Role of Preclinical Cardiovascular Disease in the Evolution From Risk Factor Exposure to Development of Morbid Events

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Conventional risk factors (especially high arterial pressure, elevated cholesterol and glucose levels, and cigarette smoking) are useful predictors of morbid atherosclerotic and hypertensive events, and their control variably reduces the incidence of events. However, both the ability to predict risk and the ability to reduce it by modification of established risk factors are limited. These limitations occur in part because the progression from risk factor exposure to morbid events depends on the variable likelihood that individuals exposed to the same risk factors will progress through two stages: the development of asymptomatic or "preclinical" anatomic and functional cardiovascular disease in response to standard risk factors and other variables, and the precipitation of morbid events by progression of preclinical disease or by the action of additional "triggering" mechanisms in the presence of preclinical disease. Advances in diagnostic methodology now make possible accurate noninvasive detection in many asymptomatic individuals of preclinical disease such as left ventricular hypertrophy, carotid atherosclerosis, and renal dysfunction. Progress in elucidating stimuli to left ventricular hypertrophy and systemic atherosclerosis suggests that focusing research separately on these two stages of disease evolution is a fruitful strategy. The closer relation of measures of preclinical disease than risk factors with the subsequent risk of complications indicates that their detection improves clinical risk stratification. However, critical testing of whether clinical outcome is improved or treatment cost is lowered by basing antihypertensive or antihyperlipidemic treatment decisions in part on the presence of preclinical cardiovascular disease is needed before this strategy is adopted on a widespread scale. (Circulation. 1993;88[part 1]:1444-1455.)

KEY WORDS • risk factors • cardiovascular disease

The risk factor concept has guided research, patient care, and public health policy to prevent cardiovascular disease for more than four decades. In simple terms, this concept states that certain factors either contribute to causing or at least help to predict the later development of cardiovascular disease. Initial astute but uncontrolled observations that a disproportionate number of patients with myocardial infarction were men, smoked, and had high arterial pressure and cholesterol levels were confirmed by prospective observations in population-based studies. The risk factor concept gained substantial support when it was shown that cardiac and stroke morbidity fell in response to reduction of high blood pressure and cholesterol and cessation of smoking. These interventions have been temporally associated with declines of up to 60% in the age-adjusted incidence of cardiac and stroke mortality since the early 1960s. Today, the risk factor concept is considered sufficiently well proven to justify public policy recommendations for treatment of hypertension and hypercholesterolemia.

Despite the encouraging experience in many trials, the value of interventions against major risk factors varies for individual patients. For example, each stroke prevented in the large Medical Research Council trial required 833 patient-years of treatment of asymptomatic, but mildly hypertensive patients. Meta-analyses of available clinical trials indicate that antihypertensive treatment has had about half the expected impact on the incidence of heart attacks and the appearance of a "J-shaped" relation between the magnitude of pressure fall during treatment and incidence of myocardial infarction in some trials suggests that too rapid pressure reduction may actually be hazardous. The net benefit of antihypertensive treatment for prevention of coronary heart disease (CHD) is positive when blood pressure can be controlled by low doses of medication in patients at relatively high risk because of age or other factors, but it may not be the same persons who receive the good and the bad. The potential to prevent CHD by drug treatment of hyperlipidemia has been rather recently defined and appears to be greater for reduction of nonfatal myocardial infarction than death. Because of the relatively short period that the most effective hypocholesterolemic drugs have been widely used, all possible hazards may not have yet been uncovered. Life-long drug treatment of millions of...
persons with mildly elevated cholesterol is a costly process that may not be warranted for primary prevention in otherwise low-risk individuals. 30

Optimal cardiovascular disease management should produce the greatest benefit with the least cost. This goal may be optimally achieved either by development of strategies that are so cost effective and risk free that they can be applied on a massive scale or by targeting highly efficacious but more expensive or potentially hazardous therapy to those at sufficient risk of morbid events that they are likely to benefit from such treatment, while sparing those at little or no risk. Population-based strategies of avoiding obesity, cigarette smoking, excessive intake of fats or salt, and a totally sedentary lifestyle appear more likely than medication-based strategies to fall into the first category. Intervention with medications is commonly initiated because one or more risk factors exceed a threshold level. This strategy is limited by the fact that many, if not most, individuals with mild risk factor elevation will not suffer cardiovascular events. Only a minority of such events occur in the small proportion of the population with severe abnormality of one or more risk factors. The present review considers the strengths and weaknesses of evidence in favor of the concepts that the evolution from risk factor exposure to morbid events proceeds through a stage marked by asymptomatic structural cardiovascular disease and that risk stratification by identification of preclinical disease may improve targeting of more expensive or potentially risky treatments to the patients most likely to benefit.

