Cardiovascular and cerebrovascular diseases combined are the leading killers worldwide today. Mortality related to chronic atherothrombotic disease is projected to grow disproportionately, with the focus being in low- and middle-income countries. In the developed world, although we have gained successes with regard to reduction in mortality attributable to a mix of preventive and treatment strategies, we have largely shifted the curve of the disease to the right, turning these conditions into chronic morbidities. In turn, this has reflected in the 368 billion dollars spent by the United States for these illnesses, a 3-fold increase in the span of a decade1 (Figure 1). In this article, we discuss some of the emerging mechanisms that simultaneously affect the atherosclerotic process in the cardiac and cerebrovascular regions and touch on management issues relevant to the clinician and population health researcher.

**Advances in Biological Concepts in Atherothrombosis**

**Defense Mechanisms**

Basic science animal and human autopsy studies have defined the role of the endothelium, vasa–vasorum, and lipids in the regulation of the atherothrombotic plaque.2 The vulnerable plaque is believed to have a thin fibrotic cap, a lipid-rich necrotic core, neovascularization, and inflammation. The body has its own defense mechanisms to maintain the plaque homeostasis. Endothelial progenitor cells have been shown to play an important role in the regulation of endothelium and abort the progression of endothelial dysfunction to plaque rupture. Similarly, the vasa–vasorum regulated in turn by extracellular matrix, fibroblasts, smooth muscle cells, and growth factors also is a critical player in the process of plaque regression. In addition, high-density lipoprotein cholesterol is believed to regulate the lipid content of the plaque preventing formation and expansion of the core of the plaque. Finally, vascular inflammation regulated by the monocyte–macrophage system plays a role in the vasa–vasorum and lipid-related defense processes. Failure in these mechanisms to protect the atherothrombotic milieu of the plaque leads to plaque rupture and thrombosis (Figure 2).

**Carotid Plaques: Histopathology**

Although there exists a large body of literature regarding the natural history and evolution of the coronary plaque, such data regarding carotid atherosclerosis had been lacking. In the largest-ever study of symptomatic carotid plaque histology, Redgrave et al4 found a high prevalence of cap rupture, large lipid core, and dense macrophage infiltrate, which suggested that the mechanisms of plaque instability in the carotid circulation were similar to those in the coronary circulation. Higher density of macrophage infiltration was strongly associated with cap rupture and time since stroke.

One of the interesting observations from this study was the difference between plaques from patients with strokes or transient ischemic attacks (TIAs). Plaques removed <60 days after the most recent event had more macrophage infiltration after a stroke than after a TIA. The plaque macrophage content declined with time in plaques associated with strokes but not for plaques associated with TIA, so that plaques removed >180 days after the most recent event had less macrophage infiltration after a stroke than after a TIA. This may explain the recurrent nature of TIAs.

In their elegant study, Peeters et al5 reconfirmed these findings regarding the temporal decline in plaque inflammation (as quantified by macrophage infiltration) after a stroke and persistence after a TIA, with histological data supplemented by assessment of inflammatory biomarkers such as interleukin-6 and interleukin-8 and caspase-3 enzymes.

**Carotid Plaques: Noninvasive Imaging**

Both above-mentioned studies clearly identified inflammation as a major player in the process of carotid atherosclerosis and associated events. In the past decade, much work has been done to study these plaque characteristics noninvasively using MRI and positron-emission tomography–CT. Our group and others have led the way in identifying the thin cap, lipid core, and neovascularization with natural, contrast-enhanced and black-blood MRI imaging. We have now been able to study plaque inflammation reliably and accurately with positron-emission tomography–CT imaging and have shown excellent correlation with histology. These noninvasive methodologies are being used to study the natural history of the disease and their correlation with clinical events in the High-Risk Plaque Bioimaging study6 and in the FREEDOM7 (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) imaging study. The High-Risk Plaque Bioimaging study has recruited 6000 active subjects and 1300 controls, of which a...
large proportion of subjects underwent 3D-carotid ultrasound, cardiac CT, positron-emission tomography–CT, and MRI. All subjects are being followed for clinical events and resource use out to 3 years. In a complementary study, the FREEDOM imaging study, 380 high-risk diabetic subjects with multivessel coronary disease who have undergone revascularization were evaluated with MRI and positron-emission tomography–CT to correlate the nature and burden of their atherosclerosis with future vascular events. Both studies are banking samples for biomarker and genetic marker studies.

In addition, building on the noninvasive plaque monitoring, both MRI and positron-emission tomography–CT are now being used in multiple studies evaluating novel anti-inflammatory and antiatherothrombotic therapies to assess their effects on plaque burden, plaque constituents, and inflammation in the carotids and other arterial regions.

Advances in Clinical Issues in Atherothrombosis

Antiplatelet Therapy for Atherothrombotic Disease

For purposes of secondary prevention in patients who are at high risk because they already have occlusive vascular disease, long-term antiplatelet therapy with aspirin reduces the yearly risk of serious vascular events (nonfatal myocardial infarction [MI], nonfatal stroke, or vascular death) by almost 25%. Against this benefit, the absolute increase in major gastrointestinal or other major extracranial bleeds is relatively smaller. Hence, for secondary prevention, the benefits of antiplatelet therapy substantially exceed the risks.

