatment of established heart disease. Stroke is the third leading cause of death and has been associated with 2% of the total health expenditure. Stroke is also the leading cause of adult long-term disability. Peripheral arterial disease affects over 8 million Americans and leads to over 50,000 amputations per year. Hypertension and hyperlipidemia account for 5% of US health spending and with atherosclerosis are also the major causes of 24% of cases of renal failure. Lastly recent evidence suggests that cerebrovascular disease combines with Alzheimer's disease to cause dementia in the elderly. Those risk factors associated with future development of ischemic complications are now being identified as significantly associated with development of dementia. The major risk factors are hypertension, elevated blood lipids, overweight, tobacco smoking and sedentary life style.

The rising US health care costs are considered unsustainable. A major component of these costs are due to the treatment of hypertensive and atherosclerotic vascular disease once it has become manifest as myocardial infarction, stroke, claudication, or hypertensive kidney disease. A comparison with disease and disability rates of other Western countries suggest that the enormous investment in US health technology does diminish disability and

prolong life in affected individuals. However, diagnostic vascular testing and surgical or endovascular revascularization procedures for coronary, carotid, intracranial, aortic, renal and peripheral arterial disease are costly and associated with substantial procedural risk. The treatment of persons with chronic heart failure, debilitating stroke, and end stage renal failure are substantial. Advances in treatment likely contribute to the decreases in the annual risk of mortality due to stroke and heart disease but these medical interventions are incurring more and more cost. Figures from the Centers for Disease Control (CDC) indicate that the deaths due to cardiovascular disease, stroke and peripheral vascular disease decreased between 2000 and 2005 by 8, 10, 12% respectively. However the prevalence of persons living with coronary artery disease, heart failure and stroke has increased much more, 24, 8 and 23% respectively.

Three major shifts in the epidemiology of vascular disease if unchecked will contribute to a 'perfect storm' in US health care. First is the fact that vascular disease is appearing at an earlier age in the US population as compared to other Western countries. This is consistent with a less effective preventative effort and is met by tremendous expenditure in vascular care and disability. The prevalence of hypertension in the US increased by 50%, from 50 million in 2000 to 73 million in 2005. The second threat is the rising prevalence of obesity which all data predicts will lead to a surge in premature hypertensive-atherosclerotic disease. The prevalence of obesity in persons over 20 years old increased 11% from 61 million in 2000 to 67 million in 2005. The third is a direct consequence of our success in treating disease and extending the lifespan. Vascular disease continues to worsen with age. Stroke risk doubles for each decade after 60 years. The prevalence of atrial fibrillation, a cardiac arrhythmia that carries risk of major stroke, also increases with age. It currently affects 2.3 million Americans but will increase to 5.6 million in the year 2050. These three factors call for continued discovery research to develop more effective interventions to prevent the progression of atherosclerotic hypertensive disease and treat its complications. However, the paradigm shift that can save lives as well as a health care system is a more effective prevention strategy. Prevention will eliminate considerable suffering and death but also substantially decrease the resources needed to treat millions of newly affected individuals. Vascular disease prevention not only makes sense from a pure health perspective but it may be the best means to curb the unsustainable growth of health care costs.

The NIH is a component of the US Department of Health and Human Services. It consists of 27 Institutes and Centers with varying related health missions. Almost all have 'intramural' research units in laboratories and the 240-bed research hospital in the Washington D.C. area. The intramural re-

search endeavor is generally assigned 10% of the NIH budget. Each of the Institutes aggressively supports training of research investigators that will contribute to the Institute's mission.

