The Framingham Study: ITS 50-Year Legacy and Future Promise

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The Framingham Study was initiated in 1948 to investigate an epidemic of coronary disease in the USA, using a prospective epidemiological approach. Insights were provided into the prevalence, incidence, full clinical spectrum and predisposing factors. The major “risk factors” (a term coined by the Framingham Study) for coronary disease, stroke, peripheral artery disease and heart failure were identified and clinical misconceptions dispelled about isolated systolic hypertension, left ventricular hypertrophy, dyslipidemia, atrial fibrillation and glucose intolerance. Average values for blood lipids, blood pressure, body weight, glucose and fibrinogen were shown to be dangerously suboptimal and to have a continuous graded relationship to cardiovascular disease without critical values. Dyslipidemia, glucose intolerance and elevated fibrinogen were shown to have smaller hazard ratios in the elderly, but this was offset by a higher absolute risk. Diabetes was shown to operate more strongly in women, eliminating their advantage over men. Serum total cholesterol was shown to derive its atherogenic potential from its LDL component and also to reflect cholesterol being removed in the HDL fraction. The total/HDL cholesterol ratio was demonstrated to be the most efficient lipid profile for predicting coronary disease. LDL was shown to be correlated with hemostatic factors, suggesting that there would be additional benefits to lowering LDL. High triglyceride associated with reduced HDL, indicating insulin resistance and small-dense LDL, was shown to be associated with excess coronary disease. All the risk factors tended to cluster, and this was shown to be promoted by insulin resistance induced by weight gain. Multivariate risk profiles were produced to facilitate risk stratification of candidates for coronary disease, stroke, peripheral artery disease and heart failure. The Framingham Study is now engaged in quantifying the independent contributions of homocysteine Lp(a), insulin resistance, small-dense LDL, C-reactive protein, clotting factors and genetic determinants of cardiovascular disease. We are now able to estimate the lifetime risk of all the atherosclerotic cardiovascular disease outcomes. J Atheroscler Thromb, 2000; 6: 60-66.

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The Framingham Study was initiated in 1948 to investigate a rising epidemic of cardiovascular disease using what was then a novel prospective epidemiological population approach. The epidemic of coronary disease rose to a peak in the 1960’s and began a dramatic down-turn in the 1970’s which we believe was in part related to a better understanding of the predisposing risk factors derived from Framingham Study research. The epidemiological approach was used to determine in what particulars those who went on to develop cardiovascular disease differed from those who managed to escape it.
over a long period of biennial surveillance. This approach to investigating the population determinants of cardiovascular disease was not universally accepted (1-5).

When the Study was initiated the prevailing concept was that we should seek a single cause of atherosclerotic cardiovascular disease that was essential and sufficient to produce the disease. It soon became apparent that the etiology was multifactorial with a number of risk factors (a term coined by the Framingham Study) that promoted the disease. These included living habits that promote atherogenic personal attributes, indicators of unstable lesions and a compromised arterial circulation, and hallmarks of innate susceptibility.

Five decades of Framingham Study research have documented and quantified the effect of multiple risk factors that strongly and independently contribute to the development of atherosclerotic cardiovascular disease at all ages in both sexes. It was found that what were considered average or normal risk factor values were dangerously suboptimal. The major risk factors were soon established and confirmed by others. These included elevated serum cholesterol, hypertension, diabetes, cigarette smoking and ECG evidence of left ventricular hypertrophy. The relationship of all the risk factors investigated were shown to have a continuous graded relationship to cardiovascular disease with no discernable critical values. There was considerable doubt expressed about the relevance of each of these predisposing conditions in the major textbooks of that era.

