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Cardiovascular Defense Challenges at the Basic, Clinical and Population Levels

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Abstract

Cardiovascular disease (CVD) is now the leading cause of mortality worldwide. Particularly in Low and Middle Income Countries, rapid urbanization and secondary factors such as increasing obesity, poor diet and lack of exercise have combined to propel CVD into this position. Given the enormous scope of this problem and the complex cultural, societal and political issues that are involved, and equally sophisticated and multipronged approach is required to combat CVD at the global level. In this review we outline the basic, clinical and population level challenges that we face in defending ourselves against this disease.

It is well known that cardiovascular disease (CVD) is among the leading causes of mortality across the globe.^{1–2} Somewhat encouragingly, the latest data from the United States (US) indicate that from 1998 to 2008, the rate of death attributable to CVD declined 30.6%.³ Nevertheless, US mortality data for 2008 show that CVD continues to account for 1 of every 3 deaths.³ Of this major cardiovascular burden of disease, atherosclerotic coronary artery disease (CAD) accounted for the major proportion of CVD morbidity, causing ~1 of every 6 deaths in the US during this time.³ Therefore, while inroads against CVD and CAD have been made, a great deal of work remains to be done. In this article we critically appraise the basic, clinical and population-level challenges that remain to be addressed to adequately defend ourselves and the next generation against this epidemic.

Transition from Complex CVD to Promoting Health

In decades past and to the present day, great effort has been devoted by both basic scientists and clinicians to pursuing the concept of the “vulnerable plaque”. These vulnerable plaques are lipid-laden arterial atherosclerotic lesions that have an attenuated overlying fibrous cap and which are prone to rupture and cause acute thrombotic arterial occlusion, which may lead to myocardial infarction or stroke.⁴ Much attention was given to identifying these lesions, in the hope that preventive interventions such as the stenting of a non-obstructive but vulnerable plaque would reduce subsequent clinical events. This has led to great advances in imaging techniques,^{5–7} and the features of “high-risk vulnerable” (HRP) plaques that are prone to rupture and cause events have been well defined.⁴ However, while there is no question that vulnerable plaques exist and that they can lead to fatal events, recent pivotal studies have helped us to understand that there is almost never a single vulnerable plaque in any given patient.⁸ Moreover, while there may be multiple vulnerable

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plaques in any patient, the recent PROSPECT study taught us that predicting which of these will rupture and cause clinical events appears to be an exceptionally difficult task.⁸ This has led to an important paradigm shift and change in our outlook towards CVD. Rather than thinking in terms of a “vulnerable plaque”, we have gradually come to think in terms of the “vulnerable patient”. That is to say, rupture-prone atherosclerotic plaques rarely exist in isolation, and rather than thinking about individual lesions, it is far more appropriate to consider the patient’s entire vascular tree.

Concurrent to our appreciation of the “vulnerable patient” and as discussed elsewhere, it is also now increasingly recognized that degenerative brain disease (DBD) is intimately linked to the vasculature and overall burden of high risk plaque (HRP).^{1,9} This HRP-DBD axis is operative across a very broad spectrum of disease, from macrovascular large vessel coronary or carotid occlusions leading MI or stroke, to microvascular small vessel changes causing dementia. Collectively, the critical importance of HRP with respect to brain, heart, kidney and other organ function, together with the concept of the “vulnerable patient”, is strong evidence that to make further progress in fighting this disease we must transition from considering primarily the coronary vessels (i.e. CAD), to looking at the entire patient in terms of systemic cardiovascular disease (CVD) (Figure 1).

Basic Challenges: Aging and HDL-Cholesterol Pathways

With a few notable exceptions (see below), CVD is in fact a disease of aging. Advances in the last decade have yielded major breakthroughs in our understanding of the aging process at the genetic and molecular level. As a focal point of these basic advances, the 2009 Nobel prize was awarded for the discovery of telomeres and telomerase. Telomeres are sections of DNA at the ends of DNA strands that may become shortened with successive cellular division, while telomerase is an enzyme that aids in maintaining proper telomere length. As a key aspect of cellular aging, when telomeres reach a critically shortened length cell division ceases and cellular senescence (from the Latin word *senex*, meaning old age or old man) then ensues. In simplistic terms, senescence is a form of “cellular hibernation” marked by growth arrest, resistance to apoptosis and altered gene expression.^{10–11} Furthermore, basic science insights from premature vascular aging disorders such as Hutchinson-Gilford Progeria Syndrome have underscored the fact that cellular senescence is closely related to systemic aging.¹¹ Adequately defending ourselves against CVD will certainly be contingent upon a complete and proper understanding of the intricacies of telomere function.