Stimuli to Preclinical Cardiovascular Disease

Pathological changes in the heart and arteries that develop early in the course of hypertensive and atherosclerotic cardiovascular disease, before symptoms or morbid events occur, may be described as "preclinical disease." Methodologic advances now make it possible to identify preclinical disease in asymptomatic individuals and to relate the presence and severity of preclinical disease to the level of risk factors, on the one hand, and to the subsequent risk of morbid events, on the other. Accurate quantitative noninvasive methods can now detect several major manifestations of preclinical cardiovascular disease: left ventricular hypertrophy, 21 abnormalities of myocardial perfusion and metabolism, 22,23 extracardiac atherosclerosis, 24 and early renal dysfunction as manifested by microalbuminuria (Fig 1).

Consistent and graded relations between established risk factors and manifestations of preclinical disease are sufficiently strong to be evident in modest-sized cross-sectional studies as opposed to the many years required to identify relations between risk factors and morbid events.

In the simplest formulation, one can conceive of cardiovascular disease as developing in two stages: risk factors $\rightarrow$ preclinical disease $\rightarrow$ morbid events.
Stimuli to Asymptomatic Coronary Atherosclerosis

Relevant data have been limited by the difficulty in characterizing coronary artery anatomy by catheterization or at necropsy in subjects who are both relatively unselected and have known risk factor status. In a necropsy study of 35 subjects ranging in age from childhood to early adult life who had been previously evaluated in the Bogalusa Heart Study, Newman et al.25 found that aortic fatty streaks were related to antemortem measurements of several risk factors, with especially close correlations (both \( r = .67 \)) for total and low-density lipoprotein (LDL) cholesterol. Among 27 adult subjects evaluated antemortem by the Framingham Heart Study,26 age was the only independent correlate of the extent of coronary atherosclerosis in women, and total serum cholesterol was the only independent correlate in men. In 7591 male participants in the Honolulu Heart Study, the levels of blood pressure, serum cholesterol, body mass index, and (inversely) alcohol intake at baseline were independent predictors in multivariate analyses of severe coronary stenosis on coronary arteriograms in the subset of 357 men who underwent this test during 20-year follow-up.27 These risk factors also predicted incident myocardial infarction, whereas cigarette smoking and serum triglyceride level predicted myocardial infarction more strongly than the severity of coronary stenoses (relative risks, 2.0 versus 0.95 and 1.28 versus 1.04, respectively).27 In addition to the traditional risk factors, the plasma level of lipoprotein(a), which appears to be predominately under genetic control, is strongly associated with both atherosclerosis and arterial thrombosis.28,29

Stimuli to Left Ventricular Hypertrophy

The ability to measure left ventricular mass by echocardiography as well as other, more precise but also more costly, techniques such as magnetic resonance imaging has made it easier to characterize the factors regulating ventricular size. Left ventricular mass has been shown to be positively related in both normal and diseased populations to blood pressure, body size and obesity, and male gender. Although left ventricular hypertrophy is more common in older than in younger populations,30 this is mostly due to age-related increases in the prevalence of hypertension and various forms of heart disease; among clinically normal individuals age per se has little effect on left ventricular mass.31

Blood pressure. Hypertension is well recognized to be the most frequent antecedent of left ventricular hypertrophy in the general population.30 However, left ventricular mass is only weakly related to single or even multiple measurements of casual blood pressure, with correlation coefficients of .25 to .45 in large clinical or epidemiologic series.32-35 Closer relations have been observed between ventricular mass and blood pressure during daily activity or physical exercise (with \( r \) values between .50 and .65 in most reports).32,36,37 The closer relation between left ventricular mass and blood pressure during normal activity than with values recorded in the physician’s office is consistent with MacMahon’s hypothesis15 that intraindividual variability of risk factors such as blood pressure as well as limitations of conventional techniques for their measurement have led to underestimation of the strength of the relations between risk factors and cardiovascular disease.

