Coronary Risk Factors Revisited

CORONARY RISK FACTORS REVISITED

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PREFACE

Ischaemic heart disease (IHD) continues to be the major public health problem even in countries like the USA and Australia which have experienced dramatic reductions in this incidence. Here in the UK we are still working to establish an environment in which IHD can be brought under control. The topic is high on the agenda of both medical and political debate but in the near future discussion must give way to action.

'Coronary Risk Factors Revisited' was organised as a gathering of theorists and practitioners in an attempt to provide the background and the methods to promote coronary prevention in primary care. Section one reviews current knowledge of established and novel risk factors – and suggests ways in which they be integrated into a score which provides assessment of overall risk. The second section presents the experiences of many who are currently involved in coronary prevention programmes. The Practice Nurse has an important role to play in the screening and initial follow-up of subjects at risk, and delegation of these duties to Nurse Practitioners is a critical step in increasing the cost of effectiveness of these activities and the book concludes with a review of the place of therapeutic agents in the treatment of diet-resistant hyperlipidaemia. We hope that it will serve as a useful handbook to those intent on a screening for coronary risk factors.

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Coronary risk factors revisited. J. Shepherd et al., editors.

CORONARY HEART DISEASE: THE VIEW FROM FRAMINGHAM

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INTRODUCTION

Forty years of experience from the Framingham Heart Study and other similar prospective studies of heart disease in the United States and Europe have provided conclusive evidence that heart disease is the major cause of death. While coronary heart disease (CHD) is uncommon in the first four decades of life, CHD rates rise rapidly after age 40 in men and age 50 in women (1). After menopause CHD rates accelerate for women and approach those for men by age 65 (2,3).

This review will discuss precursors of CHD, commonly called risk factors. Although the term "risk factor" is now taken for granted, it was first used in a presentation by T. Royle Dawber, the original medical director of the Framingham Heart Study, at a meeting in 1957 (4). At that time it was not appreciated that mild cholesterol elevations, cigarette smoking, and mildly elevated blood pressure could act synergistically to increase risk for heart disease. The later publication of the statistical methodology for logistic regression analysis, which is at the roots of the "risk factor" concept (5), and rapid growth of statistical methods for analysis of prospective data from studies such as Framingham, has allowed full use of the data from epidemiologic studies and allowed the assessment of potentially new risk factors as they become studied.

The web of causation for heart disease is complex. While a multitude of factors potentially associated with CHD have been studied, this review will emphasize the major elements: cholesterol and high density lipoprotein cholesterol (HDL-C) levels, blood pressure, and cigarette smoking.

MATERIAL AND METHODS

The Framingham Heart Study was initiated in 1948 to study

factors associated with heart disease in a community 20 miles west of Boston. Originally 5209 men and women age 30-62 attended the first clinic visit, which included a history and physical examination, standardized blood pressure measurements in a sitting position, blood drawn for chemical analyses, and a 12 lead electrocardiogram.

No coronary heart disease was found present in 5127 of the original participants, and individuals have been followed since that time for the occurrence of heart and other vascular diseases. Every two years participants were invited back for a follow-up examination, which includes the core ingredients as described above, as well as other specialized tests on a less frequent basis.

The occurrence of new cardiovascular disease was based on information obtained at clinic visits and from hospital records. All pertinent information was reviewed by a panel of Framingham physicians who used published criteria to decide whether a new cardiovascular event had occurred (6). Follow-up of 30 years is complete for all major cardiovascular events at this time, and will serve as the basis of this report.

Children of the original Framingham cohort were recruited in the early 1970's to participate in a similar study of risk factors and vascular disease. A total of 5135 men and women, largely offspring, but including their spouses, participated in the first examination in 1972. The clinical methods and criteria for events are identical to the methods for the original cohort. This second generation group, the Framingham Offspring, now returns every 3-4 years for follow-up clinic visits (7,8).