Another pivotal basic advance has been our appreciation of the importance of reverse cholesterol transport.^{12–13} In brief, this involves the transport and removal of cholesterol moieties from the periphery, and in particular from atherosclerotic plaques, back to the liver. Once at the liver, the cholesterol moieties may be excreted and eliminated. This process is largely under the purview of high density lipoprotein (HDL) cholesterol,¹⁴ and has seen intense efforts directed towards therapeutically raising the levels of this lipoprotein. While other agents exist, the cholesteryl ester transfer protein (CETP) inhibitors are the prototypical drugs developed to promote reverse cholesterol transport. CETP, a plasma protein, facilitates the shuttling of lipids and triglycerides between transporting lipoprotein particles. Clinical trials with anacetrapib, a CETP inhibitor, successfully lowered the levels of low-density lipoprotein (LDL) cholesterol while raising HDL cholesterol by 138%.¹⁵ Our group has recently reported a major study of another CETP inhibitor, dalcetrapib. In this 130 patient, double-blind, multicentre trial, the use of dalcetrapib was associated with likely beneficial vascular effects, including a reduction in vessel enlargement over 24 months. While not powered for clinical endpoints, there was no difference in event rates between the placebo and dalcetrapib groups.¹⁶ The much larger dal-OUTCOMES study, with > 15,000

patients, is now investigating the efficacy of this agent for reducing CVD events in patients that recently suffered from an index acute coronary syndrome.¹⁷

Certainly, a vast number of basic science discoveries have been made that have advanced our knowledge of CVD. However, the examples of telomeres/senescence and reverse cholesterol transport illustrate the point that the successful and timely clinical translation of basic discoveries is vital to defending ourselves against CVD.

Clinical challenges: The HRP Initiative Subclinical Study and the Polypill

While we may be in the process of transitioning from considering CAD to systemic CVD, and from the vulnerable plaque to the vulnerable patient, a lingering question that remains to be properly addressed is: who is at risk for CVD? At present, risk assessment is typically performed by simple algorithms such as the Framingham Risk Score, with simple online tools readily available to calculate 10-year risk of CAD-related adverse events (<http://www.mdcalc.com/framingham-cardiac-risk-score>). Although these tools can give a reasonable estimate of 5- or 10-year risk for events, they have very limited utility for identifying asymptomatic patients who are at risk for near-term CVD-related events.¹⁸ Aggressive primary prevention is likely to avert major morbidity and mortality in patients at risk for near-term events, and a window of opportunity exists for therapeutic intervention. In an attempt to define novel and efficacious approaches to identify and treat those at risk for near-term events, the High Risk Plaque (HRP) Bioimage study was recently initiated.¹⁸ Over 7,500 patients 'at-risk' for CVD events, but without manifestations of atherothrombotic disease, were entered into this study. Subjects underwent comprehensive baseline assessment, which included determination of CVD risk factors, quantification of coronary artery calcification by computed tomography (CT), measurement of intima-media thickness, carotid and abdominal aortic artery ultrasound, and ankle-brachial index assessment. Participants with one or more abnormal results in these screening tests underwent additional imaging evaluation. The trial is now in an active follow-up phase, and initial results will soon be at hand. Importantly, this study will identify all CVD-related events, including DBD and stroke, and will permit global measures of CVD, burden of HRP and even the genetics of this disease to be correlated and explored in depth. By arming ourselves with this information, clinicians will be far better informed to make proactive treatment decisions.

At its core, the HRP study is driving at optimizing primary prevention. While identifying at risk-patients is one aspect of this problem, many other challenges remain to be addressed at the patient- and clinical-level before we can prevent CVD. As the complexity of medical treatments continue to increase, the adherence of patients to these sometimes daunting polypharmaceutical therapeutic regimens is a growing concern. Indeed, nonadherence to prescribed therapies may occur in ~50% of patients,^{19–20} accounting for \$290 billion of US annual health care expenditure.²¹ Aligned with transitioning towards treating systemic CVD, the drive towards the widespread implementation of a polypill as a primary preventive agent or secondary treatment is gaining in momentum. The polypill has multiple potential advantages for the patient, including increased convenience and adherence, but also decreased cost. The polypill can combine several agents that tackle platelet adhesiveness (aspirin), blood pressure (ACE inhibitor, thiazide diuretic), lipid levels (statin) and other aspects of CVD primary risk management or secondary treatment. Recent estimates suggest that widespread polypill use by US adults aged ≥ 55 years may prevent 3.2 million CAD events and 1.7 million strokes over 10 years.²² Several randomized clinical trials of the polypill are now underway aiming to define their potential effects on CVD risk factors and clinical outcomes.²² Nevertheless, as the polypill potentially moves into clinical practice, physicians will need to remain cognizant of the need to balance the merits of the inexpensive

but relatively fixed combinations available via polypills, with the need to individualize therapies to the particular needs of each patient.