Other hemodynamic factors. Recent clinical and experimental studies indicate that the concomitant volume load on the heart (stroke volume or cardiac output) modifies — and under some circumstances may be more important than — the effect of blood pressure on left ventricular mass.34,38 Variables that may stimulate left ventricular hypertrophy through effects on stroke volume or peripheral resistance include exercise39 and increased sodium intake.40 or blood viscosity.41 The improved ability to predict the left of ventricular mass by taking into account several hemodynamic stimuli to left ventricular hypertrophy are illustrated in Table 1 and Fig 2. Increased activity of the renin-angiotensin system or the sympathetic nervous system may stimulate hypertrophy through effects on hemodynamic variables or by direct myocardial actions.42,43 However, activity of these systems does not consistently lead to cardiac hypertrophy.44,45

Body build and gender. Obesity is generally accepted as an independent cardiovascular risk factor, based on prolonged follow-up of many thousands of subjects.46,47 Cross-sectional studies of smaller groups of subjects have also shown that obesity is strongly and independently associated with increased left ventricular mass.30,33 Adult men have greater left ventricular mass than women, both in absolute terms and after indexation for measures of body size.30,31,33,48 Interestingly, an adverse prognosis is predicted by similar levels of indexed left ventricular mass in men and women.49,50 This suggests that greater heart size in adult men may contribute to the well known gender difference in CHD risk. Other evidence suggests that the risk of CHD morbidity may be related to the degree of body growth from infancy to adulthood,51 which is greater in men than in women.

Table 1. Relation of Left Ventricular Mass to Hemodynamic Stimuli in Normotensive and Hypertensive Adults

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation With Left Ventricular Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r )</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>.45</td>
</tr>
<tr>
<td>Stroke volume index</td>
<td>.60</td>
</tr>
<tr>
<td>ESS/ESVI</td>
<td>.48</td>
</tr>
</tbody>
</table>

Multivariate prediction of left ventricular mass

LV mass index (g/m²) = 0.87 (SBP) + 0.69 (SV index) – 17.4 (ESS/ESVI) \( (R=.81; P<.0001) \)

ESS/ESVI indicates end-systolic stress/end-systolic volume index; LV, left ventricular; SBP, systolic blood pressure; and SV, stroke volume.

Adapted with permission from data in Ganau et al.34

Stimuli to Extracoronary Atherosclerosis

The pattern of relations with risk factors is somewhat different for atherosclerosis in the cerebral and peripheral circulations than in the coronary arteries. Thus, among men who died following initial screening in the Oslo Heart Study, high-density lipoprotein (HDL) and...
Factors based total pressure Abnormal Stimuli for have similar predictor subsequent occurrence are cigarette.55 Interestingly, cigarette smoking was not associated with coronary lesions, similar to the Honolulu data.27 In large population-based studies, systolic blood pressure, smoking, and age have generally been stronger predictors than lipid levels of ultrasonically detected carotid atherosclerosis.53,54

Stimuli to Renal Disease

Fewer data are available concerning risk factors for renal dysfunction. In the large group of hypertensive patients enrolled in the Hypertension Detection and Follow-Up Program,55 black race, male gender, older age, and higher diastolic arterial pressure at baseline predicted subsequent deterioration of renal function. Abnormal baseline renal function was, in turn, a potent predictor of subsequent death.

Factors Modifying the Relation of Risk Factors to Preclinical Disease

Although the available data demonstrate strong relations between appropriate risk factor–preclinical disease pairs, considerable interindividual variability in the occurrence and severity of cardiovascular disease remains unexplained. This residual variability may be at least partially due to hereditary factors and risk factor interactions that influence susceptibility to specific risk factors. By extension, individuals without adverse genotypes or risk factor interactions may have relatively low susceptibility to developing cardiovascular disease in response to conventional risk factors.