Friedberg’s premiere textbook “Diseases of the Heart” in 1949 indicated skepticism about the importance of serum cholesterol (6). The Framingham Study was soon able to show that there was a clear relationship between antecedent serum cholesterol levels and the rate of development of coronary heart disease (7). This same textbook, in a 1966 edition, continued to express doubt about the correlation between the severity of hypertension and the rate of development of cardiac disease (8). The Framingham Study showed a continuous graded influence of blood pressure on the rate of development of cardiovascular disease (9). Likewise, the connection between diabetes and coronary atherosclerosis was doubted at the inception of the Framingham Study (5). The Framingham Study demonstrated a powerful influence of diabetes on all the major atherosclerotic cardiovascular events, particularly in women (10). The American Heart Association in 1960 questioned the role of cigarette smoking (11). The Framingham Study provided evidence of a significant influence of smoking on all the major atherosclerotic cardiovascular disease outcomes (12). Left ventricular hypertrophy was regarded as a beneficial compensatory phenomenon as late as 1966 (8). The Framingham Study found that even moderate amounts of exercise were beneficial (16).

The role of cholesterol in cardiovascular disease was questioned in the American press as late as 1989. Further investigation in the Framingham Study and elsewhere indicated that the serum total cholesterol reflected a two-way traffic of cholesterol entering and leaving the arterial intima. The risk of coronary disease was shown to be directly related to the LDL-cholesterol and inversely related to the cholesterol in the HDL, each independent of the other (Fig. 2). The progressive increase in risk associated with the serum total cholesterol was found to be many clinical misconceptions about the major risk factors. The diastolic component of the blood pressure was believed to be a more important determinant of the cardiovascular sequelae of hypertension than the systolic pressure (14). The Framingham Study showed a greater influence of the systolic component (15), and demonstrated the hazard of isolated systolic hypertension (Fig. 1). Physical activity, at the time the Framingham Study was initiated, was considered bad for the heart. Later, only vigorous activity, sufficient to achieve a training effect, was considered beneficial. The Framingham Study found that even moderate amounts of exercise were beneficial (16).

Further investigation of these risk factors dispelled
a function of the total to HDL-cholesterol ratio, which tended to increase along with the total cholesterol value. The risk of coronary heart disease was shown to increase progressively with the total/HDL-cholesterol ratio. This ratio proved to be the most efficient lipid predictor of coronary heart disease (Table 1). It predicts equally well at high or low total cholesterol values.

Triglyceride has remained a more controversial lipid that is being intensively investigated for an independent influence on coronary disease incidence. Framingham data suggest that even non-fasting triglyceride is an independent risk factor for coronary disease, taking all the major risk factors except HDL-cholesterol into account (Table 2). Analysis of the influence of triglyceride, taking the highly inversely correlated HDL-cholesterol into account in the Framingham Study, indicates an independent effect at any HDL value (Fig. 3).

These epidemiological findings provided pathogenetic clues to what is now, the current conceptualization of lipid atherogenesis (Fig. 4). Another important epidemiologic feature of blood lipids as a cardiovascular risk factor is their tendency to cluster, not only among themselves, but also with the other major risk factors. Clustering with 3 or more other risk factors occurs at 4 times the rate expected by chance. LDL also tends to cluster with most of the hemostatic risk factors (Table 3). The extent of clustering of other atherogenic traits with the blood lipids greatly influences its atherogenic potential. The risk of developing coronary disease in dyslipidemic persons varies widely depending on the extent of clustering with other atherogenic risk factors. High risk of cardiovascular disease in dyslipidemia is concentrated in those with two or more additional risk factors (Fig. 5). This raises the speculation that atherogenic dyslipidemia may be closely linked to the insulin resistance syndrome.

Interest in diabetes now focuses on lesser degrees of impaired glucose tolerance and the insulin resistance syndrome (17). Hyperinsulinemia has been shown to be associated with the occurrence of coronary disease (18). The lipid abnormality characteristic of diabetes and impaired glucose intolerance is a reduced HDL-cholesterol, a raised triglyceride and small-dense LDL. HDL and triglyceride tend to cluster with the other atherogenic traits characterizing the insulin resistance syndrome (19).

