

Risk Factors for Coronary Artery Disease: Historical Perspectives

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INTRODUCTION

We consider our current understanding and therapy of cardiovascular diseases (CVD) state-of-the-art, but heart disease is still a problem because there is still a lot that we do not know. There is still no cure for any form of heart disease. However, research is ongoing, and new clues are emerging which could lead to better treatments in the future. Results from epidemiological studies, foremost among them the Framingham study, have been crucial to our current knowledge about CVD. Emphasis is on the identification of risk factors, assessment of their predictive ability, and their implications for disease prevention.

The concept of “risk factors” in coronary heart disease (CHD) was first coined by the Framingham heart study (FHS), which published its findings in 1957. FHS demonstrated the epidemiologic relations of cigarette smoking, blood pressure, and cholesterol levels to the incidence of coronary artery disease (CAD). The findings were truly revolutionary for it helped bring about a change in the way medicine is practiced.

Beginnings of our understanding

For thousands of years, our knowledge of the causes of CVD and its therapy was static. It was only in the last half of the 20th century that research into the causes of CVDs accelerated, and with it, new therapies were found.

What stimulated this research? The premature death in 1945 of the US President Franklin D. Roosevelt

from hypertensive heart disease and stroke stimulated this research in USA.^[1] Deaths from CVD and stroke reached epidemic proportions in the USA at that time which induced the Americans to take the lead in cardiovascular research.

The death of President Roosevelt illustrated how little we knew about the general causes of heart disease and stroke. Therefore, a health project was set up in the USA– the FHS – to identify the common factors or characteristics that contribute to CVD. FHS was under the direction of the National Heart Institute, now known as the National Heart, Lung, and Blood Institute.^[2] Researchers followed the development of CHD over a long period in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke. The small town of Framingham in Massachusetts, USA was chosen due to its geographical proximity to the many cardiologists at Harvard Medical School. Furthermore, the residents had already participated in the Framingham tuberculosis demonstration study two decades earlier.^[3]

The town of Framingham is located outside Boston. It was a small, middle-class community, and its small population made it an ideal site to launch the heart study. Everybody knew everyone. It was a typical small-town in the USA. The researchers hoped they would find clues in the medical histories of the people of Framingham which might shed light on causes of CVD. They recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts. These study subjects underwent extensive physical examinations and lifestyle interviews that were analyzed for common patterns related to CVD development. Since 1948, the subjects have continued to return to the study every 2 years for a detailed medical history, physical examination, and laboratory tests, and in 1971,

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the study enrolled a second generation-5,124 of the original participants' adult children, and their spouses to participate in similar examinations.^[2] The FHS is now on its third generation of participants. The study has provided substantial insight into the epidemiology of CVD and its risk factors.

Framingham study leads the way

The Framingham study was responsible for pointing out fallacies in our understanding of CVDs and identification of its major risk factors: high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity as well as other valuable information on the effects of related factors such as blood triglyceride and high density lipoprotein (HDL) cholesterol levels, age, gender, and psychosocial issues. To date, no single risk factor has been identified to be responsible for causing CVD; rather, multiple interrelated factors seem responsible for its development. Although the Framingham cohort is Caucasian, other studies have shown that the major risk factors identified in this group apply universally to other racial and ethnic groups.

The notion of CVD risk factors is an integral part of modern medicine which has led to the development of effective treatment and preventive strategies in clinical practice.

Fallacies corrected

Physicians are sometimes taught some theories that are believed to be true without having been proven. These ideas or notions have been doctrines from centuries' old practices. Many of these concepts are taught us in medical school such as the notion that an elevated systolic blood pressure (BP) in the elderly is "normal," which of course is false as I will discuss later. Then, a study comes along to dispel these erroneous ideas. Such a study was the Framingham heart study. Its epidemiological model of research has unraveled many of the fallacies in our understanding and helped to bring about a change in the way medicine is practiced.

The development of CHD through the prism of its major conventional cardiovascular risk factors – hypertension, hypercholesterolemia, smoking, and diabetes mellitus – is interesting, and hence, I will briefly look at how they evolved as risks through the "eyes" of the FHS and other epidemiological studies.

The major risk factors

There are many risk factors for CAD and some can be controlled but not others. The risk factors that can be controlled (modifiable) are: High BP; high blood cholesterol levels; smoking; diabetes; overweight or obesity; lack of physical activity; unhealthy diet and

stress. Those that cannot be controlled (conventional) are: Age (simply getting older increases risk); sex (men are generally at greater risk of coronary artery disease); family history; and race.

