Coronary Heart Disease Epidemiology Revisited

Clinical and Community Aspects

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SUMMARY

Epidemiological research relating coronary heart disease risk to risk factors has been reviewed and condensed into simple, diagrammatic form. The predictive power of risk factors for detecting susceptibles in the population is presented. While much is now known about long-term prediction, there is an urgent need for tests to signal impending heart attacks. Against this background, the potential for preventive action is discussed in the light of current knowledge. The “clinical-individual” and “community” approaches to prevention are contrasted. To what extent is prevention on the community level warranted, pending the results of controlled prophylactic trials? The view is presented that advice on preventive measures to the population at large is justified at this time, based on education and planned change but short of an all-out campaign which must await conclusive data from intervention studies.

Additional Indexing Words:
Coronary heart disease  Risk factors and coronary heart disease  Serum cholesterol
Hypertension  Smoking and coronary artery disease

Epidemiology has been well described as the basic science of community medicine or, as stated very aptly by the late Dr. Thomas Francis, Jr., “clinical investigation on the community level.” No field of medicine has advanced more rapidly over so short a space of time, perhaps 15 years, than coronary heart disease epidemiology. As a result, there is now probably no other disease which can be predicted, in terms of predisposing factors, with similar accuracy and power. With the advent of this knowledge, the terra incognita between clinical cardiology and epidemiology is now becoming inhabited by preventive cardiology,1 community cardiology and precoronary care.2 The emphasis, therefore, is not only on the acutely ill patient who will, if within reach, receive care under any circumstances, or the patient with symptoms who should seek care, but that much larger group in the presymptomatic stage, the susceptibles in the population who need long-term preventive care.

The Burden of Coronary Heart Disease

The burden of coronary heart disease can be measured in terms of morbidity and mortality statistics. It is best, however, to start with the living, particularly the “middle-aged man” in his forties or fifties since more is known about the epidemiology of coronary disease among such men than those who are younger or older, or women of any age. By and large, the frequency of the disease among women is a third or a quarter of the male rate; however, considering the high male rate, the frequency in women is by no means low.1,5 Since the majority of available data apply to white men in the more favored social groups, there is great need to learn more about the epidemiology of coronary heart disease among the other ethnic and social groups in the community.

Figure 1 shows a diagram for coronary disease among middle-aged men, and is based on the sum total of available epidemiological data.1,3,4 It represents general magnitudes rather than precise figures but can be viewed with a fair deal of reliance. Among 1,000 men, about ten percent, or 100 men, will experience a “heart attack” within the next ten years. At least a quarter of these manifest as sudden deaths which occur before the patient reaches the hospital.5,6 A minimum of 25 deaths, more likely closer to 30, is a conservative figure for deaths within an hour. The relative frequency of sudden deaths is somewhat lower among women
than men but the difference is not marked. The national problem of coronary heart disease hinges in large part on these persons who cannot possibly benefit from any advance in acute coronary care. While provisions of speedy mobile ambulance and care units for patients who do not die instantaneously is essential, it is still uncertain how many lives can be saved by such units and how they should be organized most effectively.

Another 75 men will experience a myocardial infarction over the ten-year period and reach the hospital. Despite recent reports from Britain that home care might be safer for some of these patients, this study was designed in such a way that the conclusions must remain unsettled. Within a month, from 25–30 percent (approximately 20) of the 75 patients will die, mostly within the first few days; this estimate tends to be on the low side of reported hospital mortality before coronary care units existed. In a coronary care unit, ten of the 20 patients will probably be saved from these “electrical deaths.” Most of the remaining ten persons die because of profound myocardial damage and would be candidates for new hearts, artificial or transplanted, to be discussed shortly. The prerequisite for saving them would be a good temporary assist device—a top priority need.

The 65 survivors of myocardial infarction and the 50 men who develop angina pectoris are about five times more likely to die within the next five or ten years than the 850 men without a coronary event. The need for primary prevention is implicit in this discussion. Nor is this merely a matter of life or death because many survivors do not return to a fully productive life. A systematic community view of these people will provide a new understanding which cannot come from the ad hoc study of individual patients.