In persons with any one of the major risk factors, clustering of other risk factors is promoted by weight gain. Finally, the risk of coronary disease in diabetics, as in dyslipidemic persons, varies widely depending on the amount of clustering of the risk factors comprising the insulin resistance syndrome (20). The high-risk diabetics are those with two or more additional risk factors.

Left ventricular hypertrophy was long recognized as an important diagnostic entity, but before epidemiological investigation of this entity in the Framingham Study, there was no prospective population-based data to assess its incidence and prognostic implications. The Framingham Study showed that left ventricular hypertrophy, whether manifested on the ECG, echocardiogram, or chest film, was an ominous harbinger of cardiovascular disease, the risk increasing with the left ventricular mass, with no critical value separating compensatory from pathological hypertrophy (21). Each of the clinical indicators of hypertrophy was shown to independently contribute to the risk of cardiovascular events, those with a combination of indicators having a greater risk than those with any one alone. Because it was thought that the hypertrophy was a compensatory response to the increased workload

### Table 1. Lipid profile efficiency in predicting CHD in subjects ages 50–80 years

<table>
<thead>
<tr>
<th>Change in Lipid</th>
<th>Age-Adj. Risk Ratio (Qx/Qy)</th>
<th>Increment per S.D.</th>
<th>Framingham Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Total Chol.</td>
<td>24%</td>
<td>22%</td>
<td>1.9</td>
</tr>
<tr>
<td>LDL-Chol.</td>
<td>29%</td>
<td>31%</td>
<td>1.9</td>
</tr>
<tr>
<td>HDL-Chol.</td>
<td>-25%</td>
<td>-33%</td>
<td>0.4</td>
</tr>
<tr>
<td>T. Chol./HDL-Chol.</td>
<td>40%</td>
<td>43%</td>
<td>2.5</td>
</tr>
<tr>
<td>LDL/HDL-Chol.</td>
<td>43%</td>
<td>46%</td>
<td>2.5</td>
</tr>
</tbody>
</table>

### Table 2. Risk of CHD by non-Fasting triglyceride

<table>
<thead>
<tr>
<th>Non-Fasting Triglyceride (mg/dl)</th>
<th>Age-Adjusted 10 Yr. Rate/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>74</td>
</tr>
<tr>
<td>80–109</td>
<td>85</td>
</tr>
<tr>
<td>110–139</td>
<td>87</td>
</tr>
<tr>
<td>140–169</td>
<td>130</td>
</tr>
<tr>
<td>170</td>
<td>147</td>
</tr>
</tbody>
</table>

*P<0.05 ***P<0.001 *N.S.
imposed by hypertension or valve disease or the need to offset loss of heart muscle after a myocardial infarction, some feared that correction of this hypertrophy would be detrimental. However, improvement in the ECG features of left ventricular hypertrophy towards normal was found by the Framingham Study to be associated with almost a 50% reduction in risk of adverse cardiovascular outcomes (22).

The vital capacity is assessed primarily to diagnose and evaluate pulmonary disease. However, the Framingham Study established that it is also a powerful independent predictor of cardiovascular morbidity and mortality in apparently healthy persons (23). The vital capacity was shown to be a valuable predictor of cardiovascular disease in general, and heart failure in particular, probably indicating diastolic ventricular dysfunction.

Women were found to lag men in the incidence of coronary heart disease by 10 years with the gap in incidence closing with advancing age. Those women undergoing the menopause were found to have a 3-fold greater risk of cardiovascular disease than those remaining premenopausal at the same age (24). Aside from undergoing the menopause, a number of risk factors were identified that tend to eliminate the female advantage over men (25).