Hypertension

Hypertension is one of the risks in the development of CHD. The American President Roosevelt died from cerebral hemorrhage, sequelae of hypertension.

Old myths corrected

Many old physicians thought that high BP was necessary to force blood through the stiffened arteries of older persons and that it was a normal element of aging. The medical community believed that a permissible systolic BP was 100 plus the participant's age in millimeters of mercury.^[4,5] For those aged >70 years, some considered the acceptable upper limits of normal BP to be 210 mmHg systolic and 120 mmHg diastolic.^[6]

It was considered appropriate to ignore benign essential hypertension and isolated systolic hypertension. I remember that I was taught in medical school that diastolic pressure was a superior measure of blood pressure. The cardiovascular hazard of hypertension was believed to derive chiefly from the diastolic pressure component. Consequently, elevated systolic pressure was considered harmless, especially in the elderly.^[7,8]

FHS dispelled the concept of "benign essential hypertension." Belief in the prime importance of the diastolic pressure was convincingly refuted by Framingham study data and later confirmed by other prospectively obtained data demonstrating that the impact of systolic pressure is actually greater than the diastolic component and that even isolated systolic hypertension is dangerous.^[9,10] FHS investigators found an increased risk of CAD morbidity with rising baseline blood pressure. They challenged the existing belief "that systolic pressure is unimportant, and that labile or benign essential hypertension is of little consequence." They stated that there was "little evidence to support these contentions but considerable reason to doubt them."^[11]

The importance of controlling BP was finally embraced in practice guidelines in the first "Report of the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure" in 1977.^[12] It is now recognized universally that hypertension increases atherosclerotic CVD incidence; the risk burden is 2–3-fold. CAD is the most common sequelae for hypertensive patients of all ages.^[13] Hypertension predisposes to all clinical manifestations of CHD including myocardial infarction, angina pectoris, and sudden death. Even high normal BP values are associated with an increased risk of CVD.^[14]

It was thought that the risk ratio for intracerebral hemorrhage was greater than for atherothrombotic

brain infarction. This was not true. It was found that hypertension was as strong a risk for atherothrombotic brain infarction as intracerebral hemorrhage.^[11]

Framingham showed that the preponderance of hypertension-related strokes were atherothrombotic brain infarctions whether the hypertension was severe or mild. The proportion of strokes due to hemorrhage in mild hypertension was identical to that for severe hypertension.^[4]

The Seventh JNC on hypertension established that those with BP of 120–139/80–89 mmHg are prehypertensives, that is, these individuals may become hypertensives in the future. Starting as low as 115/75 mmHg, the risk of heart attack and stroke doubles for every 20-point jump in systolic BP or every 10-point rise in diastolic BP for adults aged 40–70.

The presence of other risk factors for CVD such as high cholesterol, obesity, and diabetes is seen more in people with prehypertension than in those with normal blood pressure. The CVD risk in prehypertensives increases with the number of associated risk factors present. Therefore, prehypertension confers a greater risk for CVD.

In persons with mild to moderate hypertension, the substantial risk was shown to be concentrated in those with coexistent dyslipidemia, diabetes, and left ventricular hypertrophy. Hypertensive elderlies were commonly found to already have target organ damage such as impaired renal function, silent myocardial infarction, strokes, transient ischemic attacks, retinopathy, or peripheral artery disease. At least 60% of older men and 50% of elderly women with hypertension in the Framingham study had one or more of these conditions.^[11]

In the past, initiation of antihypertensive treatment was often delayed until there was evidence of target organ involvement. Framingham study data indicated that this practice was unwise because 40%–50% of hypertensive persons developed overt cardiovascular events before evidence of target organ damage such as proteinuria, cardiomegaly, or electrocardiogram abnormalities.^[11]

Various guidelines and numerous updates of guidelines on hypertension have been promulgated to improve its treatment and to prevent its adverse cardiovascular consequences. There is no cure for hypertension, but there are helpful pharmacological therapy and some strategies that a person can do to lower risk such as diet and exercise and checking BP regularly.