However, for primary prevention, the balance is less clear. A recent participant level meta-analysis of 6 primary prevention studies involving 95,000 persons revisited the role of aspirin in preventing serious vascular events such as death, MI, and stroke in this population. There was no effect of long-term aspirin on vascular or nonvascular mortality. There was a miniscule absolute reduction of the risk for a serious vascular event from 0.57% to 0.51% per year, which translated into a proportional risk reduction of 12%. However, most of this benefit was restricted to a 23% reduction in nonfatal MI. There was no benefit of aspirin for prevention of strokes. Simultaneously, there was a relatively excess risk toward hemorrhagic strokes (0.10% versus 0.07% per year) and nonfatal bleeding. The meta-analysis reaffirmed the positive benefit of aspirin on total mortality and serious vascular events for secondary prevention, albeit with some increase in hemorrhagic strokes.

Atrial Fibrillation and Stroke Prevention

In the world of atrial fibrillation, 2 issues dominate: rate control versus rhythm conversion and stroke prevention. Although we continue to explore newer antiarrhythmics and catheter ablation methods for the rhythm issue, until recently, the field of stroke prevention largely revolved around triaging patients into those who required coumadin versus those for whom aspirin therapy would suffice. This was done using the popular Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke (CHADS) score (1 point each for congestive heart failure, hypertension, >75 years of age, and diabetes and 2 points for previous thromboembolic event/stroke). However, in the past few years, lot of work has been done in...
the area of coumadin alternatives such as dual antiplatelet therapy, newer antiplatelet and antithrombotic drugs, and procedural alternatives.

The ACTIVE-W trial\(^9\) randomized 6706 subjects with documented atrial fibrillation to oral anticoagulant therapy with warfarin or warfarin-like drugs versus dual antiplatelet therapy with aspirin and clopidogrel. The trial had to be terminated early because of a 45\% increase in the risk of the primary composite end point of stroke, non-central nervous system embolism, MI, and vascular death (5.64\% vs 3.93\%; \(P=0.0002\)) with dual antiplatelet therapy compared with oral anticoagulation.

The ACTIVE-A trial\(^10\) studied the role of dual antiplatelet therapy over aspirin alone for subjects ineligible for coumadin for various reasons in 7500 subjects with documented atrial fibrillation. The combination therapy reduced the primary outcome of major vascular events including stroke, non–central nervous system embolism, MI, and vascular death (6.8\% versus 7.6\%; \(P=0.01\), at the expense of increase in major bleeding (2\% vs 1.3\%; \(P<0.001\)) but not a statistically significant increase in fatal bleeding.

Probably more interesting and promising as an alternative is a newer direct thrombin inhibitor called dabigatran, which was studied in the RELY trial.\(^11\) RELY was a noninferiority trial of 18 113 subjects comparing a low (110 mg twice daily) and a high dose (150 mg twice daily) of dabigatran to warfarin therapy. Both doses of dabigatran were found to be noninferior to warfarin in terms of efficacy, with the 150-mg dose proving to in fact be statistically superior to warfarin (150-mg relative risk [RR]=0.66 CI, 0.53 to 0.82; 110-mg RR=0.91 CI, 0.74 to 1.11). Overall rates of hemorrhagic stroke, life-threatening bleeding, and intracranial bleeding were all higher with warfarin than either doses of dabigatran. Major gastrointestinal bleeding was slightly higher with the 150-mg dose of dabigatran.

Also exciting is the new data regarding ticagrelor, an oral P2Y12 inhibitor studied in the PLATO trial,\(^12\) which showed an impressive reduction in a composite of vascular death, MI, and stroke compared with clopidogrel in subjects with acute coronary syndromes with no excess bleeding risk (11.7\% vs 9.8\%). There are a host of specific inhibitors of the coagulation cascade, in various stages of development, which are bound to change the way we manage our patients over the next decade.

Finally, the other emerging option for stroke prevention are the percutaneous left atrial appendage exclusion or occlusion methods, of which the Watchman occluder device is the most studied and has shown to be a relatively safe and efficacious option in the PROTECT-AF trial\(^13\) of 800 subjects.

**Stenting Versus Carotid Endarterectomy**

The CREST (Carotid Revascularization Endarterectomy vs Stenting) trial\(^14\) compared carotid stenting with carotid endarterectomy for stroke prevention in patients with both asymptomatic and symptomatic extracranial carotid stenosis. On the composite primary end point of any stroke, MI, or death during the periprocedural period or ipsilateral stroke on follow-up, stenting was associated with a 7.2\% rate of these events versus 6.8\% with surgery, a nonsignificant difference. On reviewing the literature comparing carotid stenting with carotid endarterectomy, it becomes apparent that carotid stenting seems to be a better choice for patients with simpler local anatomic features and greater comorbidities. For patients with complex local anatomy and complicated calcified plaques, carotid stenting is a better choice. These results are very similar to those observed for multivessel coronary disease as seen in the SYNTAX trial,\(^15\) with surgery being the better option for those with complex anatomy. Results from other large ongoing studies, such as the International Carotid Stenting Study,\(^16\) are expected in the near future.

