Population Sciences Lecture

Clinical and research challenges in risk factors for cardiovascular diseases*

C. H. Hennekens

University of Miami School of Medicine, Miami, Florida, U.S.A.

Introduction

The European Society of Cardiology has a comparable organization in the U.S.A. in the American Heart Association, whose first president was Dr Lewis Atterbury Conner. Dr Connor was also the founding editor of the American Heart Journal. His contributions in the early 20th century were as significant as those of any single individual in focusing concerns about the emerging importance of cardiovascular disease. In the inaugural issue of the American Heart Journal of October 1925, Conner penned an editorial in which he stated ‘...this newly awakened interest in disorders of the cardiovascular system has led to a realization of the problem of heart diseases as extensive and important public health relations which can no longer be disregarded’[1].

In the 40 years following Connor’s visionary editorial, an epidemic of cardiovascular disease emerged. This epidemic was later blunted, however, by remarkable gains in primary prevention as well as secondary prevention and treatment that have led to unprecedented declines in mortality from coronary heart disease and stroke during the last 35 years in many developed countries[2].

Basic researchers, clinical investigators, epidemiologists and biostatisticians have contributed to a sufficient totality of evidence upon which to base rational clinical decisions and public policy. The European Society of Cardiology, the American Heart Association and other important organizations, in collaboration with health care providers, have translated research findings into clinical practice and effective public policy.

Despite the fact that the remarkable gains in prevention and treatment have led to unprecedented life expectancies in the U.S.A. (76 years) and Europe (73 years), both are far below the world leader, Japan, with a life expectancy of more than 80 years. Furthermore, despite these remarkable gains, heart disease remains far and away the leading cause of mortality in the U.S.A., Europe and most developed countries. In the U.S.A., heart disease is responsible for 31.4% of all deaths and cerebrovascular disorders account for another 6.9%, or a total of 38.3% of total mortality[3]. In Europe, coronary heart disease remains the leading cause of mortality in men over 45 years and in women over 65 years[4].

There are alarming indications that the decline in cardiovascular disease mortality that began in the mid-1960s in many countries has levelled off and that rates may even have begun rising. Beneath the overall trends lies an alarming differential in the percentage decline in coronary heart disease death rates by race among both men and women, with far smaller declines among blacks than whites. Equally alarming is the health status of U.S. teenagers. One in five high school seniors smokes cigarettes, one in three is significantly overweight, and only 32% of 12th graders exercise regularly. Thus, we have a generation of adolescents who are smoking more, are heavier and are more physically inactive than their parents were at the same age. This backslide in the health status of young people has far-reaching consequences in general for future morbidity and mortality and in particular for cardiovascular disease.

These disturbing trends in cardiovascular risk profiles of young people, the continuing enormous burden of cardiovascular disease among those in middle-age, as well as the increased frequency of congestive heart failure and ageing of the world’s population all emphasize the necessity to redouble our research and policy efforts.

Worldwide, cardiovascular disease is also assuming an increasing role as a major cause of morbidity and mortality. From 1990 to 2020, the proportion of worldwide deaths due to cardiovascular disease is expected to increase from 28.4% to 33.7%[5]. In terms of years of life lost, cardiovascular disease will jump from fourth to first. For premature death and disability, cardiovascular disease will jump from fifth to first.
The reasons for the worldwide increases in cardiovascular disease are related principally to three trends in developing countries: decreases in (1) malnutrition and (2) infection as primary causes of death are leading to an ageing of the population, and (3) steep rises in cigarette smoking rates which are already increasing rates of cardiovascular disease and will also lead to increases in cigarette-related cancers with longer duration of consumption.

There is no question that genetics play a key role as determinants of cardiovascular disease. However, the evidence from international differences in cardiovascular disease rates and from migrant studies demonstrates that cardiovascular disease has important environmental determinants as well. Specifically, Japanese migrants share genetic predispositions, yet their migration first to Hawaii, with its attendant adoption of lifestyle practices of the local population, was accompanied by an increase in annual rates of myocardial infarction after just 4–5 years from 7.3 to 13.2 per 1000. Several years after migration from Japan to California, migrants have rates of 31.4 per 1000, very similar to the 34 per 1000 rate of the overall U.S. population[6].

