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.

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

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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.