Atherosclerosis: The 21st Century Epidemic
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Cardiovascular Disease: From Treatment to Promoting Health; A Challenge for the Next Decade

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Cardiovascular disease (CVD) is the most prevalent cause of mortality across the globe [1-2]. Of every 10 deaths worldwide, 6 are due to non-communicable conditions; 3 to communicable, reproductive or nutritional conditions; and 1 to injuries. Of the noncommunicable conditions CVD is by far the most prevalent cause of death, accounting for at least 30-40% of mortality attributable to noncommunicable conditions [2]. Importantly, CVD can manifest in many ways, including as coronary artery disease (CAD) and myocardial infarction, stoke, renal failure, aortic aneurysm and degenerative brain disease (DBD). This massive burden of disease consumes a significant share of the world's fiscal and health care resources, and has a major, adverse influence on the physical and mental wellbeing of patients and their families.

Added to this, in many nations the looming 'aging epidemic' will soon compound this problem. Framed by the aging 'baby-boomer' cohort, the number of persons at risk for CAD and CVD is predicted to increase dramatically in the coming decade [1], which will place significant additional demands on health care resources. Meeting the challenges of the 'aging epidemic' is something that will assume increasing importance in the coming decade. Moreover, as can already be seen from this complex matrix of factors, attempts at reducing the morbidity and mortality attributable to CVD will require a multi-pronged approach spanning biology, treatment modalities, societal attitudes and health care resource utilization [3].

Primary cardiovascular disease prevention

Primary prevention must be the core of our efforts to promote cardiovascular health. Lifestyle modification is central to primary prevention, and one

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of the most powerful ways of illustrating the need for lifestyle change is by defining to a patient their risk for CVD-related morbidity and mortality. Current guidelines place great emphasis on CVD risk evaluation, recommending that global risk scores incorporating multiple traditional cardiovascular risk factors should be calculated for risk assessment in all asymptomatic adults without a clinical history of CAD/CVD [4]. While there are several risk assessment algorithms, perhaps the best known is the Framingham Risk Score, with simple online tools available to calculate 10-year risk of CAD-related adverse events. Physicians and patients should be encouraged to make use of these resources, and to take action to mitigate high-risk aspects of their CVD risk profile or to initiate therapy as appropriate [3].

Contemporary treatment of coronary artery disease

For those already afflicted with CAD, a treatment strategy based on medical management, rather than invasive revascularization, may be an increasingly viable option. A major turning point was the recent COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation). COURAGE compared a strategy of percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) versus OMT alone in stable patients, showing no difference in the rate of the primary endpoint (death or myocardial infarction) during a follow-up period of 4.6 years [5]. Supported by other studies such as BARI-2D in diabetic patients [6], the advent of COURAGE has seen increasing scrutiny with respect to the appropriateness of performing PCI and other revascularization procedures. In effect, COURAGE has opened the door for the use of OMT as a primary treatment for CAD, particularly in select low-risk patients. We foresee that with the increasing movement toward cost-effective, evidence-based medical practice, the next decade will see a rise in the use of OMT as a primary strategy for the treatment of patients with CAD and CVD. Furthermore, even in patients undergoing invasive revascularization, the use of OMT will be increasingly emphasized as a critical aspect of routine post-procedural care that reduces the likelihood of further cardiovascular events [7]. COURAGE also suggests that for the majority of patients who are unable to readily access or afford invasive revascularization, medical therapy is an appropriate long-term treatment option.

At the same time as COURAGE was being conducted, physicians were becoming more aware of the fact that for patients suffering from complex multivessel CAD, any consideration of a potential revascularization strategy must be made with very close attention to coronary anatomical and physiological factors. Regarding CAD anatomy, several studies have shown the

value of the SYNTAX risk score for triaging patients to either PCI or coronary artery bypass graft (CABG) surgery [8-10]. The SYNTAX score assesses coronary anatomy complexity from the perspective of potential PCI or CABG surgery, and has been shown to relate to improved outcomes when patients with especially complex disease (SYNTAX score ≥ 33) undergo CABG surgery rather than PCI [8]. In addition, if the anatomy is not overly complex (SYNTAX score < 33) and the patient is an appropriate PCI candidate, then the physiological assessment of lesions proposed for PCI by fractional flow reserve (FFR) is now advocated. FFR is a technique used in the catheterization laboratory to measure pressure differences across a coronary stenosis, and determine if a lesion is likely to be functionally significant and associated with myocardial ischemia. This drive towards FFR-based physiological lesion assessment is as a result of the FAME study, which showed that measuring FFR in patients with complex multivessel CAD who are undergoing PCI reduces death, nonfatal myocardial infarction and repeat revascularization at 1 year [11].