**Cryptogenic Stroke and Patent Foramen Ovale Closure**

Most clinicians will have screened their patients’ carotids and heart chambers and appendages for arterial sources of thrombi before labeling a stroke as cryptogenic. It is important to stress the emerging and often neglected importance of screening the verteobasilar system and the aortic arch. With regard to paradoxical emboli originating in the venous system and believed to have crossed over a patent foramen ovale, the choice of therapy needs to be individualized on a case-by-case basis. At the present time, there are no clearly approved indications for transcatheter patent foramen ovale closure in the United States. Although there are a host of smaller clinical trials with some promising data regarding the role of patent foramen ovale closure for strokes and migraine headaches in selected populations, the larger completed trials have been negative and most of the ongoing large outcomes studies will probably not reach recruitment goals. Platypnea–orthodeoxia is probably the only condition for which there seems to be consensus with regard to the immediate benefit of patent foramen ovale closure.\(^17\)

**The Microvasculature and Advances in Concepts in Alzheimer’s Dementia**

For long, degenerative brain disease, particularly Alzheimer’s disease, has been viewed purely as a disease of aging with deranged amyloid deposits in neuronal ganglia. A large body of literature now exists revealing the strong association of hypertension and other cardiac risk factors with Alzheimer’s disease.\(^18,19\) Specifically, apolipoprotein genotype, hyperlipidemia, diabetes and smoking are also believed to contribute toward the observation of microvasculature dysfunction leading to cognitive decline.\(^20\) Multiple studies testing blood pressure regulation, especially with angiotension converting enzyme inhibitor– and angiotensin receptor blocker–based regimens have shown success in preventing cognitive decline. Additional research is ongoing, which explores the concept of overlap of vascular stroke–related and Alzheimer’s dementia.\(^21\)

**Efforts in Promoting Population Cardiovascular Health**

Although noncommunicable diseases such as cardiovascular and cerebrovascular disease are the leading cause of mortality worldwide, they were not listed in the World Health Organization millennium development goals. However, there is
growing awareness regarding the magnitude and the looming expense of this pandemic.

Recently, the Institute of Medicine and the National Heart, Lung, and Blood Institute jointly released a proposal for a framework to combat and prevent cardiovascular disease. The report recommends that the National Heart, Lung, and Blood Institute, development agencies, nongovernmental organizations, and governments work toward 2 essential goals: creating environments that promote heart healthy lifestyle choices and help reduce the risk of chronic diseases, and building public health infrastructure and health systems with the capacity to implement programs that will effectively detect and reduce risk and manage vascular disease. Steps to meet these goals include improving cooperation and collaboration, implementing effective and feasible strategies, and informing efforts through research and health surveillance. The report aims to use the knowledge gained from epidemiology and health economics to make populations and health system agencies aware of their responsibilities toward promoting health through cooperation and advises on incentivizing the youth and the not so young in appropriate ways to achieve our common goal of universal health. It is clear that there is need for leadership at all levels with seamless communication between all involved for preventive efforts to succeed.

It is also necessary to explore innovative ideas and hypotheses in various spheres of prevention. An excellent example of targeting the young to modify behavior early in life is the Plaza-Sesamo project in Bogota, Colombia. This project has used simple educational materials to educate young school-age children about health habits for life with regard to diet and exercise choices. Benefits have been seen not only in the children, but a ripple effect has extended to the elders in their families. This project has now been expanded to other sites in Spain. Perhaps the strongest force to impact health-related behaviors lies in the hands of the policy and lawmakers. New York City is an outstanding example, with its stringent policies regarding smoking and cooking oils. The bans on smoking in public places and on oils with excess saturated fats have shown immediate benefits on the health of the people. Additional regulation regarding salt, sweetened beverages, and maybe even portion sizes are in the works, and governments work toward 2 essential goals: creating environments that promote heart healthy lifestyle choices and help reduce the risk of chronic diseases, and building public health infrastructure and health systems with the capacity to implement programs that will effectively detect and reduce risk and manage vascular disease. Steps to meet these goals include improving cooperation and collaboration, implementing effective and feasible strategies, and informing efforts through research and health surveillance. The report aims to use the knowledge gained from epidemiology and health economics to make populations and health system agencies aware of their responsibilities toward promoting health through cooperation and advises on incentivizing the youth and the not so young in appropriate ways to achieve our common goal of universal health. It is clear that there is need for leadership at all levels with seamless communication between all involved for preventive efforts to succeed.

There is a great need for motivated leadership at all levels of the field of vascular disease and aging research. Novel mechanisms are being explored every day in the laboratory and the clinical field. Innovative therapeutic modalities arise, strengthening our armamentarium against the scourge of atherothrombotic vascular disease and dementia. There is a great need for motivated leadership at all levels of prevention. However, more important is population education and awareness regarding simple ways to modify risk factors for vascular disease. Ultimately, from an economic and quality-of-life perspective, promotion of health should be our priority.

References


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