Increasing Burden of Cardiovascular Disease
Current Knowledge and Future Directions for Research on Risk Factors

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Lewis A. Conner was the first president of the American Heart Association and founding editor of the American Heart Journal. In the inaugural issue of that journal, in October 1925, Dr Conner wrote that the “newly awakened interest in disorders of the cardiovascular system” has rapidly led to the recognition of heart disease as a significant public health problem that “can no longer be disregarded.” In the ensuing years, the United States first experienced a 40-year increasing epidemic of cardiovascular disease, followed by remarkable gains in prevention and treatment that led to a dramatic 30-year decline in mortality from coronary heart disease (CHD) and stroke. At present, however, heart disease remains far and away the leading cause of mortality in the United States, responsible for about one of every three deaths. Stroke accounts for 6% to 7% of all deaths, so overall cardiovascular disease remains responsible for about 40% of all US deaths.

Further gains in the prevention and treatment of cardiovascular disease will require concerted efforts—and the necessary allocation of resources—on at least two major fronts. First, public policy and health efforts must vigorously promote those measures in prevention and treatment for which abundant evidence of clear benefits already exists. Second, funding must be provided for current research to evaluate new possible preventive and therapeutic interventions and to expand frontiers in genetic, thrombotic, atherogenic, and inflammatory markers of cardiovascular disease risk.

Advances in knowledge proceed on several fronts, optimally simultaneously. Basic researchers provide biological mechanisms and answer the crucial question of why an agent or intervention reduces premature death. Clinicians are providing enormous benefits to affected patients through advances in diagnosis and treatment and formulate hypotheses from their clinical experiences in case reports and case series. Clinical investigators address the relevance of basic research findings to affected patients and healthy individuals. Epidemiologists and statisticians, optimally collaborating with researchers in other disciplines, formulate hypotheses from descriptive studies and test these in analytical studies, both observational case-control and cohort as well as, where necessary, randomized trials. This strategy answers the equally crucial and complementary question of whether an agent or intervention reduces premature death. Thus, each discipline and indeed every strategy within a discipline provide importantly relevant and complementary information to a totality of evidence on which rational clinical decisions for individuals and policy decisions for the health of the general public can be safely based.

This article reviews the increasing burden of cardiovascular disease, contributions of different types of evidence, and direction of current and future research on risk factors.

Increasing Burden of Cardiovascular Disease
In the United States today, heart disease becomes the leading killer of men by 45 years of age and women by 65 years of age. Heart disease is responsible for one in three deaths in women and men and accounts for approximately 750 000 fatalities each year in the United States. Moreover, there are alarming indications that the decline in cardiovascular disease mortality in the United States that began in the 1960s has leveled off and that rates may even be beginning to rise. For the first time in decades, the age-adjusted death rate from cardiovascular disease in the United States increased slightly from 1992 to 1993, the last years for which complete data are available.

With regard to racial differences in CHD, mortality rates remain substantially higher in blacks than in whites, with 1992 age-adjusted rates of 190.3 per 100 000 among white men and 264.1 per 100 000 among black men. For women, the rates were 98.1 in whites and 162.4 in blacks. In addition, although there were decreases in CHD mortality among all groups throughout the 1980s, the percentage decline in the rates from 1980 to 1992 was much greater in whites than in blacks.

There have been alarming trends in the health status of US teenagers, among whom there are currently troubling increases in the prevalence of cigarette smoking and obesity and decreases in participation in physical activity programs. Specifically, each year from 1991 to 1996, cigarette smoking rates have increased in the United States among 8th, 10th, and 12th grade students, while more than one in five US adolescents are overweight, an increase of >50% in the prevalence of adolescent obesity since the late 1970s. In terms of physical activity levels, there was no change in the proportion of US high school students engaged in regular vigorous physical activity from 1991 through 1995, and there has been a decrease in the participation of high school students in daily physical education classes. This backslide in the health status of US teenagers has
far-reaching consequences for future overall morbidity and mortality in general and for cardiovascular disease in particular.