These are but a few examples of the many challenges we face and progress being made at the clinical level in defending ourselves against CVD. Other notable (but by no means all) clinical challenges include achieving the implementation of guideline recommendations, moving from paper-based to electronic medical record systems, improving communication and adopting a team-based approach to health care delivery.

Population challenges: IOM report, UN and Chronic Diseases and SHE Initiative

Defending ourselves against CVD is a global concern. While in Western societies mortality rates from CVD may have improved marginally, in low- and middle-income countries (LMICs) the situation remains grim. In certain LMICs up to 75% of deaths are attributable to CVD.²³ This is due to a complex set of interacting factors that include rapid modernization and “Westernization”, inadequate availability of nutritious foods and poor diet, lack of exercise, high prevalence of tobacco use and lack of attention to other CVD risk factors (hypertension, diabetes, hyperlipidemia). The Institute of Medicine (IOM; the health arm of the US National Academy of Sciences) recently began to engage these issues by establishing a high-level committee to review the relevant factors impacting global CVD health. This led to the tabling of a raft of initiatives focusing on tackling CVD in LMICs titled “Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health”.^{1,24–25} As shown in Figure 2, the report provides a comprehensive framework for attacking the global threat of CVD.

This has been echoed by the General Assembly of the United Nations. In an historic two day meeting in September 2011, non-communicable diseases were deemed a development challenge of “epidemic proportions”. The World Health Organization Chief stated that the “meeting must be wake-up call - a watershed event that replaces ignorance and inertia with awareness and right actions”.²⁶ Member states signed a declaration that addresses tobacco, industrially produced trans fats in foods, and several other key issues related to the world's leading non-communicable diseases, and CVD in particular. Further consensus was reached as to the root causes driving the increase of non-communicable diseases: the use of tobacco, excess alcohol consumption, poor-quality food, lack of exercise, and lack of access to healthcare services and medicines.²⁶ While this United Nations meeting and the IOM document have outlined the problems and the road forwards, the hard task must now begin of actually implementing these recommendations and changes.

As an extension of some of these challenges we face in enacting population level changes, a major hurdle to be addressed is the willingness of patients to adopt healthy behavioral patterns. Finding ways to motivate people to stop smoking and to “move (exercise) more and eat less” is critical. It is our personal belief and experience that teaching healthy habits from a young age is the key to success. The notion of health education and motivation among young persons is encapsulated by the SHE initiative: The Foundation for Science, Health and Education. SHE is a multifaceted program that is aiming to better educate children and young adults about how to live a healthier lifestyle. Projects run by SHE include a preschool trial to promote cardiovascular health in 6,000 children in Columbia (enrolment completed) and now a planned extension of that study to 25,000 participants, various educational children's books, a “Healthy Habits Campaign” involving youth sports programs in Spain, studies of changing cardiovascular risks in Grenada with rapid modernization, and multinational studies involving the polypill based in Europe and New York.²⁷ This type of work being undertaken by the SHE foundation, in conjunction with a

great deal of other work that remains to be done, should see the next generation far better equipped to make healthy life choices.

Conclusions

Cardiovascular health is a major global concern that cannot be effectively tackled by any single therapy, intervention or initiative. From vulnerable atherosclerotic plaques to the United Nations, major transitions are in progress which will aid in managing this problem (Figure 1). Looking ahead, a concerted effort across multiple disciplines, and a determination to move forwards and overcome inevitable obstacles, will be required if we are to effectively defend ourselves and the next generation against this disease.