Because of the tendency for risk factors to cluster and the wide variation in cardiovascular risk associated with any particular risk factor, depending on the associated burden of other risk factors, multivariate risk assessment was deemed essential to efficiently target candidates for treatment (26). Accordingly, multivariate risk profiles have been produced to facilitate risk stratification of candidates for development of coronary disease, stroke, peripheral artery disease, and heart failure. For example, by using the most recent Framingham coronary disease prediction algorithm the 10-year probability of a coronary event in a person with dyslipidemia can be estimated taking into account the associated burden of risk factors (27). Caution must be exercised in generalizing from the Framingham Study experience to low coronary incidence

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**Table 3.** Adjusted levels of hemostatic risk factors stratified by LDL cholesterol level

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>&lt;70</th>
<th>70-100</th>
<th>101-129</th>
<th>130-159</th>
<th>&gt;160</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, mg/dl</td>
<td>273.5±8.4</td>
<td>289.5±3.1</td>
<td>295.0±2.6</td>
<td>295.2±2.9</td>
<td>298.8±3.6</td>
<td>0.007</td>
</tr>
<tr>
<td>PAI-1, ng/ml</td>
<td>12.1±1.2</td>
<td>14.8±0.5</td>
<td>15.0±0.4</td>
<td>15.4±0.5</td>
<td>17.5±0.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TPA antigen, ng/ml</td>
<td>5.8±0.4</td>
<td>6.5±0.2</td>
<td>6.5±0.1</td>
<td>7.1±0.2</td>
<td>7.5±0.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Factor VII, %</td>
<td>98.5±2.4</td>
<td>97.5±0.9</td>
<td>99.5±0.7</td>
<td>100.6±0.8</td>
<td>99.7±1.0</td>
<td>0.026</td>
</tr>
<tr>
<td>vWF antigen, %</td>
<td>122.0±7.7</td>
<td>131.0±2.9</td>
<td>125.6±2.4</td>
<td>126.9±2.6</td>
<td>126.0±3.3</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Values expressed as mean±SEM. *P for trend adjusted for age, sex, BMI, smoking, diabetes, alcohol, and use of anti-HBP medication. From: Circulation, 1997; 95 (4)
population samples where the absolute risk of a combination of risk factors may be overestimated. However, reasonable accuracy in predicting multivariate risk of coronary disease has been demonstrated when prediction equations were applied to population samples from Honolulu, Puerto Rico, Albany, Chicago, Los Angeles, Minneapolis, Tecumseh, the Western Collaborative Group and a national US sample (27).

The Framingham Study is now engaged in quantifying the independent contribution of novel risk factors recently identified. These include homocysteine, Lp(a), small-dense LDL, C-reactive protein, clotting factors, insulin resistance, anti-oxidants and genetic determinants of cardiovascular disease and its predisposing risk factor (28). These are prevalent in the population.

Clinically, fibrinogen values within the usual range were not considered pathological. The Framingham Study, along with others, has found high normal fibrinogen to be an independent risk factor for development of cardiovascular disease in general, and coronary disease in particular (29). Likewise, high normal leukocyte counts were found to increase the risk of cardiovascular disease (30). Both of these and the C-reactive protein, with which they are correlated, could signify the presence of unstable lesions undergoing inflammatory changes. All these tend to further enhance the risk imposed by dyslipidemia. We have been able to confirm that Lp(a) is a risk factor for atherosclerotic cardiovascular disease in the Framingham Study (31). Also confirming the findings of others, elevated homocysteine promoted by deficient intakes of vitamins B-12, B-6 and folic acid, has been found to be a risk factor for cardiovascular disease and the excess mortality it imposes (32). Coronary cases were found to have a greater amount of small-dense LDL particles (28).

The Framingham Study showed that the resting heart rate was related to the rate of occurrence of cardiovascular events. For example, risk of a coronary sudden death increased the higher the resting heart rate. A rapid heart rate was found to escalate the hypertensive risk of cardiovascular mortality (33). Subsequently, reduced heart rate variability was confirmed as a risk for cardiovascular events (34) and failure to reach target heart rate on the treadmill was found to be associated with a high long-term risk of coronary events (35).