Interactions Between Risk Factors and Preclinical Diseases

The observation that the adverse consequences of multiple risk factors are more nearly multiplicative than additive may be partially explained by interactions that are being increasingly defined. Evidence that intermittent ischemia—as might occur in the presence of coronary artery obstruction—and increased arterial stiffness—an expected consequence of systemic atherosclerosis—are associated with myocardial hypertrophy56,57 suggests the possibility that atherosclerosis may promote left ventricular hypertrophy. Cross-sectional studies have in fact demonstrated an association between carotid atherosclerosis and left ventricular hypertrophy.58 At present, it is uncertain whether atherosclerosis is the cause or consequence of these associated abnormalities, as more forceful ejection of blood by a hypertrophied left ventricle and greater elevation of systolic blood pressure in the presence of stiffened arteries might be proatherogenic stimuli. Recent research has documented that carotid atherosclerosis is more likely to be present or progress in individuals with clinically apparent vascular disease in other portions of the circulation,59 independent of the level of established risk factors.59,60 As an example of how biological systems may contribute to both preclinical and clinical cardiovascular disease, activation of the renin-angiotensin system may lead to both blood pressure elevation43 and vascular damage,62 contributing to an increased complication rate in patients with high-renin forms of hypertension.53,64
Preclinical Disease Without Evidence of Risk Factors

Although most instances of preclinical disease occur in individuals with at least one of the many established cardiovascular risk factors, this is not always the case. As an example, high normal values of left ventricular mass in normotensive children and adults have been shown to predict subsequent blood pressure elevation.65,66 As prognostically adverse levels of left ventricular mass, arterial wall thickness, and other measures of preclinical disease become better defined, it will be possible to determine whether there is any appreciable prevalence of preclinical disease in individuals without standard risk factors and, if so, to begin to define the pathogenesis of these abnormalities.

Role of Heredity

While the inheritance and underlying defect of familial hypercholesterolemia are well recognized, it is only recently that a variety of genetically determined entities have been shown to underlie a substantial portion of the dyslipidemias encountered in clinical practice.67 Similarly, a strong influence of inheritance on left ventricular mass appears to be additive to the effects of body size and blood pressure.68-70 Evidence has also been obtained of a genetic condition that predisposes to both hypertension and an abnormal lipid profile.71 However, even when a specific genetic mutation strongly determines a clinically deleterious phenotype, some individuals with the mutation may not express the phenotype. For instance, lipid levels were within the range of control values in 20% of individuals with a large LDL-receptor gene deletion that caused clinically detectable familial hypercholesterolemia in the remaining genetically affected individuals (Reference 72 and Charles F. Sing, PhD, personal communication). This phenomenon may reflect the well-known impact of environmental factors on the manner of reaction of genes.

Relation of Preclinical Cardiovascular Disease to Morbid Events

The following section reviews the relation between preclinical cardiovascular diseases and morbid events in subjects known to be or likely to have been previously free of symptomatic heart disease.

Coronary Atherosclerosis

Available direct data derive from selected patients who underwent cardiac catheterization without having experienced angina or myocardial infarction or from autopsy findings in victims of sudden death or accidents. Follow-up of asymptomatic individuals in whom coronary calcification is detected by ultrasound or computed tomography may provide more representative data in the future.

Similar to symptomatic patients, the risk of subsequent myocardial infarction or death in asymptomatic or minimally symptomatic individuals undergoing catheterization is related to the number and severity of narrowed coronary arteries.72-75 The risk associated with a given degree of angiographic abnormality may be less in asymptomatic than in symptomatic subjects.75 Autopsy studies of patients dying without previously known heart disease show coronary atherosclerosis in virtually all who suffered myocardial infarction and in most adults who die suddenly.76,77 However, significant coronary atherosclerosis is also present in a substantial percentage of the entire middle-aged to elderly population. Prevalences of more than 50% narrowing of coronary artery diameter range from a low estimate of 4% based on screening by exercise tests and subsequent catheterization of those with abnormal test responses in a population-based survey of 2000 men aged 40 to 50 in Norway78 to 20% or more in necropsy studies of adults over age 45 dying accidentally or of noncardiac disease.79,80

The annual incidence of sudden death or first myocardial infarction in previously asymptomatic adults in the United States can be estimated as approximately 200 000 and about 400 000 per year, respectively (about 50% of sudden deaths1,2 x 400 000 sudden deaths per year62 and about 50% of 800 000 first myocardial infarctions81). Taken together with the size of the US population over age 45 (about 87 million in 1990), this would suggest that among as many as 17 million prevalent cases with 50% luminal narrowing of coronary arteries about 600 000, or as few as 4%, would experience major morbid events each year. Similar estimates for the numerator in this calculation would be obtained by using the incidence rates of major coronary disease events of 1% to 2% for men and 0.5% to 1% for women over age 45 found in Framingham.83,84 While these estimates admittedly are crude, they confirm that the development of obstructive coronary atherosclerosis does not immediately lead to clinical morbid events.