The National Heart Lung and Blood Institute (NHLBI) is the major funder of basic research on atherosclerosis, hypertension, myocardial ischemia, and heart failure. Within NHLBI is the Division of cardiovascular disease with branches in atherosclerosis and coronary heart disease, vascular biology and hypertension. The NHLBI Division of Prevention and Population Sciences also carry out large population and epidemiology studies that uncover important risk factors. The Framingham Heart Study has led to establishment of the major vascular risk factors as well as the Framingham Risk Index which has been validated for its ability to integrate various risk factors into a predictive scale. The Atherosclerotic Risk in Communities Study (ARIC) intensively studied middle aged individuals and tracked them over time to determine those characteristic that are predictive of heart disease and cognitive decline (references). Treatment trials in myocardial infarction and heart failure have led to major advances that reduced death and disability. Current investigation and trials of stem cell replacement therapy and gene therapy are focused on improving heart function in persons with heart failure. Primary and secondary prevention trials from NHLBI have had a major impact on health care in the US. Most recently there has been concerted effort to determine whether there is increased benefit in lowering blood pressure below the currently recommended limits. The recent NHLBI/NIDDK study called ACCORD showed no improvement in cardiovascular outcomes from aggressive lowering in patients with diabetes. However there was reduction in stroke. The NINDS SPS3 study will examine aggressive blood pressure lowering to prevent subsequent stroke in persons with small vessel disease. A new NHLBI/NIDDK/NINDS/NIA funded study, called SPRINT, will examine aggressive blood pressure lowering in persons with renal failure or vascular risk. NHLBI Public information programs based at NHLBI work to inform the US population on how to best prevent heart and vascular disease. The 'Red Dress Campaign' has raised awareness of the great danger of undiagnosed and untreated vascular disease in US women.

The National Institute of Neurological Disorders and Stroke (NINDS) is the major funder of stroke research. NINDS research covers the landscape of cerebrovascular disease and includes basic research on the interconnection of brain metabolism and blood flow, integration of function at the tissue level, i.e. how the cell types (neurons, glia, endothelial cells and inflammatory cells) integrate their function, the brain response to ischemia and hemorrhage, and

how the brain recovers after injury. NINDS often collaborates with NHLBI on the large epidemiologic, genetic, or treatment studies with stroke and/or cognitive endpoints, i.e. ARIC, SPRINT. NINDS clinical trials have established the substantial effectiveness of warfarin in preventing stroke in persons with atrial fibrillation and defined the risk/benefit ration of carotid endarterectomy and endovascular stents in persons with carotid artery stenosis.

The demonstration of the timely infusion of tissue plasminogen activator has led to decrease in disability due to acute ischemic stroke. The Brain Attack Coalition, a partnership between professional societies, non-profit stroke associations and government, based at the NIH, has also led to a revolution in the care of acute stroke patients into organized stroke centers. Substantial benefit in stroke outcome is likely and is also derived from the benefit of an organized stroke unit. Treatment trials are now underway studying acute reduction of blood pressure in persons with intracerebral hemorrhage, removal of blood from patients with hemorrhage into the ventricles, and intra-arterial clot removal/dissolution after intravenous tPA treatment. Basic research in 'neuroplasticity' and 'neurodevelopment' are now being integrated into basic and translational studies on how the brain recovers after stroke. Given the explosion of basic science of neuroplasticity and neurodevelopment, future breakthroughs in promoting stroke recovery seem quite possible. Like the variability in global rates of stroke and heart disease, the United States also has great regional variability. The southeastern US is a 'stroke belt' with extremely high stroke mortality. The Reasons for Geographic and Racial Differences in Stroke study (ReGARDS) is ongoing to determine the underpinnings of these disparities. Secondary stroke prevention studies for persons with small subcortical strokes (lacunar stroke), cardioembolic stroke in persons with heart failure, intracranial stenosis and TIA/non disabling strokes are underway. NINDS's 'Know Stroke Campaign' focuses on raising awareness about the warning signs of stroke and transient brain ischemia, which should be triggers to seek emergency attention. A few research studies focus on developing best practices in stroke prevention, emergency access to stroke treatment some of which are targeted at specific racial-ethnic groups.

The National Institute of Diabetes, Digestive and Kidney Disorders (NIDDK) has been a lead in research on obesity and the complications of diabetes. Obesity and lack of physical activity are causally related to the development of type 2 diabetes with its complication of dyslipidemia and hypertension. The long-term consequence is atherosclerosis and its disease manifestations. Unfortunately obesity is becoming more prevalent in both developed and developing countries. CDC figures indicate that the preva-