Hypercholesterolemia

The other major risk for CVD was cholesterol. In 1953, an association between cholesterol levels and CHD mortality was reported in various populations.^[15] Animal and clinical observation have suggested such relationship. This association was confirmed by epidemiological

studies showing a strong relation between serum total cholesterol and cardiovascular risk.^[16–18]

It was shown that changes in cholesterol levels were associated with changes in CVD incidence rate.^[19] Clinicians and epidemiologists accepted these findings, agreeing that total plasma cholesterol was a useful marker for predicting CVD. It was found that its component— the low-density lipoprotein cholesterol (LDL-C) which is the principal lipoprotein transporting cholesterol in the blood, was also directly associated with CVD.^[20–22] It was also found out that LDL cholesterol levels in young adulthood predict development of CVD later in life.^[22]

Current guidelines identify LDL-C as the primary target for high blood cholesterol therapy.^[23] The benefits of LDL-C lowering drug therapies has been shown in various clinical, observational and experimental studies.^[24] It has been shown that the benefits of reducing serum cholesterol for CHD risk are age-related: a 10% reduction in serum cholesterol produces a drop in CHD risk of 50% at the age of 40, 40% at age 50, 30% at age 60, and 20% at age 70.^[25]

Now, high density lipoprotein cholesterol (HDL-C) is accepted by the medical community as an important factor in atherosclerosis and consequently, raising HDL-C has become an accepted therapeutic strategy for decreasing CHD incidence rate. There are some drugs that increase HDL-C such as fibrates, niacin, and torcetrapib, a cholesterol ester transfer protein but only fibrates have been shown to reduce risk of major coronary events. It is estimated that a 1 mg/dL increase in HDL level is associated with a decrease in coronary risk of 2% in men and 3% in women.^[26]

Smoking

The Framingham study showed that smokers were at increased risk of myocardial infarction (MI) or sudden death and that risk was associated to the number of cigarettes smoked each day.^[27] These results were confirmed by other epidemiological studies.^[28–30] The deleterious effect of smoking on health has been proven in many studies, in particular on atherosclerosis.

The harmful effects of smoking on the heart can be appreciated in the following statistics:

- Cigarette smoking approximately doubles the risk of morbidity and mortality from ischemic heart disease compared with a lifetime of not smoking, and the risk is related to the duration and amount of smoking.^[31,32]
- There is evidence that in patients with CHD, smoking cessation reduces the risk of all-cause mortality and nonfatal MI.^[33] Therefore, all patients with ischemic heart disease should be advised to stop smoking because it is a strong risk factor for a first MI and for fatal and nonfatal recurrences.

- The risk of morbidity and mortality associated with cigarette smoking falls immediately after stopping smoking, although it may be >20 years, if at all, before the risk associated with smoking is completely reversed.^[31,34]
- About 20% of patients will give up smoking after an acute MI with resultant 40% reduction in mortality rates and infarct recurrences.^[35,36]
- For smokers under the age of 50 years the risk of developing CHD is 10 times greater than for nonsmokers of the same age.^[37]
- Passive smoking also increases the risk of CHD.^[38]

Diabetes

The role of diabetes in the pathogenesis of CVD was unclear until 1979 when Kannel *et al.* used data from the Framingham heart study to identify diabetes as a major cardiovascular risk factor. Based on 20 years of surveillance of the Framingham cohort, a two-fold to threefold increased risk of clinical atherosclerotic disease was reported. It was also one of the first studies to demonstrate the higher risk of CVD in women with diabetes compared to men with diabetes.^[39] These results have been duplicated by multiple studies. The Kannel article changed the way the medical community thought about diabetes. It is now accepted as a major cardiovascular risk factor. There is a clear-cut relationship between diabetes and CVD. The American Heart association cites the following statistics:^[40]

- At least 68% of people age 65 or older with diabetes die from some form of heart disease; and 16% die of stroke.
- Adults with diabetes are two to four times more likely to die from heart disease than adults without diabetes.
- The American Heart association considers diabetes to be one of the seven major controllable risk factors for CVD.

Diabetes is treatable but even if glucose levels are under control it greatly increases the risk of heart disease and stroke because people with diabetes also have other conditions that are risks for developing CHD such as hypertension, smoking, abnormal cholesterol, obesity, lack of physical activity, and metabolic syndrome. The good news is that by managing these risk factors, people with diabetes may avoid or delay the development of CVD.

Physical inactivity

"Conductors on London's double-decker buses (up and down stairs 11 days a fortnight, 50 weeks a year, often for decades) experienced half or less the incidence of acute MI and "sudden death" ascribed to CHD in the sedentary bus drivers."^[41] Thus, began Morris *et al.* in his landmark article in 1953 which appeared in The Lancet on the association of physical activity and coronary

artery disease. Since then a number of epidemiological studies have confirmed the relationship. The relative risk of death from CHD for sedentary compared with active individuals is 1.9 (95% confidence interval).^[42] The recommendation of physical exercise has become an important element of preventative policies for the general population (in adults, elderly, and children).