Worldwide, cardiovascular disease is also assuming an increasing role as a major cause of morbidity and mortality. Between 1990 and 2020, the proportion of worldwide deaths from cardiovascular disease is projected to increase from 28.9% to 36.3%.

Moreover, in terms of number of years of life lost, it is projected that cardiovascular disease will jump in ranking from fourth to first, while as a cause of premature death and disability, it will rise from fifth to first. The projected increases in the importance of cardiovascular disease worldwide are related principally to two trends in developing countries: (1) the eradication of malnutrition and infectious diseases as primary causes of death, which is allowing for an aging of the population, and (2) marked increases in cigarette smoking.

Thus, the enormous and increasing burden of cardiovascular disease among those in middle and older age in developed countries, the alarming trends in cardiovascular risk profiles of young people, and the emerging pandemic of cardiovascular disease all underscore the crucial need to redouble both policy and research efforts in treatment and prevention.

**Contributions of Different Types of Evidence**

It is crucial to consider the totality of evidence for any question because each research discipline has its unique strengths and limitations (Table 1). Basic research has the unique strength of precision, meaning the ability to achieve virtually complete control of all exposures, including both environment and genetics. Further, basic research provides the scientific underpinnings for all applied research in humans. Thus, basic research provides unique and crucial information that is of great value in setting priorities for studies in free-living humans to test their relevance.

Epidemiology, on the other hand, because it is based directly on observations of free-living humans, has the unique advantage of relevance. However, for this very reason, epidemiological studies have the potential disadvantage of imprecision. Indeed, in contrast to basic research, epidemiology is crude and inexact because observations in free-living humans can never take place under the controlled conditions possible in the laboratory. Nonetheless, epidemiology provides essential information to a totality of evidence, which then can support a judgment of a cause-effect relationship.

Making such a judgment involves several steps, the first being to establish whether there is in fact a valid statistical association. To conclude that an association is valid, alternative explanations for the finding must be ruled out, including the potential roles of chance, bias, and confounding. If a valid statistical association is present, the question then becomes, Is it one of cause and effect? To render this judgment, the totality of evidence from all sources must be considered, with particular attention given to the strength of the association, the consistency of the evidence from different studies, and the existence of a plausible biological mechanism to explain the findings.

Epidemiological studies can be either descriptive (case reports and case series, correlational studies, and cross-sectional surveys) or analytical (observational case-control or cohort studies and randomized trials). Descriptive studies are useful primarily for the formulation of hypotheses; analytical studies, for hypothesis testing. Whereas observational analytical studies are often criticized because of their potential for bias—case-control studies in the selection of individuals into the study and in their recall of prior events and cohort studies in losses to follow-up—many exposure-disease relationships have been well established from observational evidence.

There are two chief strengths of observational evidence. The first relates to the evaluation of exposures that require long duration; the second is the ability to detect moderate to large effects, which can be roughly translated to mean those effects with relative risks >1.5. With respect to the evaluation of exposures that require long duration, one example of the strength of observational studies is the evaluation of the relationship between blood pressure and risk of myocardial infarction (MI). Basic research had suggested mechanisms for a benefit of blood pressure lowering on risks of stroke and MI, and observational studies had consistently demonstrated a statistically significant 40% to 45% increase in risk of stroke and a 25% to 30% increase in risk of MI associated with a prolonged 6 mm Hg difference in diastolic blood pressure. In contrast, although individual randomized trials of pharmacological therapy of mild to moderate hypertension indicated that blood pressure lowering by 6 mm Hg resulted in a comparable 40% decrease in risk of stroke, there was a far smaller and less