While these studies remain important new guides in how to best manage complex CAD patients, lingering questions remain. One of these continues to be the role of PCI versus CABG surgery in diabetic patients. The ongoing FREEDOM trial is poised to answer this question (FREEDOM, Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) [12]. The study population comprises 2,400 patients with diabetes mellitus and multivessel CAD amenable to either PCI or CABG surgery, with indication for revascularization based upon chest pain symptoms or other evidence of myocardial ischemia. This study is expected to report initial findings in the near future.

A final group of patients that we know very little about is those with asymptomatic CAD/CVD who are at risk for near-term events. Aggressive primary prevention in these patients is vital to avoiding morbidity and mortality and a window of opportunity exists for averting CAD/CVD events if these at risk patients can be identified. However, most cardiovascular events occur in persons who would be classified as low or intermediate risk by a risk factor-based approach. Thus, although attention to risk factors is of critical importance, it has been estimated that >75% of all coronary events may occur in persons classified at low or intermediate risk [13]. In an attempt to discover novel and efficacious approaches to identify and treat these at risk persons, the High Risk Plaque (HRP) Bioimage study was recently initiated [13]. A total of 7,687 patients without evidence of atherothrombotic disease but presumed to be at risk for near-term CVD events were enrolled. The majority then underwent comprehensive baseline

assessment, including determination of CVD risk factors, quantification of coronary artery calcification and assessment of numerous other measures of CVD burden. Participants with one or more abnormal screening test then underwent additional multi-modality imaging and other testing to further evaluate their vascular disease burden. The trial is now in an active follow-up phase and will provide a wealth of information about these at risk individuals. The results of the HRP Bioimage study will provide novel directions in the drive to promoting cardiovascular health in the next decade and epitomizes the goal of maximizing primary prevention efforts to avert CAD/CVD. Most importantly, this study will facilitate the aggressive treatment of at risk patients to avert CVD events.

Optimal medical therapy for CAD and medication adherence

Regardless of whether a patient is to be managed by PCI, CABG surgery or OMT alone, risk factor modification in terms of comprehensive medical therapy (aspirin, lipid lowering therapy, anti-hypertensive medication) and lifestyle modification (healthy diet, regular exercise, weight loss, smoking cessation) is the cornerstone of secondary prevention. Indeed, even in the very elderly (nonagenarians and centenarians) with unstable CAD, adherence to guideline-recommended therapies is associated with decreased mortality [14]. However, what has emerged from studies such as COURAGE [5] and BARI-2D [6], is that only approximately 50% of patients are achieving treatment goals for blood pressure, cholesterol and glycemic control. Medication non-adherence is thought to be a large part of this problem, and across all health-care categories non-adherence is believed to account for $290 billion dollars of annual health care expenditure in the USA [15]. Multiple socio-economic factors play into the equation of why patients stop taking their medications and a major initiative to combat this problem is the increasing drive towards the polypill. The idea of combining numerous medications into a single tablet that targets risk factors associated with CVD was first proposed almost a decade ago [16]. Most cardiovascular polypill formulations address several CVD risk factors at once (hypertension, lipid levels, platelet adhesiveness). Not only does this increase patient convenience, but by combining several compounds in a single tablet, out-of-pocket costs to patients and insurers are reduced. Estimates suggest that the across-the-board use of the polypill by US adults aged ≥ 55 years may prevent 3.2 million CAD events and 1.7 million strokes over 10 years, while among those with a history of CVD, the potential to prevent 0.9 million CAD events and 0.5 million strokes is projected [17]. With this huge potential to benefit such a large number of persons, several randomized clinical

trials have now been initiated to study the potential effects of polypills on CVD risk factors and clinical outcomes [17].

Cardiovascular disease, degenerative brain disease and reverse cholesterol transport

Promoting cardiovascular health in the coming years will see redoubled efforts to improve our understanding of the biologic nature of HRP and CAD/CVD. While significant strides have recently been made in this direction, particularly major advances in our understanding of the interactions of cellular senescence, inflammation, aging and CVD have served to underscore the systemic nature of the atherothrombotic disease process [1,18]. As an example and as we have recently reviewed elsewhere [1,3,18], not only is atherosclerosis and HRP responsible for strokes, but it is now clearly implicated in Alzheimer's and other degenerative brain diseases (DBDs); conditions previously thought to be solely due to degenerative neurologic processes [18-19]. This 'HRP-DBD axis' of disease highlights the systemic inflammatory nature of atherosclerosis, and emphasizes the fact that the local opening of an isolated coronary artery obstruction does not treat the entire patient. Again, the burden of this disease is enormous. Alzheimer's disease is the most common form of dementia, accounting for 50 to 56% of cases [20]. More than 35 million people worldwide – 5.5 million in the United States – suffer from this condition. The principal risk factor for Alzheimer's disease is age. However, vascular disease affecting the brain is thought to affect 60-90% of patients with Alzheimer's disease, and contributes to a worsened clinical outlook [20]. As the aging of the population increases, the prevalence will approach 13.2 to 16.0 million cases in the USA by mid-century. Our current understanding of the mechanisms whereby HRP and CVD contribute to DBD is rudimentary, but aging, hypertension, the deposition of certain proteins and inflammation likely act in concert with vascular mechanisms to induce neuronal and brain dysfunction. It is at this intersection point that the interactions between atherosclerosis, aging and DBD can be readily appreciated, and the pathways forward from risk to health are most sharply brought into focus (Figure 1).