The Framingham Study was able to provide an undistorted appreciation of the way cardiovascular disease evolves in the general population, including those too mild to reach medical care and those who die too suddenly (36). We were able to determine the true incidence of cardiovascular disease in the US general population, and determine that coronary disease was the most common and most lethal manifestation of atherosclerotic cardiovascular disease, equaling in incidence that of all the other manifestations combined. Because of the five decades of surveillance of the population it has been possible to estimate the lifetime risk of developing coronary disease. At age 40 years one in every two men and one in every three women can expect to develop the disease during their lifetime (36). Sudden death was shown to be a prominent feature of coronary mortality, accounting for almost half of the deaths in men (37). One in every six coronary attacks was found to present with sudden death as the first, last and only symptom. The Framingham Study ascertained that one in every three

![Graph](image_url)

**Fig. 5** Risk of coronary heart disease in subjects with serum cholesterol 240-262 mg/dl by level of other risk factors. Subjects aged 42-43 years.
myocardial infarctions were silent or went unrecognized (37). It was also determined that these unrecognized infarctions had as serious a prognosis as recognized infarctions (38). The Framingham Study was also able to point out the serious consequences of overt heart failure, showing it to have a prognosis as ominous as cancer (39). Recently a risk appraisal function was devised based on Framingham Study data, to assess the hazard of heart failure in persons who are predisposed by coronary disease, hypertension or valvular heart disease (40). This provides general practitioners and internists with a cost-effective method to select people at high risk of having impaired left ventricular function who require further evaluation and aggressive preventive measures. The risk factors used in constructing the profile include age, ECG-LVH, cardiomegaly on chest film, heart rate, systolic blood pressure, vital capacity, diabetic status, evidence of myocardial infarction and valvular heart disease. Using the risk factors that make up the risk formulation, derived from ordinary office procedures, the probability of developing heart failure can be estimated and compared to average risk for persons the same age and sex. The proportions of persons with heart failure who have normal systolic left ventricular function and their mortality experience were recently assessed (41). About half of the Framingham Study participants who developed heart failure had normal systolic function and they were predominantly women. Although they have a substantially lower mortality rate than those with systolic dysfunction, compared to controls free of heart failure, they had a 4-fold increased risk.

The application of the Framingham Study findings to preventive cardiology has been most gratifying to the investigators. Public health measures, health education for the public and preventive medicine for high risk persons have been widely implemented. Because of this, and innovations in medical care, cardiovascular mortality rates have declined dramatically in the US. However, the rates are still double those reported for Japan. Curiously, the prevalence of cardiovascular disease has not declined along with the mortality. Trials have documented the efficacy of controlling the blood pressure, and the blood lipids. Recently, it has been shown that aggressive lipid-lowering therapy in low risk patients with stable coronary disease is at least as effective as angioplasty and usual care in reducing the incidence of ischemic events (42). However, the full potential of risk factor control for primary prevention of coronary disease has yet to be achieved. There is still an unacceptably high prevalence of risk factors in the US. Trends in food intake in countries in transition to a Western lifestyle need to be curbed if they are to avoid the penalty of an epidemic of coronary disease. In an examination of longitudinal trends in serum cholesterol levels in a Japanese cohort, it was found that the levels increased dramatically, particularly in younger members of the cohort of both sexes (43). In a review of nation-wide surveys in Japan it was found that in the 1960’s serum cholesterol levels in urban populations were higher than those in the rural areas. A progressive yearly increase in cholesterol values was observed in all rural population samples between 1960 and 1990. This increase coincided with a per capita daily increase in meat consumption from 23.9 to 66.2 g in the rural population samples (44).

References

(6) Diseases of the Heart. ed by Friedberg CK, Philadelphia, Saunders, 1949
(18) Pyorala K. Hyperinsulinemia as a predictor of athero-