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**TABLE 1. Sources of Evidence in Identifying Risk Factors for Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Type of Evidence</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Basic research</td>
<td>Unique strength of precision, ability to achieve virtually complete control of all exposures.</td>
</tr>
<tr>
<td>Epidemiological research</td>
<td>Descriptive (case reports, case series, correlational studies), Analytical (observational case-control, cohort studies, randomized trials).</td>
</tr>
<tr>
<td>Descriptive</td>
<td>Observational studies useful primarily for the formulation of hypotheses.</td>
</tr>
<tr>
<td>Analytical</td>
<td>Analytical studies useful for hypothesis testing.</td>
</tr>
<tr>
<td>Observational</td>
<td>Epidemiological studies are either descriptive or analytical.</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>Descriptive (case reports, case series) or analytical (observational case-control or cohort studies).</td>
</tr>
<tr>
<td>Cohort studies</td>
<td>Descriptive (case reports, case series) or analytical (observational case-control or cohort studies).</td>
</tr>
<tr>
<td>Randomized trials</td>
<td>Descriptive (case reports, case series) or analytical (observational case-control or cohort studies).</td>
</tr>
</tbody>
</table>

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certain benefit on MI than that suggested by the observational evidence. The apparent inconsistency remained even after the availability of results from 14 individual randomized trials of drug therapy in 37,000 subjects. This led some to conclude that treatment of hypertension did not benefit the risk of subsequent MI. However, a comprehensive overview, or meta-analysis, of the trials demonstrated that a decrease of 6 mm Hg in diastolic blood pressure significantly reduced stroke by 42% and MI by a smaller but statistically significant 14%. A subsequent meta-analysis, which included several additional trials, demonstrated the reduction in risk of MI to be 16%. The 14% to 16% reduction in risk of MI seen in the randomized trials over 3 to 5 years of treatment was about half the 28% reduction one would predict from the results of observational studies of blood pressure lowering over decades. This discrepancy may well have been due to chance but also could have been due to the fact that stroke risk immediately decreases after blood pressure levels are lowered, whereas MI risk may be affected by prolonged effects of hypertension on the more chronic processes of atherogenesis and thus would require far longer than the usual 3 to 5 years of treatment in trials to observe the full impact. Thus, basic research and observational studies with long durations of exposure have been crucial components of the totality of evidence concerning the relationship of blood pressure lowering with risk of MI.

The second strength of observational studies lies in evaluating associations in which the relative risk is moderate to large in size—relative risks >1.5. In this regard, observational evidence has provided both the necessary and sufficient information on which to judge a cause and effect relationship for a large number of important questions of clinical importance and public health significance. Chief among these has been the health effects of cigarette smoking. Starting in 1950 with case-control studies by Doll and Hill in the United Kingdom and Wynder and Graham in the United States, observational epidemiological studies established a clear association between smoking and lung cancer, with risks among long-term smokers about 20 times greater than those of nonsmokers. Based on their observational evidence, Doll and Hill judged smoking to be a cause of lung cancer years before there was any clear understanding of the actual mechanism of alterations in DNA by initiators or promoters of cancer. In 1964 the US Surgeon General also judged smoking a definite cause of this disease, still years before the biological mechanism was clearly understood. Thus, although basic research is crucial in identifying mechanisms that explain causal or preventive factors, direct answers to the questions of whether particular exposures are associated with risks of disease may derive from straightforward observation of what actually happens in free-living human populations.

With regard to smoking and CHD, the finding that current cigarette smokers have about an 80% increased risk has been consistently demonstrated over the last 30 years by different investigators in a large number of case-control and cohort studies involving millions of person-years of observation. It is interesting that smoking was not judged to be a cause of CHD until far later than the judgment that it caused lung cancer. Part of this related to the lack of a clear biological mechanism. However, another reason related directly to a limitation in interpreting the findings from any observational study; namely, that as the relative risk gets smaller, there is increasing concern that some factor other than the exposure being studied may explain all or at least part of the findings. For example, cigarette smokers may share other characteristics or lifestyle practices that independently affect their risk of CHD. Information can be collected on any potential confounding variables known to the investigator and then used in the data analysis to adjust for any impact of these factors. However, there can be no adjustment for the effects of unmeasured or unmeasurable confounding variables.