Left Ventricular Hypertrophy

Increased left ventricular muscle mass is of functional as well as prognostic importance, both generating the force to sustain cardiac function in the face of increased hemodynamic load and serving as a harbinger of morbid events.85 The latter role was first conclusively shown by the results of autopsy studies26,86 and by the increased risk of cardiovascular events during prospective follow-up in patients with ECG evidence of left ventricular hypertrophy.87,88 Because autopsy studies, by their nature, evaluate highly selected populations and the ECG provides only indirect and insensitive measures of left ventricular mass,89 these studies did not permit direct estimation of the level of risk associated with increased ventricular mass.

The availability of anatomically validated echocardiographic methods52,90-92 has made it possible to document prospectively the independent predictive value of measured left ventricular mass for the risk of CHD events that is independent and in addition to all conventional risk factors (blood pressure, cholesterol levels, cigarette smoking, etc.)90,93-94 and to the presence or absence of obstructive coronary artery disease.95 After adjustment for age and other risk factors, the incidence of morbid events in these studies92,95,97,98 was twofold to fourfold higher in subjects with left ventricular mass above somewhat arbitrary upper limits of normal than in those with lower left ventricular masses (Figs 3 and 4 and Table 2). Furthermore, the predictive value of blood pressure measurements for subsequent morbid events was reduced (or even eliminated in some instances) when left ventricular mass was also considered in multivariate analyses.50,93 Interestingly, the incidence of morbid or mortal events in middle-aged hypertensive patients with echocardiographic left ventricular hyper-
Extracardiac Atherosclerosis

It is well established that the presence of an asymptomatic carotid bruit predicts an even higher risk of subsequent CHD events than of strokes.96 Similarly, patients with peripheral vascular disease—manifested by as simple a finding as a ratio of ankle to brachial systolic pressure of less than 0.90—without signs or symptoms of cardiac disease are at high risk of cardiac morbidity.97,98 The recent development of sensitive and reproducible methods of measuring arterial wall thicknesses and detecting carotid and peripheral arterial atherosclerosis by ultrasound24 has allowed demonstration of a strong association between carotid atherosclerosis and coronary artery stenosis, independent of standard risk factors.99 Positive relations have also been shown between the severity of carotid atherosclerosis and the short-term risk of acute CHD events100 and between carotid atherosclerosis and left ventricular hypertrophy.28 Noninvasive measurements have also shown that increased arterial stiffness parallels the severity of coronary heart disease.103

Renal Disease

The kidney plays a major role in overall circulatory control and suffers “target organ” damage from hypertension and atherosclerosis, with declines in renal function strongly linked to increased cardiovascular mortality.55 Until recently, the most accurate means of detecting preclinical renal disease has been detection of elevated serum creatinine levels or declines in creatinine clearance on serial evaluation. To these has been added the sensitive measure of microalbuminuria. Its presence is associated with a higher prevalence of cardiac and peripheral vascular disease in nondiabetic adults,102,103 independent of the level of blood pressure or other risk factors. Microalbuminuria may also predict an adverse prognosis in hypertensive patients.104

Precipitation of Morbid Events: The Role of ‘Triggers’ in the Presence of Preclinical Disease

Because myocardial infarction and sudden death occur with only a moderate incidence even among patients with preclinical disease, it would be useful to know the factor or factors that precipitate these dramatic events. Presumably, these precipitators or triggers could be found in susceptible individuals.