Angina pectoris, involving another 50 men, has epidemiological features which distinguish it from survivors of myocardial infarction despite the similarity in prognosis. The accumulated experience with angina patients from the several longitudinal epidemiological studies has only been partially exploited. Recent work in Edinburgh on what the WHO group working on ischemic heart disease registers has termed “unstable angina” is of interest. This refers to chest pain of recent onset, half-way between angina and myocardial infarction, including “coronary insufficiency.” All physicians in a defined area in Edinburgh refer such patients to a study center. Preliminary experience suggests that few die suddenly but a substantial number progress to frank myocardial infarction.

This observation raises a question of profound importance. How many of the 100 patients with heart attacks (fig. 1) have premonitory symptoms? Even more important: are any of these specifically predictive of sudden death? Work is now proceeding on several fronts. At least a quarter to a third of the patients who experience a heart attack have seen a physician within the previous week, either because of cardiac symptoms or seemingly unrelated complaints. This is clearly a matter for intense study, with a view toward professional and public education.

Before leaving this deceptively simple chart, it may be mentioned that a screening survey of middle-aged men in the United States would yield about five men in a hundred with probable, manifest coronary heart disease; two of the five would have angina, the remaining three being survivors from myocardial infarction. In about 20 percent of the survivors, the attack will have been "silent" or "unrecognized," as evidenced by the appearance of significant Q waves not previously present. The prognosis in such men is similar to myocardial infarction survivors. Depending on the criteria of an abnormal exercise electrocardiogram, one other man could be added to the five as having demonstrable coronary heart disease by this test. Are exercise electrocardiograms worthwhile in asymptomatic persons, as opposed to a diagnostic aid in patients with symptoms? Medicine used to be a matter of doing what seemed best. Now, the question of cost-benefit pervades much of the planning. The matter of large-scale exercise electrocardiogram testing is but a minor illustration of this very large problem.
Considerations of cost-benefit were a major factor in appointing a task force to assess cardiac replacement, not only from the medical and ethical but also the economic point of view. Some findings relate to some previous remarks (fig. 2). By 1968, there were 183 cardiac deaths under age 65 in the combined experience of the Framingham and Tecumseh studies. It is of interest that a quarter (48) died with concomitant, severe non-cardiac, life-limiting illnesses which alone would have made them unsuitable as candidates for cardiac replacement. Of the remainder, 50 died in hospital; three had prior heart disease of such severity that they would not have been candidates for replacement while as many as 20 of the 50 could only have been saved by a temporary assist device prior to replacement. Five of the 85 persons who died outside the hospital might have lived if they had been given a new heart earlier. This and other information led to the estimate that there would be maximally 200,000 candidates for new hearts per year in the United States—given a temporary assist device, fully efficient nation-wide emergency transportation facilities and other prerequisites. Cost, as such, did not turn out to be a decisive limiting factor.

There are at least some 160,000 deaths, half of them sudden, from coronary heart disease in the United States per year under age 65. The vast majority must be considered premature. Eighty-thousand sudden deaths per year among persons in that age range represent a staggering figure—as difficult to fathom and comprehend in its total impact as some of the individual tragedies hidden behind it.

**Predicting Risk**

It was shown how many men in the general population develop coronary heart disease in its various manifestations. How can such men be identified prior to the clinical event so that preventive measures might be instituted?

Most is known about serum cholesterol, blood pressure and smoking. When these three risk factors are viewed in combination (table 1), two or all three are in the upper range, as defined, among 38 percent of the men—a rather sorry commentary on the risk factor status of so-called healthy American men! These 38 percent of the men generate 59 percent, close to two-thirds, of all subsequent events of heart attacks. The actual risk, in terms of incidence rates, is almost 9 times higher when all three risk factors are elevated, as compared with men in whom all three are in the lower range. The data come from the Report of the Inter-Society Commission for Heart Disease Resources on the Primary Prevention of the Atherosclerotic Diseases, based on the National Cooperative Pooling Project.
which provides the largest and longest available experience for prediction estimates and represents the combined experience of the Framingham, Albany and Los Angeles studies, the two Chicago studies and the original Minneapolis study.