When a large effect is seen, such as with smoking and lung cancer, the amount of uncontrolled confounding may affect the magnitude of the relative risk estimate, making it, for example, as high as 22 or as low as 18. It is unlikely, however, that complete control of confounding would materially change the conclusion that there is a strong positive association between smoking and lung cancer. Even in the case of current smoking and CHD, although uncontrolled confounding may mean that the true relative risk is as small as 1.6 or as large as 2.0 instead of the 1.8 most consistently seen in observational studies, that range of uncertainty does not materially affect the conclusion that current cigarette smoking increases the risk of CHD. On the other hand, when the most plausible effect size is only 20% to 40%, as is the case with most promising interventions today, a small amount of uncontrolled confounding could mean the difference between a relative risk of 0.8, indicating a 20% decreased risk; 1.0, indicating no effect; or 1.2, indicating a 20% increased risk.

A recent example that illustrates some of these issues is the possible role of antioxidant vitamins in prevention of cardiovascular disease and cancer. Basic research has provided evidence of plausible mechanisms for antioxidant vitamins in the prevention of these diseases. As regards cardiovascular disease, antioxidant vitamins can inhibit the oxidation and/or uptake of LDL cholesterol, the particularly atherogenic form of cholesterol. In addition to descriptive studies, a large number of analytical observational studies have examined the antioxidant hypothesis. Several large-scale prospective cohort studies have found decreased cardiovascular disease risks among subjects with higher intake of antioxidant vitamins, either through diet or supplements.

The problem with all these studies, however, is that the decreased risk seen in those with the highest intake or blood levels tended to be modest in size, on the order of 20% to 40%. Such small to moderate benefits may have a tremendous public health impact for a common and serious disease, but they are statistically very difficult to demonstrate reliably. In the case of antioxidant vitamins, it may be, for example, that those with greater intake of antioxidant vitamins share other dietary or nondietary lifestyle practices that account for all or some of the observed association with antioxidant vitamins. Adjustments can be made for known confounding variables for which data are collected. However, observational studies are unable to control for the potential effects of confounding variables not collected or known to the investigators. In searches for modest-sized effects, the amount of uncontrolled confounding may be as large as the most likely effect.
For all these reasons, only randomized trials of sufficient sample size and duration of treatment and follow-up are able to detect reliably small to moderate treatment effects. If the trials are large enough, the randomization process will, on average, evenly distribute among treatment groups known and unknown confounding variables. In addition, very large trials will be necessary to avoid the possible uninformative null result of no benefit when in fact a modest-sized benefit truly exists. For many, if not most, hypotheses, randomized trials are neither necessary nor desirable. For detecting small to moderate effects, however, they represent the most reliable research design strategy.

With respect to antioxidant vitamins, four large-scale randomized trials of beta-carotene supplementation have been completed. Overall, their results for CHD have not supported the promising evidence that accumulated from basic research, descriptive studies, and analytical observational investigations. The results certainly do not preclude the possibility that some benefit may yet emerge for antioxidants. Indeed, several trials ongoing trials are evaluating antioxidants in both primary and secondary prevention of cardiovascular disease, and the evidence remains particularly promising for vitamin E. However, with respect to beta-carotene supplementation, the data currently available from completed trials indicate no overall benefits on cardiovascular disease among well-nourished populations. These data suggest that the findings from observational studies of possible benefits may indeed have reflected some influence of confounding variables associated with beta-carotene intake that explain all or some of the decreased risks of cardiovascular disease among those with high intake levels. The findings also raise the possibility that the antiatherogenic mechanisms for beta-carotene described in basic research may not have direct relevance to the effects of supplementation with this antioxidant on human disease risk.