Obesity

The association of obesity and CHD was first noted by Kannel *et al.*^[43] in Framingham 50 years ago. Obesity is also an independent risk factor for all-cause mortality. It is a metabolic disorder associated with comorbidities such as CHD, type 2 diabetes, hypertension, and sleep apnea. Alterations in metabolic profile and various adaptations in cardiac structure and function occur as excess adipose tissue accumulates.^[44] A recent study reported that higher body mass index (BMI) during childhood is associated with an increased risk of CHD in adulthood.^[44]

The prevention and control of overweight and obesity in adults and children has become a key element for the prevention of cardiovascular diseases.^[45,46]

Cardiovascular diseases risk assessment

Absolute prediction of CVD risk of a person can be made using prediction charts issued or published by the WHO and ACC/AHA. The recommendations are made for management of major cardiovascular risk factors through changes in lifestyle and prophylactic drug therapies.

The ACC/AHA have produced guidelines for the procedures of detection, management, or prevention of CVD. In November 2013, The ACC and AHA released updated risk-assessment guidelines for atherosclerotic CVD. Changes and recommendations include the following.^[47-51]

- Stroke is added to the list of coronary events traditionally covered by risk prediction equations.
- The guidelines focus primarily on the 10-year risk of atherosclerosis-related events; they focus secondarily on the assessment of lifetime risk for adults aged 59 or younger without high shorter-term risk.
- The strongest predictors of 10-year risk are identified as age, sex, race, total cholesterol, HDL-C, blood pressure, blood-pressure treatment status, diabetes, and current smoking status.
- Adjunct formulas for refining risk estimates by gender and race are provided.
- If risk prediction needs to be further sharpened after risk prediction equations have been performed, the guidelines indicate that coronary-artery calcium scores, family history, high-sensitivity C-reactive protein, and the ankle-brachial index can be used.

- The guidelines recommend that statin therapy be considered in individuals whose 10-year atherosclerotic cardiovascular disease (ASCVD) event risk is 7.5% or greater.

Guidelines from AHA/ACC recommend use of a revised calculator for estimating the 10-year risk of developing a first ASCVD event, which is defined as a nonfatal MI, death from CHD, or stroke (fatal or nonfatal) in a person who was initially free from ASCVD.^[51] The calculator incorporates the following risk factors: sex, age, race, total cholesterol, HDL, systolic blood pressure, treatment for elevated blood pressure, diabetes, and smoking.

For patients 20–79 years of age who do not have existing clinical ASCVD, the guidelines recommend assessing clinical risk factors every 4–6 years. For patients with low 10-year risk (<7.5%), the guidelines recommend assessing 30-year or lifetime risk in patients 20–59-year-old.

The guidelines note that regardless of the patient's age, physicians should communicate risk data to the patient and refer to the AHA/ACC lifestyle guidelines, which cover diet and physical activity. For patients with elevated 10-year risk, physicians should communicate risk data and refer to the AHA/ACC guidelines on blood cholesterol and obesity.

SUMMARY

CVD is a major cause of disability and premature death throughout the world. The underlying pathology of atherosclerosis develops over many years and is usually advanced by the time symptoms occur, generally in middle age. The risk of developing CAD increases with age, and includes age >45 years in men and >55 years in women. A family history of early heart disease is also a risk factor, such as heart disease in the father or a brother diagnosed before age 55 years and in the mother or a sister diagnosed before age 65 years. Acute coronary and cerebrovascular events frequently occur suddenly, and are often fatal before medical care can be given. I have discussed above the major traditional risk factors.

Many traditional risk factors for CAD are related to lifestyle, therefore preventative treatment can be tailored to modifying specific factors. It is very important to know these risks to reduce disability and premature deaths from CHD, cerebrovascular disease and peripheral vascular disease in people at high risk, who have not yet experienced a cardiovascular event. People with established CVD are at very high risk of recurrent events.

Current guidelines provide advice on screening and identifying asymptomatic individuals at risk of developing CVD. The objectives of these guidelines are to reduce the incidence of first or recurrent clinical events due to CHD, ischemic stroke, and peripheral artery disease.

The focus is on prevention of disability and early death. The guidelines emphasize the importance of lifestyle changes and use of different prophylactic drug therapies in the management of risks.

The understanding of such risk factors is critical to the prevention of cardiovascular morbidities and mortality.

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