When it is the aim to assess risk in a single individual, the most useful measure is incidence rate, which permits the calculation of risk, i.e., the probability, of developing clinical disease associated with one set of characteristics as compared with another. An approach which is more telling for assessing risk in the population is to ask to what extent a minority of the population generates a majority of the new events of disease. Such data which define the proportion of the population exposed to excessive risk and the proportion of new events occurring in that high risk group, combined with incidence rates, provide the scientific basis for screening programs and permit tentative estimates of the impact of preventive measures on the disease in the population. It is therefore worthwhile to pursue further the question of the distribution of risk factors and their predictive power in the population.

Using the criteria and definitions shown in table 1, it appears that slightly more than a third of the population at risk, in terms of two or three factors in the upper range, generates about two-thirds of the subsequent cases! The choice of other definitions for what constitutes an elevated level will, of course, yield different results. For instance, if serum cholesterol and blood pressure are called "elevated" when they are in the upper third (tertile) of age-specific frequency distribution, and smoking is again defined as any amount of cigarettes, almost 25 percent of the men pooled from seven studies will smoke and will have both serum cholesterol and blood pressure in the top tertile; they will generate almost 50 percent of the new events (unpublished data based on the experience of the five studies quoted in table 1, combined with the Railroad Workers study, also coordinated in Minneapolis, and the Tecumseh Study). In the Tecumseh Study, as another example, blood glucose one hour after a standard load has been measured along with the three risk factors already considered. Elevated values are defined by the upper tertile of serum cholesterol, blood pressure and blood glucose, or smoking a pack or more a day. In this total population, 15 percent of the men aged 35-64 have two, three or all four of these risk factors in the upper range and they generate about one-third of the new events of myocardial infarction and sudden death over a seven-year period (unpublished data).

Could this prediction be enhanced by triglyceride measurements? The Framingham group reported that triglyceride-rich lipoproteins do not add to the predictive value of serum cholesterol among men\textsuperscript{18} but such an independent effect is seen in the data from a prospective study in Sweden.\textsuperscript{19} The Framingham and Swedish groups do not report on a possible, concomitant influence of hyperglycemia while our group in Tecumseh, so far, has no prospective data on serum triglycerides. However, there are such data from the Tecumseh Study based

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* Data from National Cooperative Pooling Project, American Heart Association

Table 1

Prediction of Myocardial Infarction and Sudden Death According to Three Risk Factors:* Hypercholesterolemia $\geq 250$ mg/100 ml, Hypertension $\geq 90$ mm Hg diast., Cigarette Smoking in Any Amount

Circulation, Volume XLVIII, July 1973
on prevalence. Only 15 percent of the men with manifest coronary disease did not have one or more of five risk factors in the upper tertile range, the factors being cholesterol, triglyceride, glucose one hour after challenge, systolic blood pressure and smoking a pack a day or more. These data bear on a frequent statement that physicians often see patients with coronary heart disease who are “risk-factorless.” This, of course, depends on one’s definition of the troublesome term “normal.” According to the definitions used in the above example from a general population, patients with coronary disease devoid of risk factor elevations are quite uncommon. To be sure, the same statement is true for men without manifest coronary disease—only 20 percent of Tecumseh being in the lower range for all five variables, confirming what was already said about risk factor status in American men. The situation among American women is not much different.

It may seem surprising that the foregoing discussion has not included obesity as a risk factor. Most epidemiological data indicate that obesity makes only a small, independent contribution to the risk of myocardial infarction and sudden death if other risk factors, notably blood pressure, are included in the prediction. Blood pressure and obesity are strongly associated and it would appear that the ill-effects of obesity are largely mediated by its effect on blood pressure and other correlated risk factors—in particular, triglycerides, hyperglycemia and, to some extent, serum cholesterol. Thus, obesity is an important contributor to risk only in association with other risk factors. Presumably, in terms of mechanisms, what is involved is not only caloric excess but its source; Keys pointed out long ago that, in some countries like Italy, obesity may be common but coronary heart disease fairly uncommon because the relatively low proportion of fat in the diet maintains serum cholesterol in a lower range. Moreover, the relation between physical activity and coronary heart disease has been deliberately omitted from discussion because limitations of space preclude doing justice to this important field.