**Risk Factors: Current Knowledge and Future Directions for Research**

Genetics certainly plays a role in cardiovascular disease risk, but there is also clear evidence from international differences in disease rates and migrant studies that cardiovascular disease must have important environmental determinants. Studies of Japanese migrants have been particularly informative in this regard. The Ni-Hon-San study tracked the health experience of Japanese men living in the Japanese cities of Hiroshima and Nagasaki, men of Japanese ancestry living in the Honolulu area of Hawaii, and Japanese men in the San Francisco Bay area in California. The study revealed substantial differences in CHD mortality rates between the three groups, with men in Japan having the lowest rates, those in Hawaii having somewhat higher rates, and men in the San Francisco area having the highest rates. Thus, in these findings among genetically similar populations, migration and the adoption of lifestyle practices of the local population were accompanied by a substantial increase in CHD death rates.

With respect to the identification of modifiable risk factors, during the 20th century, the contributions of basic research, clinical investigation, observational epidemiology, and randomized trials have yielded a totality of evidence on which it has been possible to judge proof beyond a reasonable doubt that modification of several factors decreases risks of cardiovascular disease (Table 2). These include cigarette smoking, elevated cholesterol levels, and hypertension. Other factors, such as obesity, physical inactivity, and diabetes, are clearly associated with increased risks of cardiovascular disease, but the evidence currently is less clear that modification of these factors yields decreased risks of CHD. For all of these risk factors, however, public policy recommendations have been issued by such major health organizations and institutions as the AHA, the NHLBI, and the National Institute for Neurological Diseases and Stroke, and efforts must be redoubled to achieve wider implementation of these existing recommendations.

Although substantial gains can be achieved through control or elimination of established risk factors for cardiovascular disease, it is also important to consider that in data from the United Kingdom Heart Disease Prevention Project and other cohorts, approximately half of all patients suffering a CHD event have no established risk factors. This situation has prompted the investigation of promising interventions that could have widespread utility in treatment and primary prevention of cardiovascular disease. These include antioxidant vitamins, low-dose aspirin, and hormone replacement therapy in women.

With respect to low-dose aspirin, in 1971, Sir John Vane, who later received the Nobel prize for his work, demonstrated that in platelets, small amounts of aspirin irreversibly acetylate the active site of cyclooxygenase, which is required for the production of thromboxane A2, a powerful promoter of platelet aggregation. Higher doses provided additional benefit, and it has been postulated that far higher doses might reverse this tendency because of activation of vessel wall enzymes. A totality of evidence is now available, which includes randomized trials in secondary prevention or treatment among patients with a wide range of occlusive vascular diseases, in the acute phase of evolving MI, and in primary prevention among apparently healthy individuals. For secondary prevention and acute evolving MI, there is conclusive evidence in both men and women of net benefits of aspirin on subsequent MI, stroke, and overall vascular death. Thus, extensions of the existing labeling indications for aspirin are clearly needed to include virtually all patients who have suffered an occlusive vascular disease event. Wider use of aspirin in these conditions would avoid 10 000 premature deaths each year in the United States. For primary prevention, there is conclusive evidence in men of benefit on risk of a first MI, but the data are currently inconclusive on stroke and vascular death. Further, there is a possible increase in hemorrhage.

### TABLE 2. Causal and Preventive Risk Factors for Cardiovascular Disease

<table>
<thead>
<tr>
<th>Causal</th>
<th>Preventive</th>
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</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Low-dose aspirin?</td>
</tr>
<tr>
<td>Elevated cholesterol</td>
<td>Estrogen replacement therapy in women?</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Antioxidant vitamins?</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td>Physical inactivity</td>
<td></td>
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<tr>
<td>Diabetes</td>
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</tbody>
</table>
TABLE 3. Potential New Risk Factors for Cardiovascular Disease

