Review

Identifying the Risk and Preventing the Consequences of Cardiovascular Disease

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Efforts to prevent cardiovascular morbid events have focused predominantly on identification of population risk factors with intervention based on the level of these risk factors. Individualised care is now possible by identification of early, asymptomatic vascular or cardiac disease likely to progress to morbid events. Intervention aimed at slowing or reversing the progression of the vascular or cardiac abnormalities can then become the therapeutic target. Since early disease commonly occurs in the absence of abnormal threshold levels of risk factors, this approach is more sensitive and specific than risk factors in matching treatment to individual risk. Preliminary data with a series of 10 non-invasive tests and a unique scoring system developed at the University of Minnesota provides a quantitative assessment of the health of the small arteries, large arteries and left ventricle. This scoring system has been shown to be remarkably sensitive in identifying the risk and time course of future morbid events. Therapy aimed at restoring vascular and cardiac health shows great promise as an individualised approach to cardiovascular disease prevention.

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Cardiovascular disease and its associated target organ morbid events are predominantly a consequence of progressive ageing and atherothrombotic disease involving the arteries and the left ventricle. Since this progressive disease process is a cause of death and disability in over 50% of the population [1], and the cost of care for these diseases consumes more than half of our health care expenditures [2], the need to identify those at risk and to intervene with effective preventive strategies has become a priority in the developed world [3].

The effort to prevent morbid events involves two very different constituencies, the population and the individual patient. Welfare of the population is the responsibility of government agencies, public health care associations and health care funding bodies. Their concern is the reduction in their communities of the prevalence of morbid events that adversely affect the health of the public and the expenditures on health care. Individual health is the responsibility of people and their health care providers.

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For the past few decades the population approach has dominated the agenda for identification of risk and its management. Epidemiologic observations in populations have identified the association of markers, such as age, blood pressure and cholesterol levels, with subsequent event rates [4]. Clinical trials in populations have documented that interventions that lower cholesterol and blood pressure have a favourable effect on outcome [5,6]. This population risk has been translated into individual risk, and this treatment response has become a mandate for therapy aimed at these markers of cardiovascular risk [7]. Population risk and response has thus been extended from the population, where it originated, to individual patient care where the observations have remarkably little statistical impact.

The problem is that by relying on so-called risk factors for symptomatic cardiovascular disease the epidemiologists and clinical trialists are focusing on markers that are statistically associated with the disease process but are not the biological disease process itself. The association of blood pressure and cholesterol with event rates is continuous at all levels of the risk factors, and the slope of risk is modest [8,9]. The current recommendation to treat blood pressure and cholesterol when levels exceed a certain threshold is neither statistically nor medically justified. Indeed, most morbid events now occur in individuals whose blood pressure and cholesterol are below these
thresholds [10]. Thus the population approach—to lower everyone's blood pressure and cholesterol by lifestyle alterations to reduce population risk—is rational, but the health care provider recommendation to treat individuals with values above an arbitrary threshold is not.

Management strategies to prevent cardiovascular disease morbidity and mortality have differed strikingly from those in cancer. Early detection of cancer has become the standard approach for reducing its impact. Routine screening for early disease, including unpleasant colonoscopies and radiation exposure have become standard health care insurance-supported procedures that are advocated for all. This effort at early detection and eradication is credited with accounting for the decline in cancer mortality noted in the last decade [11]. The well known adverse effects of invasive procedures spawned by the screening has created some controversy about the prudence of this population-wide screening, but the public is largely convinced of its value.

Since early disease in the arteries and left ventricle can now be detected non-invasively and without radiation, and progression of this early disease is biologically and statistically associated with the development of morbid events, it now seems rational to follow the path of cancer prevention by the detection of early disease. The striking advantage of this cardiovascular approach, as opposed to that of oncology, is that the detection is simple and non-invasive, and management of the disease if detected is pharmacologic and non-threatening.

How to detect early disease and the strategy for slowing its progression are issues that have only recently gained attention. Indeed, the focus for the past 30 years has been on the diagnosis and treatment of morbid events rather than on their prevention. I shall therefore explore some issues related to early detection, review the changes in vascular and cardiac function and structure that culminate in morbid events, discuss the impact of therapy on these cardiovascular abnormalities, and provide an overview of our own program for early detection and treatment.