There are other predictors of risk. A very simple questionnaire on chest symptoms and the resting electrocardiogram read according to the Minnesota Code gives remarkable predictive power: symptoms or ECG findings were recorded among 16.4 percent of the men aged 35-59 and these generated over a third (37 percent) of the new coronary events. Quite likely, indices of psycho-social stress, behavior patterns of personality, scores for physical activity and ratings for family history would add some further predictive power, taking into account that predictiveness is not simply additive because of the complex biological and statistical interactions between the many risk variables. Unfortunately, addition of variables not only puts more persons with events into the numerator but also increases the denominator. The need is for an approach which will concentrate a majority of the new events among a minority of the population at risk. Multivariate analysis methods attempt to achieve this aim.

Such a biostatistical technique, the multiple logistic function, was developed by Cornfield and applied to the Framingham data in 1967. This mathematical function ranks persons at risk in terms of any number of variables and assigns to each individual a score which measures the probability of developing a heart attack within a specified period of time. Using the median value of a discriminant score distribution for seven variables as the cutting point, 67 of the 88 new events, or three-quarters, occurred among half the population above the median. Just over half of the new events occurred among the 30 percent of the men with the highest scores. Keys and his colleagues have reported that the multiple logistic function may put as many as 49 percent of the new major coronary events among men aged 40-59 into 20 percent of the population at risk. As might be expected, multivariate risk functions refer only to groups from which they were derived and cannot necessarily be applied to different populations in the same or other countries. Mathematical risk functions of this sort also have much potential application in coronary risk factor detection programs and multiphasic health testing systems.

In the foreseeable future, risk functions can most likely be derived placing half of the new events into 20 percent of the population at risk. This may be illustrated in a diagram (fig. 3) where 50 (15 + 35) of the 100 “new events” (see fig. 1) are seen to occur among the 200 men at the highest risk, out of a total of a thousand men. Ideally, one would wish to put as many as perhaps three-quarters of the new events into the high-risk, upper 20 percent of the population, but this is hardly realistic unless it becomes possible to measure processes which are connected more closely with the pathological processes in the coronary arteries and the myocardium than are currently recognized risk predictors.
CORONARY HEART DISEASE and RISK FACTORS:
HYPOTHETICAL MODEL* for MIDDLE AGED MEN

![Diagram]

Figure 3
Coronary heart disease and risk factors: hypothetical model for middle-aged men.

This model which, however, is realistic assumes that a major coronary event occurs within ten years among 25 percent (50 out of 200) of the men at high risk, while the risk among the remaining 800 men is four times less. Sudden deaths are also shown to be more common among high risk men, as suggested by unpublished data from the Tecumseh Study.

A good many experts advocate limiting preventive action—at the present state of knowledge—to high risk individuals, because they consider scientific evidence still insufficient to warrant a preventive effort directed at the entire population. If half of the events in the top risk group could be prevented by such limited action—and there is no good reason to believe that the effect would be greater, short of starting prevention in childhood—there will now be 75 instead of a hundred major events. Such a 25 percent reduction, while not negligible, would still not substantially reduce the national burden of atherosclerosis and its major complication.

Potential for Prevention

The burning issue of coronary heart disease prevention is intimately tied to the question of causality. Is the relation between serum cholesterol, blood pressure, smoking, carbohydrate intolerance, and perhaps others a matter of cause-and-effect? At present, the evidence is only circumstantial but, at least for the first three risk factors mentioned, very persuasive and strong. The provision of direct, rather than circumstantial, evidence requires controlled, preventive trials which Fredrickson has called "The Indispensable Ordeal." Yet, ever since the conclusion of the Diet-Heart Feasibility Study, reported in 1968, there has been protracted and at times heated discussion over its design and even whether the indispensable ordeal is, in fact, indispensable. Meanwhile several European groups are decisively forging ahead with preventive trials. All the argument and hesitation in this country which has been the pioneer in the field is not entirely beyond comprehension. Trials of this sort present formidable logistic and technical problems, quite apart from their cost. Fortunately, a new phase has now been entered. The Task Force on Atherosclerosis has strongly backed the critical and crucial need for preventive trials, building on earlier recommendations, and contracts for collaborative intervention studies are now being awarded.