<table>
<thead>
<tr>
<th>Atherogenic and/or Thrombotic Markers</th>
<th>Genetic Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homocysteine</td>
<td>Arterial</td>
</tr>
<tr>
<td>Plasma fibrinogen</td>
<td>MTHFR gene</td>
</tr>
<tr>
<td>Factor VII</td>
<td>ACE gene</td>
</tr>
<tr>
<td>Endogenous tissue-type plasminogen activator</td>
<td>Angiotensinogen</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor</td>
<td>Venous</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>Factor V mutation</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
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</table>

rhagic stroke. Thus, while we await the results of primary prevention trials, such as the ongoing Women’s Health Study among 40,000 female health professionals, the decision to prescribe aspirin in primary prevention must be an individual clinical judgment between the healthcare provider and each of his or her patients. Such a judgment must take into account the patient’s risk profile, the side effects of aspirin, and its clear benefit in reducing the risk of a first MI. In addition, the use of aspirin should always be as an adjunct, not alternative, to control or elimination of the established risk factors for cardiovascular disease.

With respect to hormone replacement therapy, basic research has provided plausible mechanisms for benefits, including improvements in lipid profile, and observational epidemiological studies have indicated that women who self-select for hormone treatment have decreased risks of CHD. Women using hormones also experience reductions in menopausal symptoms and osteoporosis but increased risks of uterine cancer with unopposed estrogen and increases in gallbladder disease and breast cancer.

However, it is important to note that all these findings have been made in case-control and observational cohort studies, so the self-selection by women and their healthcare providers of hormone replacement therapy may be responsible, in part or perhaps even wholly, for the observed associations. Thus, despite the fact that MI kills about eight times as many women as breast cancer, whether the benefits of hormone replacement therapy outweigh the risks for all women is not yet clear. Several ongoing randomized trials, the largest of which is the Women’s Health Initiative, will provide the necessary direct evidence for this question.

In addition to these promising hypotheses, we are also markedly increasing our understanding of the multifactorial causes of CHD. These genetic and environmental determinants include both atherogenic and thrombotic factors. For acute MI, the primary underlying cause is atherosclerosis, whereas the proximate cause of virtually all cases is thrombosis. In this context, many potential new markers of CHD are under investigation (Table 3). These include the primarily atherogenic marker homocysteine, the primarily thrombotic marker fibrinogen, and other primarily inflammatory markers, such as C-reactive protein.

With respect to possible atherogenic markers, there is increasing interest in the possible role of homocysteine in cardiovascular disease. Basic research has shown methionine to be an essential amino acid that depends on several enzymes related to B12 and folate metabolism for conversion from homocysteine. In clinical studies, individuals with homocystinuria develop very premature onset of severe CHD. Regardless of the source of the defect, all patients with elevated levels of homocysteine have increased risks of CHD.

Several observational epidemiological studies, both case-control and cohort, have shown that those with higher levels of homocysteine tend to have increased risks of CHD. This emerging totality of evidence has raised the question of whether reducing levels of homocysteine would, in turn, decrease risks of cardiovascular disease.

In the Physicians’ Health Study, the significant predictors of higher homocysteine are age, the 5,10-methylenetetrahydrofolate reductase (MTHFR) genotype, and current smoking; whereas predictors of lower homocysteine levels are current multivitamin use and higher intakes of folate. These and other data have raised the hypothesis that folate may lower homocysteine and decrease risks of MI. Only randomized trials can address this issue definitively. Currently, one secondary prevention trial of folate is ongoing among patients with prior stroke, and several other trials have been proposed.

With respect to thrombotic markers, >40 years ago, plasma fibrinogen levels were demonstrated to be higher among patients with acute thrombosis. The first prospective study to show an association between fibrinogen levels and subsequent cardiovascular disease risk was the Swedish Gothenborg Heart Study in 1984. In the Northwick Park Heart Study in the United Kingdom, fibrinogen and factor VII appeared to be as effective as total cholesterol in predicting future risk of CHD. It remains unclear, however, whether elevated fibrinogen level is a cause or consequence of atherosclerosis.