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REFERENCES

1. Kovacic JC, et al. From Treating Complex Coronary Artery Disease to Promoting Cardiovascular Health: Therapeutic Transitions and Challenges, 2010–2020. *Clin Pharmacol Ther.* 2011; 90:509–518. [PubMed: 21900892]
2. Kovacic JC, et al. Cellular senescence, vascular disease, and aging: part 1 of a 2-part review. *Circulation.* 2011; 123:1650–1660. [PubMed: 21502583]
3. Roger VL, et al. Heart Disease and Stroke Statistics-2012 Update: A Report From the American Heart Association. *Circulation.* 2012; 125:e2–e220. [PubMed: 22179539]
4. Moreno PR, et al. Promoting mechanisms of vascular health: circulating progenitor cells, angiogenesis, and reverse cholesterol transport. *J Am Coll Cardiol.* 2009; 53:2315–2323. [PubMed: 19539140]
5. Rudd JH, et al. Imaging atherosclerotic plaque inflammation by fluorodeoxyglucose with positron emission tomography: ready for prime time? *J Am Coll Cardiol.* 2010; 55:2527–2535. [PubMed: 20513592]
6. Underhill HR, et al. MRI of carotid atherosclerosis: clinical implications and future directions. *Nat Rev Cardiol.* 2010; 7:165–173. [PubMed: 20101259]
7. Klink A, et al. Diagnostic and therapeutic strategies for small abdominal aortic aneurysms. *Nat Rev Cardiol.* 2011; 8:338–347. [PubMed: 21304473]
8. Stone GW, et al. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med.* 2011; 364:226–235. [PubMed: 21247313]
9. Kovacic JC, et al. Cellular senescence, vascular disease, and aging: part 2 of a 2-part review: clinical vascular disease in the elderly. *Circulation.* 2011; 123:1900–1910. [PubMed: 21537006]
10. Campisi J, et al. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol.* 2007; 8:729–740. [PubMed: 17667954]
11. Olive M, et al. Cardiovascular pathology in hutchinson-gilford progeria: correlation with the vascular pathology of aging. *Arterioscler Thromb Vasc Biol.* 2010; 30:2301–2309. [PubMed: 20798379]
12. Fayad ZA, et al. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet.* 2011; 378:1547–1559. [PubMed: 21908036]
13. Fayad ZA, et al. Rationale and design of dal-PLAQUE: a study assessing efficacy and safety of dalcetrapib on progression or regression of atherosclerosis using magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography/computed tomography. *Am Heart J.* 2011; 162:214–221. e2. [PubMed: 21835280]
14. Navab M, et al. HDL and cardiovascular disease: atherogenic and atheroprotective mechanisms. *Nat Rev Cardiol.* 2011; 8:222–232. [PubMed: 21304474]

15. Cannon CP, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N Engl J Med.* 2010; 363:2406–2415. [PubMed: 21082868]
16. Fayad ZA, et al. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet.* 2011; 378:1547–1559. [PubMed: 21908036]
17. Soe K, et al. Cardiovascular risk reduction via increasing HDL cholesterol: the promise of the dal-OUTCOMES Trial. *Curr Diab Rep.* 2011; 11:4–6. [PubMed: 21069482]
18. Muntendam P, et al. The BioImage Study: novel approaches to risk assessment in the primary prevention of atherosclerotic cardiovascular disease--study design and objectives. *Am Heart J.* 2010; 160:49–57. e1. [PubMed: 20598972]
19. Boden WE, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007; 356:1503–1516. [PubMed: 17387127]
20. Frye RL, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med.* 2009; 360:2503–2515. [PubMed: 19502645]
21. Epstein RS. Medication adherence: hope for improvement? *Mayo Clin Proc.* 2011; 86:268–270. [PubMed: 21454729]
22. Muntner P, et al. Projected impact of polypill use among US adults: Medication use cardiovascular risk reduction, and side effects. *Am Heart J.* 2011; 161:719–725. [PubMed: 21473971]
23. World Health Organization 2009 World Health Statistics. [Accessed 5/10/2011] Available at <http://www.who.int/whosis/whostat/2009/en/index.html>.
24. Fuster V, et al. Promoting global cardiovascular health: moving forward. *Circulation.* 2011; 123:1671–1678. [PubMed: 21502585]
25. Kishore SP, et al. Promoting global cardiovascular health ensuring access to essential cardiovascular medicines in low- and middle-income countries. *J Am Coll Cardiol.* 2011; 57:1980–1987. [PubMed: 21565635]
26. [Jan 16th 2011] Non-Communicable Diseases Deemed Development Challenge of 'Epidemic Proportions'. Accessed at <http://www.un.org/News/Press/docs/2011/ga11138.doc.htm> on.
27. Taylor J. Science is the fundamental building block for every project in The Foundation for Science, Health, and Education (SHE). *European Heart Journal.* 2011; 32:662–663.

Therapeutic Transitions from Cardiovascular Disease to Health

CAD – Coronary Artery Disease
HRP – High Risk Plaque
IOM – Institute of Medicine

CVD – Cardiovascular Disease
DBD – Degenerative Brain Disease
SHE – Science, Health and Education

Figure 1.

Overview of proposed therapeutic transitions from CAD to promoting global cardiovascular health. Adapted and reproduced with permission from Kovacic et al.¹

Figure 2. Barriers to control global CVD and essential functions and recommendations to overcome those barriers arising from the Institute of Medicine document “Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health.” Figure reproduced with permission from Fuster et al.²⁴