Most myocardial infarctions, and most cases of sudden death, are associated with the presence of coronary thrombosis in the setting of advanced atherosclerotic disease.105 Rupture of atherosclerotic plaques with extrusion of plaque material, activation of platelets, release of vasoconstrictor substances, and elevated fibrinogen and plasminogen activator inhibitor are all potential precipitating phenomena whose association with the occurrence of events has been demonstrated.106-114 The evidence that acute thrombolytic therapies can prevent death and reduce infarct size115,116 or that chronic aspirin and anticoagulation prevent myocardial infarction117,118 supports the belief that thrombotic factors trigger acute episodes. The reversal of the risk for myocardial infarction that occurs within 1 year of the discontinuation of smoking suggests that its effect may also be mediated by its thrombogenic effect.4 Because sudden death is, by definition, not amenable to therapeutic intervention and because so many of its victims have either occlusive coronary arterial thrombi or recent myocardial infarction, preventive measures offer the greatest promise of reducing mortality.119

Implications of the Two-Stage Model of Cardiovascular Disease for Clinical Practice and Research

Often, but not always, risk factor exposure leads over time to the gradual development of preclinical disease.
TABLE 2. Incidence of Morbid Events in Subjects With and Without Different Forms of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Measure of Preclinical Disease</th>
<th>End Point</th>
<th>With Preclinical Disease</th>
<th>Without Preclinical Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al(^3)</td>
<td>Angiographic coronary stenosis</td>
<td>Death</td>
<td>2.7</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>(\geq 75%) narrowing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kent et al(^4)</td>
<td>Angiographic coronary stenosis</td>
<td>Death</td>
<td>3.0</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>(\geq 50%) narrowing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casale et al(^5)</td>
<td>Echocardiographic LV mass</td>
<td>Death, MI, CVA, severe angina</td>
<td>4.6</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>(&gt;125\ g/m(^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levy et al(^6)</td>
<td>Echocardiographic LV mass</td>
<td>Angina</td>
<td>2.8(\dagger)</td>
<td>0.6(\dagger)</td>
</tr>
<tr>
<td></td>
<td>(&gt;150\ g/m(^2))</td>
<td>CHD other than angina</td>
<td>3.2(\dagger)</td>
<td>0.7(\dagger)</td>
</tr>
<tr>
<td>Levy et al(^7)</td>
<td>Echocardiographic LV mass</td>
<td>All-cause mortality</td>
<td>2.0(\dagger)</td>
<td>0.8(\dagger)</td>
</tr>
<tr>
<td></td>
<td>(&gt;140\ g/m(^2) ((&gt;116\ g/m(^2))</td>
<td>All cardiovascular events</td>
<td>3.3(\dagger)</td>
<td>1.4(\dagger)</td>
</tr>
<tr>
<td>Koren et al(^8)</td>
<td>Echocardiographic LV mass</td>
<td>Cardiovascular death</td>
<td>1.4</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>(&gt;125\ g/m(^2))</td>
<td>All cardiovascular events</td>
<td>6.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Ghali et al(^9)</td>
<td>Echocardiographic LV mass</td>
<td>Death: Patients with CAD</td>
<td>5.3</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>(&gt;131\ g/m(^2) (men), (&gt;100\ g/m(^2) (women)</td>
<td>Patients without CAD</td>
<td>2.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Salonen and</td>
<td>Carotid ultrasonography</td>
<td>Myocardial infarction</td>
<td>3.4(\ddagger)</td>
<td>1.5(\ddagger)</td>
</tr>
<tr>
<td>Salonen(^10)</td>
<td>Intimal-medial thickness &gt; 1 mm</td>
<td></td>
<td>4.4(\ddagger)</td>
<td>1.5(\ddagger)</td>
</tr>
<tr>
<td></td>
<td>discrete plaque</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yudkin et al(^1)</td>
<td>Microalbuminuria &gt; 20 (\mu)g/min</td>
<td>All-cause mortality</td>
<td>9.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

CAD indicates angiographic coronary artery disease; CHD, coronary heart disease; CVA, cerebrovascular accident; LV, left ventricular; and MI, myocardial infarction.