Whether modification of fibrinogen levels will lower risks is now being evaluated in several secondary prevention trials. With regard to the fibrinogen hypothesis, however, because the agents being tested all have potential benefits on other markers of risk, including lipids, the results, even if positive, may be difficult to interpret. Nonetheless, randomized trials to determine the ability of an agent to modify a thrombotic factor and to assess whether such modification in fact decreases risks of subsequent occlusive events will be a crucial component in translational research on any of the new markers from being a focus of research investigation to clinical and public health relevance.

C-reactive protein, a marker of systemic inflammation, has recently been evaluated as a potential risk factor for cardiovascular disease in the Physicians’ Health Study, a randomized trial of aspirin and beta-carotene in the prevention of cardiovascular disease and cancer. In a prospective nested case-control analysis using baseline blood specimens, increased levels of C-reactive protein were associated with increased risks of subsequent MI and ischemic stroke. The use of aspirin was associated with significant reductions in the risk of MI (55.7%, P=0.02) among men in the highest quartile but with only a small, nonsignificant reduction among those in the lowest quartile (13.9%, P=.77). These findings on MI raise the possibility that antiinflammatory agents may have clinical benefits in preventing cardiovascular disease.

With respect to inflammation and cardiovascular disease, proinflammatory cytokines raise markers such as C-reactive
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protein. Proinflammatory cytokines also increase coagulation and cause an unfavorable lipid profile of a peculiar form, with decreased cholesterol, decreased HDL cholesterol, and increased triglycerides. It also appears that infection, smoking, diabetes, and periodontal disease all increase proinflammatory cytokines, whereas aspirin, nonsteroidal antiinflammatory drugs, antioxidants, and glucocorticoids may decrease proinflammatory cytokines. These complex interrelationships and their possible clinical relevance require further evaluation in basic, clinical, and epidemiological research.

Thus, we are now entering new frontiers of research that have the potential for greatly expanding our understanding of risk factors for cardiovascular disease. In addition to homocysteine and fibrinogen, the promising atherosclerotic and/or thrombotic markers include factor VII, endogenous tissue plasminogen activator, plasminogen activator inhibitor, D-dimer, and lipoprotein(a). From a pathophysiological perspective, further research is needed on the balance between procoagulant factors—such as factor VII, impaired fibrinolysis, tissue plasminogen activator levels, and plasminogen activator inhibitor—and evidence of ongoing clot formation—such as fibrinogen or D-dimer. Potential genetic markers requiring further research include possible predictors of arterial disease, such as the MTHFR genotype, the ACE gene, and angiotensinogen, as well as possible predictors of venous disease, such as the factor V mutation. There is also increasing interest in the relationship of psychosocial factors, socioeconomic status, environmental stresses, and social disparity with cardiovascular disease risk.

The current totality of evidence supports a complex multifactorial model as more plausible than any single genetic marker to predict risk of CHD. Because we are at the early stages of research on all these new fronts, many important questions remain, including whether measurement of these potential new risk factors will complement or overlap with established risk factors. Specifically, the research on these new markers raises three important questions. First, does the assessment of any new marker add to the ability to predict who is at elevated risk over and above the predictive value of established risk factors? Second, are there means of favorably modifying levels of atherosclerotic and/or thrombotic markers? And third, would knowledge of genetic factors affect clinical practice?

With continued research, it seems likely that some environmental factors, including atherosclerotic, thrombotic, and inflammatory markers, as well as genetic factors, may well become routinely measured as part of the assessment of the cardiovascular risk profile of an individual. It seems less likely, however, that such measurements would ever replace our focus on established risk factors.