Of all the potential pathways whereby CVD and atherosclerosis may give rise to DBD, increased inflammation is likely to be a critical mechanism. An exciting mode of decreasing vascular inflammation is to reduce the amount of cholesterol in atherosclerotic plaques. This concept of 'reverse cholesterol transport' – the removal of cholesterol from plaque – is evolving rapidly. The prototypical family of drugs which promote reverse cholesterol transport is the cholesteryl ester transfer protein (CETP) inhibitors. CETP

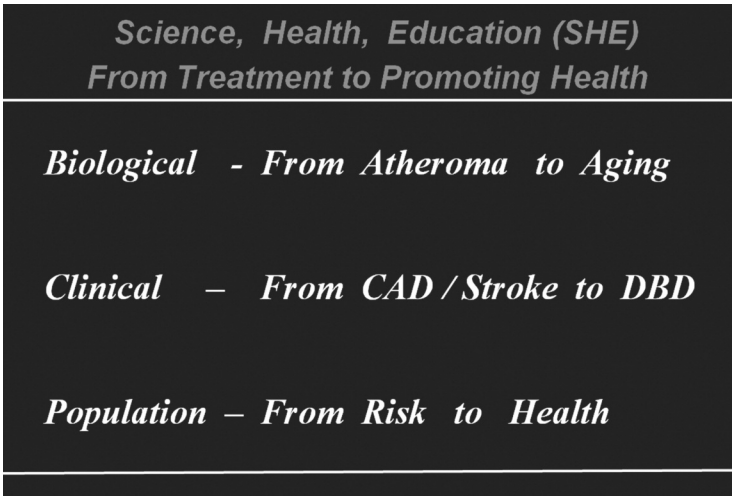

Figure 1. Overview of the interactions between atherosclerosis, aging, CVD and DBD, and the proposed therapeutic transitions from CVD risk to global cardiovascular health.

is a protein which facilitates the shuttling of different cholesterol-related particles in the body, in particular the reverse transport of cholesterol from the tissues back to the liver. Recently, treatment with anacetrapib, a CETP inhibitor, was found to lower low-density lipoprotein (LDL) ('bad') cholesterol and dramatically raise HDL ('good') cholesterol by 138%, with an acceptable side-effect and adverse event rate [21]. Our group will soon embark on the study of another CETP inhibitor, dalcetrapib, with the specific aim of investigating its effect on reducing the size of atherosclerotic vascular lesions.

Promoting global cardiovascular health

With the rapid 'Westernization' of many low- and middle-income countries (LMICs), rates of smoking, obesity, physical inactivity and other adverse factors associated with CVD are rising dramatically in these regions. A veritable explosion of global CVD appears certain if high-level action is not taken [3]. The Institute of Medicine (IOM; the health arm of the US National Academy of Sciences) has undertaken an extensive review of the problems faced in LMICs and has produced a report titled *Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health* [22-23]. The document lays out a strategic path forwards for how

we might form broad partnerships and strategic alliances which allow a multipronged attack on CVD in LMICs. A summary of these recommendations is provided in Figure 2, and provides a comprehensive framework for addressing the global threat of CVD.

Equally as important, in May 2010 a resolution was passed by the United Nations to move forward with a high-level meeting on noncommunicable diseases. This meeting, scheduled for September 2011, is a clear signal that CVD is now seen as a critical factor in worldwide health. Areas where inroads can most readily be made have already been identified: raising public awareness; avoidance of risk-taking behavior (e.g. smoking, physical inactivity); and improved access to effective and affordable CVD medicines by generic availability, removal of legal restrictions, enhanced bulk procurement and the elimination of mark-up and tariffs [24]. The development of a polypill may play a major role in expediting a number of these objectives.

Now that the global problem of CVD has been defined and an initial path forward laid out, the greatest challenge ahead will be translate these plans into actions. Moving from IOM recommendations and United Nations meetings to global cardiovascular health will require an iterative approach grounded in science, health and education (Figure 1).

Figure 2. Recommendations for improving global cardiovascular health from the IOM document *Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health* [22-23].

Conclusions

We are facing an epidemic of CVD. However, there are many potential advances and strategies that might be implemented to address this problem. At all levels, from the scientific laboratory, subsistence-level LMICs and to the highest international political platforms, maintaining a comprehensive and energized (but yet achievable) outlook toward this problem will be paramount. Maximizing the use of current knowledge, infrastructure and resources while minimizing factors such as political gain and corporate agendas will be key. Motivating ourselves, our families and our societies to take the required steps towards cardiovascular health is something we must all strive towards.

Conflicts of interest/Disclosures and acknowledgements

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