Established risk factors

During the 20th century, the contributions of basic research, clinical investigation, epidemiology and, where possible, randomized trials have yielded a totality of evidence upon which it has been possible to judge proof beyond reasonable doubt that modification of established risk factors decreases risks of cardiovascular disease. Those judged to be causal include cigarette smoking, elevated cholesterol, hypertension, obesity, physical inactivity and diabetes. For all these risk factors, public policy recommendations have been issued by major health organizations and institutions such as the European Society of Cardiology[4]. For these established risk factors, a major focus today must include continuing efforts to achieve wider implementation of existing policy recommendations.

Promising primary prevention hypotheses

At present, several primary prevention hypotheses are receiving much attention. These include moderate alcohol consumption, low-dose aspirin, antioxidant vitamins and hormone replacement therapy.

In the case of alcohol, observational epidemiological studies have been remarkably consistent showing, for example, 30% decreases in coronary heart disease among men and women in Framingham, U.S.A., 54% benefits for Honolulu men and 40% benefits for U.S. women among those who consume small to moderate amounts of alcohol. These data are supported by studies showing large increases in high-density lipoproteins associated with moderate alcohol consumption. The findings are similar for beer, whisky and wine. Red wine may confer an incremental benefit but this is perhaps more likely due to other constituents of this beverage or to residual confounding by social class.

The evidence concerning low-dose aspirin includes randomized trials in secondary prevention or treatments among patients with a wide range of occlusive vascular diseases, in the acute phase of evolving myocardial infarction and in primary prevention among apparently healthy individuals. For secondary prevention and acute evolving myocardial infarction, there is conclusive evidence in both men and women of net benefits of aspirin on subsequent myocardial infarction, stroke and overall vascular death. Thus, we need extensions of the existing labelling indications worldwide along with far wider utilization of aspirin in these conditions, which would avoid 10 000 premature deaths each year in the U.S.A. For primary prevention, there is conclusive evidence of benefit on risk of a first myocardial infarction, but the data are currently inconclusive on stroke and vascular death. Thus, at present, the decision to prescribe aspirin in primary prevention must be an individual clinical judgment between the health care provider and each of his or her patients. This judgment must weigh the patient’s risk profile, the potential side-effects of aspirin, and the clear benefit of reducing the risk of a first myocardial infarction. The use of aspirin should be an adjunct to, not an alternative to, control or elimination of established risk factors for cardiovascular disease.

For antioxidant vitamins, basic research has suggested plausible mechanisms for benefits, and clinical and observational epidemiological studies have shown that people who consume high amounts of these compounds through diets rich in fruits and vegetables or supplements, particularly vitamin E, tend to experience lower risks of cardiovascular disease. At present, however, it remains unclear whether observed decreases in risks of cardiovascular disease are due to the antioxidant vitamins themselves, or to other dietary factors, or perhaps even non-dietary lifestyle practices of individuals who self-select for higher intakes through diet or supplements. The available observational evidence is inconsistent. For example, the Nurses Health Study showed benefits for women who consumed increased vitamin E from supplements but not from food, while the Iowa Women’s Health Study showed benefits for women who consumed increased vitamin E from food but not from supplements. A number of large-scale randomized trials are currently ongoing in both secondary and primary prevention which will provide a sufficient totality of evidence upon which to base rational clinical recommendations and policy decisions.

In the case of hormone replacement therapy, basic research has provided plausible mechanisms for benefits of oestrogen and observational epidemiological studies have indicated that women who self-select for hormone replacement therapy have decreased risks of coronary heart disease, osteoporosis and menopausal symptoms, but increased risks of uterine cancer with unopposed
oestrogen, gall bladder disease and breast cancer. It is important to note that all these findings have been derived from case-control and observational cohort studies, so the self-selection of women and their healthcare providers to take hormones may be responsible, in part or perhaps even wholly, for the observed associations. Thus, despite the fact that myocardial infarction kills about six times as many women as breast cancer, it is not yet clear whether the benefits of hormone replacement therapy outweigh the risks for all women. The only direct evidence on this question will accrue from ongoing randomized trials.

The totality of evidence seems most persuasive for moderate alcohol consumption and low-dose aspirin and is less complete, at present, for antioxidant vitamins and hormone replacement therapy.