The Concept of Early Detection
Cardiovascular morbid events are a consequence of structural changes in the arteries and left ventricle, and these abnormalities can be detected long before symptoms become apparent. In the absence of demonstrable structural abnormalities the vast majority of these morbid events cannot occur. The time frame from detectable abnormalities to subsequent events is likely quite variable, depending on the sensitivity of the detection methodology and the nature of the event. Nonetheless, it is likely that most events occur years after abnormalities in the arteries and heart can be identified.

Functional changes in the arteries and heart often accompany the structural changes. In some instances the functional changes may appear to precede the structural changes, but their relationship is critically dependent on the sensitivity and specificity of the methodology used to assess function and structure. For example, constriction and stiffening of small arteries are functional changes that will raise blood pressure, but thickening of the wall may both reduce lumen size and reduce the artery's compliance or elasticity. Whether thickening, a structural change, preceded or followed constriction, a functional change, would be difficult to determine. Similarly, a fall in left ventricular ejection fraction is often identified as a functional change, but structural remodelling that enlarges left ventricular chamber size will usually also result in a reduced ejection fraction. It is therefore often unclear whether the change is functional or structural.

So-called risk factors for morbid events are therefore actually risk factors for functional and structural abnormalities of the arteries and heart. The insensitivity and non-specificity of risk factors is that the relationship between risk factors and early disease is dependent in large part on intrinsic individual differences in response. This individualised sensitivity is largely inherited and might someday be detectable in genomic analysis, but the complexity of the multi-genomic nature of these variables makes this a long-term problem. In the meantime, phenotypic rather than genotypic characterisation appears to be the more useful approach.

Early detection is useful only if intervention can alter the natural history of disease progression. Over the past few decades a number of lifestyle characteristics have been associated with event occurrence and, by implication, their alteration should slow progression. A recent Italian study has now shown for the first time that dietary intervention, in this instance with a Mediterranean-style diet supplemented with olive oil or nuts, can reduce the occurrence of morbid events [12]. In regard to drug interventions, a number of pharmacologic agents have clearly documented efficacy not only in reducing morbid events but also in slowing or even reversing the cardiovascular abnormalities that lead to morbid events [13–15].

Arterial and Cardiac Abnormalities
Atherosclerosis and ageing affect the wall of the large and small arteries. The process probably begins in the endothelial layer, which normally maintains vascular relaxation, inhibits growth and prevents infiltration of lipids [16]. Endothelial dysfunction is a manifestation of ageing and occurs prematurely in those with an inherited risk of disease and in response to abnormal risk factors [17]. The result of this dysfunction is vascular smooth muscle growth and remodelling as well as plaque formation in conduit arteries.

The small arteries and the large conduit arteries react differently to endothelial dysfunction. The small artery calibre is reduced as a consequence of the remodelling process whereas the conduit arteries' lumen is often enlarged as plaque burden develops [18]. The small artery changes result in a reduction of their compliance or elasticity and contribute to an increase in vascular resistance that raises blood pressure. The large artery changes contribute to vascular stiffening that raises systolic pressure and widens pulse pressure [19].

Cardiac changes include myocyte hypertrophy, fibrosis and wall thickening that reduce ventricular compliance.
Chamber dilation that portends heart failure is often a consequence of myocardial injury, often ischaemic from co-existent coronary artery disease. Cardiac structural changes may be accompanied by hormonal changes that can be detected in peripheral blood [20]. These cardiovascular functional and structural changes can be detected long before the disease processes advance to the point of morbid events. Thus the opportunity for early detection provides the potential for effective intervention.

Response to Therapy

Anti-hypertensive and lipid-lowering drugs have served as the cornerstone of preventive pharmacotherapy. The traditional view is that these drugs favourably affect the course of disease by their influence on blood pressure and LDL-cholesterol levels. Guidelines therefore recommend instituting drug therapy when these two risk factor levels exceed arbitrary thresholds [7]. This approach has been successful in demonstrating that individuals who meet these criteria fare better when these drugs are prescribed rather than a placebo [5,6]. The fallacy of this approach, however, is that the majority of morbid events actually occur in individuals whose risk factor levels do not exceed these arbitrary thresholds [10]. Therefore the current strategy leaves untreated the majority of individuals destined to suffer from such events.

A more useful concept is to view these drugs as having their favourable effects on the artery or left ventricular wall. That favourable effect occurs regardless of the level of the target risk factor. In that paradigm the presence of an abnormality of the wall is the justification for treatment. Such an approach will not only open therapy to a larger proportion of the population at risk but will also exclude from therapy individuals without early vascular or cardiac disease who are not at risk. If the search for early disease is carried out sequentially, such as at five-year intervals, then early disease should be detectable in time for effective intervention if needed.