There are two distinct, though related issues. The first (fig. 4) concerns the preventive approach which the individual physician should take toward his individual patient or, rather, pre-patient before he becomes a patient. The idealized curve in the figure depicts the hypothetical frequency distribution of risk factor levels, defined as shown on the abscissa, in the population at risk. In reality, these frequency curves, as in the case of serum cholesterol
or blood pressure, are more or less skewed to the right. There will be levels where there would be little argument that preventive action is essential, such as a serum cholesterol level of 300 mg/100 ml. However, what is the lowest level above which prophylactic treatment becomes essential? The broad, vertical bar, in lieu of a line, is intended to indicate that there is no sharp line of demarcation. To some extent, the decision is clinical. For the remainder, it depends on what one considers high risk and to what extent one desires to reduce it, based on the epidemiological information presented earlier. The important point is to realize that there is a risk factor level above which failure to institute preventive action might be considered more serious than the risk of taking an action for which there is as yet no scientific basis in terms of direct evidence from a controlled, preventive trial. In the middle-range, a decision on the desirability of action depends on one's views on the strength of the circumstantial evidence in favor of causality and, to put the matter perhaps too bluntly, on how long one thinks, in terms of probabilities, a person should be permitted to live without experiencing a heart attack.

In the low range of risk, the decision on preventive action is considered "conditional." The main issue here is not the adult but his children. There is no serious doubt that true primary prevention of atherosclerosis must start in childhood. Before telling a man who has maintained a serum cholesterol level of, say, 195 mg/100 ml at age 35 in the face of eating one or two eggs a day and much saturated fat, that he has lucky genes and can go on eating without bothering, one should know about his children's levels. Data from the studies in Tecumseh, reported in 1965 and 1966\textsuperscript{31,32} and recently confirmed (unpublished data), show a rather striking relationship between parents' and children's risk factor levels; this leaves open the question to what degree the correlation is due to environmental and genetic factors. While the relationships between children and their parents are marked, it cannot be assumed—returning to the "conditional" range in the figure—that a parent with a low level necessarily has a child whose level is or will remain low.

The second issue relating to preventive action concerns the community approach (fig. 5). The aim is to shift the whole risk factor distribution curve to the left so that the total population be exposed to a lower level of risk. This would require the adoption of preventive measures by the entire population—and at an early age. Here the matter of modifying national eating habits to lower serum lipids is, of course, the main area for controversy. It is asked whether such far-reaching changes are justified without supportive evidence from controlled, preventive trials\textsuperscript{33,34} or whether the circumstantial evidence and the results from trials already conducted\textsuperscript{35} despite all their shortcomings,\textsuperscript{24,26} warrant preventive action on the community level now\textsuperscript{1,36}.

What is the solution? For the practicing physician, the matter is relatively simple. He will be guided by the location of the pre-patient within the continuum "prevention essential, desirable or conditional." The practical details of prophylactic treatment are not being considered here; the focus of this discussion is on "who" and "why" rather than "how." Iatrogenic disease is a problem in curative medicine. Iatrogenic anxiety is an even greater potential problem in preventive medicine. A person

\textbf{Circulation, Volume XLVIII, July 1973}
in the “prevention essential” category must be motivated most strongly but, at any level or risk, instilling fear is probably not only a poor, but an ineffective motivating force. Those in need of prevention must be told with sympathetic care that, though not a certainty, their chances of developing heart trouble are greater than if their risk factor levels were lower, that it would be sensible, therefore, to do something about it. There is at least as much need for the blessed physician in preventive as in curative medicine!