New markers of cardiovascular disease

While substantial gains can be achieved through control or elimination of the established risk factors for cardiovascular disease, it is also important to consider that data from the Framingham study, the U.K. Heart Disease Prevention Project and other large cohort studies show that approximately half of all patients suffering a coronary heart disease event have no established risk factors.

Such knowledge has further focused attention on the multifactorial aetiologies of coronary heart disease, from genetic and environmental factors to atherogenic and thrombotic factors. Most importantly, coronary heart disease results from a complex interplay of all these factors. For acute myocardial infarction, the primary underlying cause is atherosclerosis, while the proximate cause of virtually all cases is thrombosis.

Many potential new markers of coronary heart disease are under investigation. These include the primarily atherogenic marker, homocysteine, the primarily thrombotic marker, fibrinogen, as well as other primarily inflammatory markers, such as C-reactive protein. Randomized trials to determine the ability of an agent to modify an atherosclerotic or thrombotic factor and to assess whether such modification decreases risks of subsequent occlusive events, will be a crucial component in developing any of the new markers from being a focus of investigation to clinical and public health relevance.

Homocysteine

Basic research has shown methionine to be an essential amino acid which depends on several enzymes related to vitamin $B_{12}$ and folate for conversion from homocysteine. In clinical studies, individuals with homocysteinuria quickly develop premature onset of severe coronary heart disease. Regardless of the source of the defect, all patients with elevated levels of homocysteine have increased risks of coronary heart disease. In eight out of nine observational epidemiological studies, both case-control and cohort, subjects with higher levels of homocysteine tended to have increased risks of coronary heart disease. The emerging totality of evidence has raised the question of whether reducing levels of homocysteine would, in turn, decrease risks of cardiovascular disease. Since the conversion of homocysteine to methionine is dependent on folate, it has been suggested that increased folate intake will decrease homocysteine levels. It is certainly clear that individuals with higher levels of folate have lower levels of homocysteine, and recent research has shown that serum folate levels predict subsequent risk of coronary heart disease. However, whether increased folate intake can lower homocysteine and decrease risks of myocardial infarction have not yet been tested in randomized trials[7].

Fibrinogen

More than 40 years ago, plasma fibrinogen levels were found to be higher among patients with acute thrombosis. The first prospective study to show such an association was the Gothenborg, Sweden Heart Study in 1984. Specifically, participants with higher levels of fibrinogen at baseline later suffered higher rates of myocardial infarction and stroke. In the Northwick Park Heart Study in the U.K., fibrinogen and factor VII appeared to be as effective as total cholesterol in predicting future risk of coronary heart disease. In a prospective study of healthy physicians, we recently showed that those with high fibrinogen levels had a twofold increase in myocardial infarction risk independent of other coronary risk factors, atherogenic factors such as lipids and antithrombotic factors such as aspirin use[6]. Whether modification of fibrinogen levels will lower coronary heart disease risk is now being evaluated in a secondary prevention trial of a fibrinogen-lowering agent.

C-reactive protein

For many years, chronic inflammation has been thought to play a role in the development of coronary heart disease. Pro-inflammatory cytokines increase coagulation and cause an unfavourable lipid profile of a peculiar form, with decreased cholesterol, decreased high-density lipoprotein and increased triglycerides. It is also clear that infection, smoking, diabetes and periodontal disease all increase pro-inflammatory cytokines, whereas aspirin, non-steroidal anti-inflammatory drugs, antioxidants and glucocorticoids all decrease pro-inflammatory cytokines. These complex interrelationships and their possible clinical relevance are now being evaluated in various basic, clinical and epidemiological studies.

Levels of C-reactive protein, an acute phase reactant, are increased by pro-inflammatory cytokines. The earliest prospective study of C-reactive protein showed that, among individuals with stable and unstable angina, those whose C-reactive protein levels were in the highest quartile were at significantly increased risk for myocardial infarction or sudden death. Since then, other investigations have shown that elevated levels of C-reactive protein and other markers of inflammation are associated with increased risk of cardiovascular disease in men[9] and women[9].