\(\dagger\)Age-adjusted rate; \(\ddagger\)percent of subjects with events over 1- to 36-month follow-up period.

of the coronary and cerebral vessels and of the myocardium, which in turn predisposes to (but do not inevitably cause) myocardial infarction, sudden death, and stroke. The precise nature of the relationship of risk factors to preclinical disease remains uncertain. We propose, in Fig 5, a schematic representation of a conceptual framework for examination of the natural history of atherosclerotic and hypertensive disease. This schema suggests that in addition to serving as an intervening variable between risk factors and morbid events, preclinical disease may predispose to morbid events in the absence of clearly elevated levels of standard risk factors but also may be bypassed when morbid events occur in the absence of measurable preclinical disease. Instances of the former include sudden death or myocardial infarction in young patients with hypertrophic cardiomyopathy or congenital coronary artery anomalies,\(^19,20\) whereas the latter is exemplified by the decrease in cardiovascular risk within the first year after cessation of smoking,\(^4\) an effect too prompt to be due solely to changes in atherosclerosis. Another prediction of this schema is that some patients with risk factors do not develop preclinical disease, as documented by the variable presence or absence of coronary atherosclerosis in patients with hyperlipidemia and of left ventricular hypertrophy in hypertensive patients.

In general, the evolution from exposure to cardiovascular risk factors to morbid events may be thought of as proceeding in two steps, each of which may have naturally occurring “forward reactions” (to borrow a term from chemistry) and “backward reactions” that may be induced by therapy or occur spontaneously. An example of the latter is compensatory enlargement of atherosclerotic arteries,\(^22\) which may delay the time at which developing atheromas become sufficiently large to cause hemodynamically significant obstruction. Selected factors influencing the development of preclinical disease in response to risk factor exposure and the precipitation of morbid events in the setting of preclinical disease are listed in Tables 3 and 4. Initial observations concerning these steps in disease evolution have already begun to influence clinical practice, albeit often before critical questions have been resolved.

**Diagnosis and Management of Disease**

National health policy panels have recommended active treatment of hypertension and hyperlipidemia when clinical measurements of blood pressure and cholesterol or its subfractions fall outside predefined normal limits,\(^6,9\) yet epidemiologic data indicate that most cardiovascular events occur among individuals with moderate levels of risk factors. As a result, most asymptomatic individuals whose blood pressure or lipids fall outside “normal” limits will not suffer morbid events over the medium term in the absence of specific therapy. Recent analyses suggest that use of hypolipidemic drugs for primary prevention of CHD has not yet been proven to be of benefit.\(^19,20\)

A majority of middle-aged patients with mildly elevated blood pressure or lipid levels do not exhibit left ventricular hypertrophy or atherosclerotic plaques.\(^123,124\) Conversely, the coincidental detection of left ventricular enlargement in mildly hypertensive adults identifies a
dramatically increased risk of morbid and, especially, mortal events. Some physicians have acted on these observations by using the presence or absence of left ventricular hypertrophy to triage patients with borderline or mild established hypertension into groups at low or relatively high risk of complications as a basis for deciding to institute pharmacologic treatment. Preliminary evidence that atherosclerosis detected by ultrasound in the carotid artery predicts, apparently independently of serum lipid levels subsequent myocardial infarction suggests that the same strategy could be used to target expensive hypolipemic therapy to mildly hypercholesterolemic patients at greatest risk. The prevalence of preclinical disease increases with age among individuals with hypertension, dyslipidemia, or other risk factors, perhaps accounting for the apparently greater benefit of pharmacologic therapy in elderly compared with younger populations.

Although the logic of this approach is appealing, its adoption as standard practice should depend on prospective studies that determine whether such targeting of treatment actually improves clinical outcome or lowers health care costs. The cost effectiveness of basing treatment strategies on assessment of absolute risk by detection of preclinical disease may depend on whether more expensive antihypertensive or hypolipidemic agents provide appreciably greater clinical benefit than diuretics or dietary change. An additional implication of this line of reasoning is that it may be appropriate to raise or lower the “threshold” levels of such risk factors as arterial pressure and lipid fractions that are used to trigger initiation of pharmacologic treatment to accommodate the differing level of risk of individuals with and

**FIG 5. Schematic representation of the pathways from risk factor exposure to preclinical disease and ultimate development of clinical morbid events.** Note that at each step some individuals do not make the next transition. Selected factors influencing the transition from risk factor exposure to development of preclinical disease and the precipitation of morbid events in individuals with preclinical disease are given in Tables 3 and 4.
without preclinical disease. Finally, the evidence reviewed earlier suggests that population-based preventive strategies for the avoidance of overweight, physical inactivity, and excessive dietary fat and salt intake will reduce the prevalences of the several measures of preclinical disease as well as of overt cardiovascular diseases.