The foregoing remarks assume that a decision has already been made whether, in a given person, prophylactic measures are indicated. Some guidelines toward this decision were provided in the discussion related to figure 4. It would obviously be helpful to devise sharply defined criteria for who should, might and should not be treated. This is difficult for two reasons. First, as already mentioned, there is no level for any of the single risk factors under consideration where risk changes abruptly from “low” to “high”; in general, the lower the level, the less the risk. All the same, to give an example, the tendency would be, depending somewhat on age, to let a diastolic blood pressure of 90 mm Hg or below go untreated, to treat pressures of 100 or above, and to worry about those hovering between 90 and 100, pending the results of preventive trials for “borderline pressures.” The decision in this twilight zone brings up the second difficulty: if a man with a diastolic pressure of 96 also had a serum cholesterol level of 280 mg/100 ml which, even after treatment, could still remain rather high, one would lean more toward antihypertensive therapy than at a concomitant serum cholesterol of, say, 200 mg/100 ml. It is here that the total risk score from the multivariant function, which takes into account cumulative effects, assumes practical value for the treatment of individuals; it is also a population screening device and research tool. Knowledge of this total risk facilitates a decision on “treatment versus no treatment” with regard to the separate “ingredients,” such as blood pressure or serum lipids, from which the score is derived.

On the community level of prevention, interrelationships between the health professions, official and voluntary health agencies, government, agriculture and industry complicate the matter. If one disagrees with those who maintain that no action on this level can be taken without firm, supporting scientific evidence from definitive preventive trials, one must also disagree with the opposite position, that the evidence is strong enough to launch an all-out national campaign to change eating habits and other factors, taking such actions which, although considered preventive to the development of coronary artery disease, have not been so proved. Such a frontal attack could not fully succeed, in any case, without supporting evidence from a decisive preventive trial! The need is to work with agriculture and the food industry, to improve labelling and advertising, to spread knowledge on preventive cardiology among the public and the profession and, last but not least, to establish pilot preventive programs. These aims will be accomplished more effectively in a less heated and polarized atmosphere and this is already beginning. The above remarks particularly apply to advice and actions involving living habits like eating, smoking and exercise. There has been less controversy regarding drug prophylaxes where controlled trials are also underway both here and abroad.

There is an apparent paradox in advocating preventive advice addressed to the population at large to change certain habits of living and, at the same time, calling for scientific proof from preventive trials that such advice will be based on scientific fact. There is a justification for this strategy. As shown before, around half of the new events of heart attacks occur among persons who are not at top risk in terms of the three “major” risk factors. Without buttressing evidence from preventive trials, there is currently no way of sufficiently motivating people in this critical “middle-risk” category to change their habits or to take prophylactic medication. Without the full weight of evidence from preventive trials, there can never be an all-out national effort to prevent atherosclerosis and its consequences, starting in youth.

Prevention Programs

Prevention programs primarily provide a service, as opposed to being a vehicle for research. There is probably agreement that such programs should presently be on a pilot basis in selected populations in order to learn the best ways to integrate them into comprehensive health care systems. Earlier enthusiasm for coronary risk factor screening, in isolation or as part of multiphasic health testing, has now given way to a more sober assessment. It would be a gross disservice to tell people that they are at high risk without teaching them preventive measures. Screening is but the first step in an integrated preventive program. On a national scale, these are enormous undertakings in terms of
organization, trained personnel and cost. At least 20 percent of American men are at top risk toward coronary disease and another 30 or 40 percent are at less risk although still excessive! This in itself argues in favor of community prevention programs, supplemented as needed by the clinical-individual prevention approach. The total problem cannot be solved until new, comprehensive preventive and curative health delivery systems are created. In the meantime, there should be carefully designed and controlled pilot programs, with emphasis not only on modifying risk factors, but also on testing different approaches to motivating health behavior and achieving optimal cost-effectiveness.

At present, a man age 35 stands a 30 percent chance of developing a myocardial infarction by age 65 if he is in the highest ten percent risk range in terms of the multiple logistic function score; in the lower 30 percent risk range, his chances are less than ten percent, still an appreciable figure.\textsuperscript{37} For sudden death, the difference is similar but even sharper.\textsuperscript{37} To get the vast majority of the population into the low risk range presently enjoyed by only a minority is the ultimate target.

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Circulation. 1973;48:185-194
doi: 10.1161/01.CIR.48.1.185

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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