Inhibition of the renin–angiotensin system with ACE inhibitors or angiotensin receptor blockers, and statin drugs to lower LDL-cholesterol have been the best studied and most effective interventions to slow progression of atherosclerotic disease [21,22]. These drugs appear to improve endothelial function. Calcium antagonists also restore endothelial function [23]. Beta blockers have demonstrated striking inhibiting effects on left ventricular remodelling [24]. Lifestyle adjustments can enhance the favourable effect of drugs, especially in those individuals where environment is playing a key role in progression. Individualised care is far more effective than population intervention, although the latter has been key to demonstrating efficacy of interventions.

A Program for Early Detection and Treatment

The traditional approach for identifying risk for cardiovascular disease morbid events has been the measurement of risk factors. Whereas the levels of these risk factors are statistically associated with the likelihood of morbid events, they are neither sensitive nor specific in identifying an individual’s risk. For that purpose evaluation for early disease identifies the biological rather than the statistical risk. Furthermore, the assessment of early disease provides an opportunity for monitoring disease severity over time and its response to therapeutic intervention. Risk factors cannot offer such dynamic insight.

In recent years the assessment of coronary artery calcium by radiological tools has been advocated as a guide to pre-clinical disease in the coronary circulation [25]. Coronary artery calcification is a reliable guide to atherosclerotic plaque formation but it is highly insensitive for detecting early disease. Since coronary atherosclerosis often begins progressing in the fourth and fifth decade, when calcium is rarely detectable, waiting for high calcium scores for detection of disease will likely delay diagnosis until therapy may be less effective than if introduced years before. Furthermore, the radiographic detection of calcium involves considerable radiation exposure, Ultrasound can be used to detect plaques in the carotid arteries. Although these plaques may not necessarily be the cause of future morbid events they provide insight into the health of all the conduit arteries, including the coronary circulation.

Artery stiffness can be quantitated by simple radial artery tonometry and computer analysis of the decay of the pulswave [26]. This technique allows the separate assessment of both small and large artery stiffness with a diagnostic test that usually takes only 10 min. The measurements reflect the total body small and large artery stiffness, not any specific regional stiffness. Pulswave velocity, usually obtained by simultaneous registration of femoral and carotid pulswaves, provides a pressure-dependent measure of large artery stiffness. It has emerged as the most commonly employed measure of artery health [27], but it cannot assess the small arteries, where early disease exerts its effect.

Our approach at the University of Minnesota has been to provide a comprehensive assessment for early disease that includes 10 tests that evaluate the health of the small arteries, the large arteries and the left ventricle. This includes the measurement of resting sitting blood pressure, the change in blood pressure during a 3-min treadmill exercise at 5 METS, small artery and large artery elasticity, carotid ultrasound for wall thickness and plaque formation, a urine test for microalbumin/creatinine ratio, an electrocardiogram, an ultrasound of the left ventricle for wall thickness and mass, and a blood test for NT-ProBNP. Each of these tests is scored as normal, borderline or abnormal, and several are age-adjusted. The evaluation also includes blood testing for cholesterol fractions, glucose and high-sensitivity CRP.

Our preliminary outcomes data reveal remarkable sensitivity of the 10 tests to identify early disease likely to lead to morbid events, and, perhaps more importantly, to identify individuals with no risk for subsequent morbid events [28]. Using the early disease score, rather than risk factors, has the potential for far better discrimination of who needs treatment and who can be reassured for an interval of at
least five years. Repeat testing is encouraged at intervals, either to document continued cardiovascular health or a favourable response to intervention.

In order to make the program more cost-effective we have introduced a 4-test screen which can identify with 90% accuracy those individuals who should go on to the full evaluation because of the likelihood of disease in need of treatment.

What is of course still needed is a cost-effectiveness analysis that can document the savings that would accrue to widespread utilization of screening and evaluation for early disease. Alternate approaches have also been proposed using single tests or radiological procedures. All approaches need to be evaluated.

The era of risk factors as the sole criterion for intervention is no longer tenable. The emergence of effective drug therapy mandates improved diagnostic precision that can be accomplished by the emerging methods for non-invasive evaluation of the health of the arteries and heart.

References