Research on Pathogenesis, Prevention, and Treatment of Cardiovascular Diseases

The two stages of evolution of cardiovascular disease (and the probability of a third “bypass tract” directly from some risk factors to morbidity events) may be thought of as having separate “forward” and “reverse” reactions as depicted schematically in Fig 5. The strength of the forward reactions is related to the power of underlying pathophysiologic relations and the promoter effects of modifying influences and disease “triggers” while that of “reverse reactions” reflects the efficacy of therapeutic interventions and possible counterregulatory physiologic mechanisms. Unfavorable genotypes may enhance adverse transitions (“forward reactions”), and favorable genotypes might confer partial resistance to specific risk factors.

This schema is sufficiently well supported by existing data to serve as a useful “traffic pattern” to identify fruitful areas for clinical and laboratory research. The ability to detect systemic atherosclerosis before it is clinically apparent in prospectively studied unselected populations makes it possible to characterize the factors that govern “forward reactions” from risk factor exposure to development of atherosclerosis, similar to what has already been accomplished for left ventricular hypertrophy. Availability of accurate measures of preclinical disease also makes it possible to determine whether there is a genetic basis for relevant phenotypic patterns (eg, hypertension associated with left ventricular hypertrophy) and, if so, provides a reference point for appropriate molecular genetic analysis. Similarly, study of patients with atherosclerosis and/or left ventricular hypertrophy should—by enhancing the incidence of morbidity events—make it possible to analyze prospectively the effect of procoagulant systems or genetic factors on the incidence of CHD events.

Perhaps the most important immediate potential implication of the present schema concerns the feasibility and organization of clinical trials. For example, the incidence of morbidity events among patients with initially uncomplicated mild-to-moderate essential hypertension makes it extraordinarily expensive (more than $100 million for proposed studies) to determine whether newer agents are superior to diuretic-based therapy for prevention of morbidity events. Because the incidence of death and myocardial infarction in hypertensive patients are twofold to fourfold higher in the presence of left ventricular hypertrophy, a clearly beneficial difference between agents (eg, 25%) in the incidence of “hard” morbidity events could be detected in a far smaller study population if only patients with this abnormality were used. If ongoing epidemiologic studies using ultrasonography of the carotid or other arteries show the expected concentration of CHD and cerebrovascular events in those with atherosclerosis, this would be another suitable group in whom to compare different antiatherogenic regimens. Although this research strategy entails additional screening costs to identify subjects with preclinical disease and its results may not be precisely applicable to low-risk patients, it remains the most reasonable way to distinguish the relative value of alternative therapies for at least the “highest” risk patients.

One benefit of therapeutic trials with serial measurement of left ventricular mass or systemic atherosclerosis would be to determine whether reversal or prevention of development of preclinical disease reduced the subsequent rate of morbidity events. This has been suggested by observational studies in which hypertensive patients in whom left ventricular mass diminished during antihypertensive therapy were shown to be at significantly lower risk of subsequent morbidity events than those whose left ventricular mass increased.125,126 If this is confirmed by prospective, controlled studies, measurements of left ventricular mass and systemic atherosclerosis would become prognostically validated “surrogate end points”127 that could be used to judge the efficacy of new treatments, in far smaller therapeutic trials than needed when clinical morbidity events are the end points. Finally, there is post-hoc data to suggest that a subgroup of mild hypertensives might do as well if not better without drug therapy as with therapy. In one study, we found that patients with initially uncomplicated hypertension who did not smoke, had fasting glucose and total serum cholesterol levels below 140 mg/dL and 6.2 mmol/L, respectively, and had normal left ventricular geometry by echocardiogram had an incidence of subsequent cardiovascular morbidity events of only 0.6 per 100 patient-years.80 Controlled trials to determine whether such patients remain free of preclinical disease or progressive blood pressure elevation without pharmacologic therapy are needed to determine the safety of this strategy. If “low-risk” mild hypertensives, who are free of preclinical disease, could be managed without drugs, the individual and communal benefit could be enormous since as many as one fourth of all mild hypertensives may fall in this category.80

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Role of preclinical cardiovascular disease in the evolution from risk factor exposure to development of morbid events.
R B Devereux and M H Alderman

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