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The current situation
We are now entering new frontiers of research that have the potential for expanding our understanding of risk factors for cardiovascular disease. The primarily atherosclerotic and/or thrombotic markers include, in addition to homocysteine and fibrinogen, factor VII, endogenous tissue plasminogen activator, plasminogen activator inhibitor, d-dimer and lipoprotein(a). Genetic markers include possible predictors of arterial disease, such as the methylenetetrahydrofolate reductase genotype, the ACE gene and angiotensinogen, as well as possible predictors of venous disease, such as the factor V mutation. The current totality of evidence supports a complex multifactorial model as being more plausible than any single genetic marker to predict risk of coronary heart disease. Since we are at the early stages of research on these new fronts, many important questions remain unanswered, including whether measurement of these potential new risk factors will complement or overlap with established risk factors.

Specifically, three important questions are raised by research on these new markers: (1) Does the assessment of any new marker add to our ability to predict who is at elevated risk, over and above the predictive value of established risk factors? (2) Are there means of favourably modifying levels of atherosclerotic and/or thrombotic markers? (3) 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.

Clinical challenges
We should not let ‘the perfect’ be the enemy of ‘the possible’. We must not lose sight of the substantial benefits that can be gained from control or elimination of established risk factors\[11\]. Specifically, as regards blood cholesterol, a 10% decrease corresponds roughly to a 30% decrease in risk of coronary heart disease. With the publication of the Scandinavian 4S study, the West of Scotland Coronary Prevention Study, the Cholesterol and Recurrent Events Trial, the AFCAPS/TexCAPS Trial and the Lipid trial, the totality of evidence now indicates clear benefits of cholesterol lowering on myocardial infarction, stroke, cardiovascular death and total mortality\[12,13\]. In terms of blood pressure, a 6 mmHg decrease in diastolic pressures above 90 mmHg through pharmacological therapy among those with mild-to-moderate hypertension results in a 16% decrease in coronary heart disease and a 42% decrease in stroke. Cessation of cigarette smoking yields about a 50% decrease in risk of coronary heart disease, perhaps even within a matter of 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 is causing a substantial increase in cardiovascular disease rates and will continue to do so over the next several decades. Maintaining an ideal body weight is associated with a 35–55% decrease in the risk of coronary heart disease. In that regard, the continuing epidemic of obesity is perhaps second only to smoking as the leading avoidable cause of premature deaths. Finally, maintenance of an active lifestyle is associated with a 35–55% lower risk of coronary heart disease\[11\].

The clear need for more public education is reflected by the fact that in Europe, the U.S.A., and elsewhere, most people find prescription of pills far more acceptable than prescription of harmful lifestyles. Yet, at the turn of the millennium it is the proscription of harmful lifestyles for which we have proof beyond reasonable doubt and which will yield the most benefits.

Conclusions
Without question, we must redouble our clinical and policy efforts to help patients modify established risk factors for cardiovascular disease. 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. In the U.S.A., the total budget of the National Institutes of Health rose by 31% from 1985 to 1995. At the same time, funding for one of its divisions, the National Heart, Lung and Blood Institute, rose by only 4.5% — and the portion allocated for heart disease research decreased by 5%. We have, in some senses, been victims of our own success. 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.

In conclusion, as is the case with cardiovascular disease, it is important to remember that advances in medical knowledge proceed on several fronts, optimally simultaneously. Basic researchers provide explanations or mechanisms to answer the crucial question of why a particular agent or intervention reduces premature death. Health care providers offer enormous benefits to patients through advances in diagnosis and treatment and, in addition, formulate most of the best hypotheses from their own clinical experiences — that is, their case reports and case series. Clinical investigators test the relevance of basic research findings to healthy individuals and affected patients. And epidemiologists and biostatisticians test the relevance of basic research to populations by formulating hypotheses from descriptive studies and testing hypotheses in case-control, observational cohorts or randomized trial designs to answer a complementary question of whether a particular agent or intervention reduces premature death. Each discipline, and every research strategy within a discipline,
contributes important relevant and complementary information to a totality of evidence upon which rational clinical decision-making and public policy can be safely based.

Whether we are concerned with cardiovascular disease as basic researchers, health care 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 global epidemic of cardiovascular disease and in securing increased funding for the promising new frontiers of research that will aid both 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 when he spoke them 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