lence of diagnosed diabetes increased from 0.9% in 1958 to 6.9% in 2009. This underlies much of the coming epidemic in heart disease and stroke. The NIH responded to the growing epidemic of obesity by creating a multi-institute task force on obesity. Although most NIH research is initiated by investigators, the Obesity Task Force is an example of how the NIH stimulates the research community to focus on high priority health or scientific problems. They have issued a number of program announcements calling for grant applications in topics such as school nutrition and physical activity policies, obesogenic behaviors, and weight outcomes. Home and Family Based Approaches for the Prevention or Management of Overweight or Obesity in Early Childhood, Geographic and Contextual Influences on Energy Balance-Related Health Behaviors (R01), Identifying and Reducing Diabetes and Obesity Related Health Disparities within Healthcare Systems (R01). In addition to these three institutes, others such as the National Institute of Aging (NIA) for issues related to cognitive decline, National Institute of Nursing Research (NINR), the National Institute of Bioimaging and Bioengineering, have programs in vascular related research.

Many aspects of the problem have been defined by NIH funded research. Biological events that begin early in life lead to the development of lipid deposition in the wall of aorta. Over time this process occurs in most large- and middle-sized arteries in the body. Uncovering the genetic causes of atherosclerosis, knowledge of lipid metabolism, vascular biology, and the role of inflammation have given scientists a strong but still incomplete understanding of atherosclerosis. Similarly changes in vascular tone, volume and sodium regulation, hormonal and neural circuits, are known to contribute to cause hypertension. The interaction between the clotting system and the vascular wall is the third major piece to the puzzle. Many ischemic manifestations, especially stroke, heart attack and peripheral embolism occur when thrombus forms on the diseased vessel wall. In the case of acute coronary syndrome the thrombus occludes flow to the heart muscle. In stroke and hypertension the thrombus breaks free to travel in the arterial system till it enters a vessel that is too small to allow it to pass. Hemorrhage into the brain occurs when a vessel damaged from chronic hypertension leaks blood into the brain substance. From the biological discoveries have come medications that reduce blood pressure and create a partial block in decreasing lipid deposition, and tolerable reduction in thrombus formation. These medical interventions have been extensively studied and show definite benefit in reducing important endpoints like death, myocardial infarction and stroke.

There is every reason to expect that further scientific research will lead to more effective medications that can control hypertension, prevent pro-

gression of atherosclerosis or prevent the acute thrombotic consequences such as stroke, myocardial infarction and embolism. NIH has recently placed greater emphasis in developing translational programs that aim to bring promising new therapies to patients. The NINDS office of translational research funds cooperative agreements which focus on developing compounds as drugs to the point of application to the Food and Drug Administration (FDA) for an Investigational New Drug application. New agents are surely to be more expensive than the older effective therapies which have come off patent. The new agents generally have a side effect or effectiveness profile that is an advance over older, less expensive medications. However the incremental value is often small. Many effective medications are now inexpensive. In both developed and underdeveloped countries the lack of medical treatment of persons who need it is often a logistical or systems problem and not related to the expense of medications. Major research questions in the future will focus around who should receive preventative medications. Age is one of the most important risk factors and many with atherosclerosis-related MI stroke have few risk factors. An argument has been made in the literature to treat all persons above a certain age with combined lipid lowering agent, antiplatelet agent, and an anti-hypertensive polypill. A major question will become how early to begin medical treatment in persons who are asymptomatic and how aggressive to lower blood pressure, and blood lipids, in addition to the risk/cost/benefit relationship for treating patients with few risk factors.

Guidelines for the prevention of vascular disease focus around control of the evidence-based risk factors of hypertension, blood glucose and blood lipids. Weight loss and increased physical activity are recommended first, with medications to follow if this has not led to normalization. The paradigm shift that is necessary to stave off the epidemic of vascular disease is a culture change that emphasizes exercise and maintenance of healthy body weight from an early age. The latter is even more important given that the lack of physical activity and obesity in children has been identified as causes of Type 2 diabetes in children. Such a strategy would be expected to decrease the proportion of the population with Type 2 diabetes, hypertension and dyslipidemia. Tobacco smoke is an extremely important preventable risk for cardiovascular disease and public health has profited from reductions in smoking. However there has been less reach in specific groups especially young people and those of low socioeconomic strata where smoking rates are still high.