In that regard, we should not let the perfect be the enemy of the possible. Substantial benefits can still be gained from control or elimination of established cardiovascular risk factors. Specifically, in terms of blood cholesterol, a 10% decrease corresponds to roughly a 30% decrease in risk of CHD. With the publication of the Scandinavian Simvastatin Survival Study, the West of Scotland Coronary Primary Prevention Study, and most recently the Cholesterol and Recurrent Events trial in the United States, the totality of evidence now indicates clear benefits of cholesterol lowering by Hmg-CoA reductase inhibitors, or statins, on MI, stroke, cardiovascular death, and total mortality. For blood pressure, a 6 mm Hg decrease in diastolic pressures >90 mm Hg through pharmacological therapy among those with mild to moderate hypertension results in a 16% decrease in CHD and a 42% decrease in stroke. Cessation of cigarette smoking yields about a 50% decrease in risk of CHD, even among the elderly, beginning within months of cessation. The benefits of smoking cessation assume particular importance in light of the epidemic of tobacco use now occurring in developing countries, which will cause a substantial increase in their cardiovascular disease rates during the next several decades. Finally, the continuing epidemic of obesity in the United States is perhaps second only to smoking as the leading avoidable cause of all premature deaths.

The clear need for more public education concerning the continuing epidemic of cardiovascular disease is reflected in the results of a recent Gallup poll, in which 46% of women perceived breast cancer to be their major health risk, while only 4% believed this to be the case for heart disease. The reality, however, is that although 1 in 25 women will die from breast cancer, 1 in 3 will die from heart disease.

Thus, for established risk factors, we clearly must redouble our clinical and public policy efforts. The dividends this will yield are clear and immediate. For the promising newer potential risk factors, we need an increase in the commitment of research funding. From 1985 to 1995, the total NIH budget increased by 31.3%. At the same time, however, NHLBI funding rose by just 4.5%—and the portion allocated for heart disease research actually decreased by 5%. We have, in some senses, been victims of our own success, as the remarkable progress made over the past several decades in decreasing mortality from cardiovascular disease has contributed to a widespread misperception that the cardiovascular disease “problem” has been solved.

More than 50 years ago, in the landmark federal report “Science: The Endless Frontier,” presidential adviser Vannevar Bush wrote, “Progress in the war against disease depends on a flow of new scientific knowledge. New products, new industries and more jobs require continuous additions to knowledge . . . and the application of that knowledge to practical purposes. Science provides no panacea for individual, social, and economic ills. But without scientific progress, no amount of achievement in other directions can insure our health, prosperity, and security as a nation in the modern world.”

Praising the far-reaching effects of Bush’s report, Harvard University president Neil Rudenstine wrote in a recent commentary, “We have pursued this path over the past 50 years, and our nation’s health, prosperity and security have benefited enormously as a result. . . . If our drive to bring the federal budget closer to balance, we must keep in mind that our short-term choices will have profound long-term effects. . . . In the past 50 years, we have built a research enterprise that is the pride of the world. If we damage it, it will not be easily mended. And, in the long run, it will cost far more to rebuild something that has been allowed to slip into disrepair than to keep a strong and productive enterprise running well.”
In conclusion, whether we are concerned with cardiovascular disease as basic researchers, healthcare providers, clinical investigators, or epidemiologists and statisticians, it is crucial that we maintain a united front in calling for increased public health efforts to combat the current epidemic in the United States and the emerging pandemic of cardiovascular disease. It is equally critical that a steady flow of funding be ensured for the promising new frontiers of research that will greatly aid our understanding of the causes—and our ability to prevent and treat—cardiovascular disease.

In this vein, the words of Benjamin Franklin seem as important and timely today as at the signing of the Declaration of Independence on July 4, 1776: “We must all hang together, or assuredly we shall all hang separately.”

References

Research on Cardiovascular Disease Risk Factors


KEY WORDS: cardiovascular diseases ■ epidemiology ■ risk factors ■ trials
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_Circulation_. 1998;97:1095-1102
doi: 10.1161/01.CIR.97.11.1095
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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