Reduction, or at least significant delay, in the development of atherosclerotic complications could be expected if physical activity increases and obesity and smoking decline. Without the discovery of an agent that pow-

erfully prevents atherosclerosis, our country's shift toward an 'unhealthy lifestyle' will eventually be met by an explosion in the burden of vascular disease. Attacking this cultural issue is not fixable with medication. We know that atherosclerosis begins at young age. The health decision to begin medication at young age is fraught with concerns for safety and cost. However a healthy lifestyle has no downside and is likely to be more effective, more sustainable if started young. A concerted education effort must be made to educate at every level. But only disseminating information is not likely to have the needed impact. NINDS and NHLBI recently held a workshop on the Science of Behavior change focusing on the vascular risk factors. The workshop pointed to lessons from the behavioral and communication sciences, with a focus on health related behavioral economics, to enable the development of healthy habits. Communication tools are now far advanced over the print media of most health campaigns. Harnessing the power of social networks is now possible to promote healthy behavior if properly targeted at specific segments of society. The new technologies: YouTube, Facebook, Twitter, the global penetration of cell phones and the internet offer both more personalized and greater regional reach. Indeed, the feasibility of widely accessible global communication also enables the consideration of international cooperative programs aimed at segments of populations with the optimized 'message'. Technology also allows the design of personalized 'coaches', methods can be developed that interact with the individual's decision-making environment; i.e., automated calorie counters, food classifiers, pedometers, cell phone reminders, even systems that capture real-time data from individuals followed by analysis and feedback.

An individual effort to rearrange one's environment to increase the probability of a healthy behavior is possible on the individual level but population effects likely require an integration of policy with healthy behaviors. Those who make decisions that affect the work or school environment, 'planners', can contribute over years to health. Most do not have any realization of their potential to affect health. Because caloric intake and physical activity have not come into the decision-making by 'planners' their decisions have had random effects, sometimes positive, sometimes negative or neutral. It's easy to understand that the absence of healthy food choices in a work or school cafeteria will predispose to an unhealthy outcome. However less obvious is that the arrangement by which foods are presented, or offering choice with regards to portion sizes can increase the probability of health choices. Planning of communities and the workplace can have major effects on the amounts of physical activity of those who live and work in the environment. Placing stairs but not elevators at the entrance to the

building encourages walking. Safe bike lanes and bike racks encourage biking to work or school. Realization that cardiovascular disease is actually a cost to companies has even led to active programs focused on healthy lifestyle among employees. Because so little has been done to increase the probability of healthy choices there may be considerable population level gains to be made from a concerted cultural change toward healthy lifestyle. In most cases the goal should not be to restrict choice but instead to engineer the environment to make healthy choices more likely.

A proportion of the NIH's effort focuses on global health. The Fogarty International Center (FIC) coordinates international programs. Joint programs with the other Institutes fund research training and joint research grants with international investigators. Relevant to vascular diseases are the FIC's *International Tobacco and Health Research and Capacity Building Program*, *Millennium Promise Awards: Non-communicable Chronic Diseases Research Training Program* and *Brain Disorders in the Developing World*. Recently, Dr. Francis Collins, the NIH Director, has called for NIH to redouble its impact on global health. NHLBI has developed 11 Centers of excellence around the globe. In 2009 NHLBI joined as one of the founding members of the Global Alliance for Chronic disease. The Global Alliance is composed of national health research institutions and intends to coordinate and support research activities that address, on a global scale, the prevention and treatment of chronic non-communicable diseases. The alliance's focus is on the needs of low- and middle-income countries – where 80% of deaths from chronic diseases occur – and on those of low-income populations of more developed countries. NHLBI is also involved in a partnership with World Health Organization and the Pan American Health Organization. A variety of Institutes execute clinical research with sites distributed around the world.

The research supported by the NIH holds the potential to inform individuals, health care providers, payers, and policy makers on how best to combat the epidemic of vascular disease. Though it studies how best to disseminate information to improve health it does not provide healthcare or set policy. In truth a great deal is currently known about how to prevent vascular disease and its consequences. There is a gap between the knowledge base and translation into the culture and fabric of society. Coordinated action on the part of governmental and educational agencies, church, community and industry leaders is required to turn what is known about decreasing disability, mortality and health care costs into a reality.

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