RESULTS

The incidence of coronary heart disease is closely associated with age and cholesterol level. As seen in Table 1, which is based on more than 25,000 person exams over the course of 30 years of follow-up from the Framingham Study, increasing cholesterol levels across each age group are generally associated with rising rates in coronary heart disease over the course of the Framingham Study (trends for cholesterol are statistically significant for the three youngest age groups). There is a

consistent effect of age, and for the same cholesterol level, older individuals generally experience higher CHD rates.

TABLE I
ANNUAL INCIDENCE (PER 1000) OF CORONARY HEART DISEASE
FRAMINGHAM HEART STUDY 30 YEAR FOLLOW-UP
MEN

Age Group (years)	Cholesterol level (mmol/L) <5.28	5.28-6.03	6.03-6.80	6.80-7.60	>7.60
35-44	2	3	6	9	12
45-54	6	11	11	11	28
55-64	13	20	21	22	31
65-74	21	22	23	25	37
75-84	27	33	37	16	45

Based on more than 35,000 person exams, the Framingham data for cholesterol, age and coronary disease in women are similar (Table II), and statistically significant trends for the effect of cholesterol are observed for the four youngest age groups. Rates are generally lower than for men. At older ages, and for higher cholesterol levels, the rates for women approach those for men, and occasionally exceed the male rates.

TABLE II
ANNUAL INCIDENCE (PER 1000) OF CORONARY HEART DISEASE
FRAMINGHAM HEART STUDY 30 YEAR FOLLOW-UP
WOMEN

Age Group (years)	Cholesterol level (mmol/L) <5.28	5.28-6.03	6.03-6.80	6.80-7.60	>7.60
35-44	0	1	1	3	6
45-54	2	4	2	4	6
55-64	7	8	7	12	16
65-74	9	11	13	14	23
75-84	17	24	21	21	15

The number of coronary events at specified levels of cholesterol provide another perspective on the data. As seen in Table III, about half of all coronary events occur at cholesterol levels in the 5.28-6.80 mmol/L range. High cholesterol levels, above 6.80 mmol/L, are responsible for approximately 20% of coronary disease in men and about 45% in women. Conversely, at the lower range of cholesterol levels, less than 5.28 mmol/L, about 25% of the male events and 10% of the female events are observed.

TABLE III
DISTRIBUTION OF CORONARY EVENTS
BY AGE AND CHOLESTEROL LEVEL
10 YEAR FOLLOW-UP

Age Group (years)	Cholesterol level (mmol/L) <5.28	5.28-6.80	>6.80	Number of Events
Men				
35-64	16%	56%	28%	499
65-94	30%	54%	16%	243
Women				
35-64	11%	40%	49%	291
65-94	11%	49%	40%	268

Classification of individuals at risk for coronary heart disease improves with measurement of lipoprotein cholesterols. High density lipoprotein cholesterol (HDL-C) has attracted the most attention because it is readily measured. When the endpoint myocardial infarction was compared to HDL-C quartiles for men and women, strong associations were seen for each sex (Table IV). The overall CHD rate for men is twice the rate for women, and a significant excess of events was observed at the lower HDL-C quartiles when compared to the fourth quartile.

TABLE IV

AGE ADJUSTED MYOCARDIAL INCIDENCE (PER 1000) AND HDL-C LEVELS
FRAMINGHAM ADULTS 50-79 YEARS
12 YEARS FOLLOW-UP

	HDL Cholesterol level (mmol/L)				
Men					
HDL-C Level	0.3-0.9	0.9-1.1	1.1-1.3	1.3-3.3	Overall
Rate	15.3*	14.8	14.9	9.4	13.5
Women					
HDL-C Level	0.6-1.2	1.2-1.4	1.4-1.7	1.7-3.6	Overall
Rate	10.6***	7.4***	6.5**	1.4	6.5

(Key * p <0.05, ** p <0.01, *** p <0.001)

The cross tabulation of coronary events according to HDL-C and triglyceride levels in Tables V and VI show a tendency for higher rates within each triglyceride category when the HDL-C levels are low. This relationship is not statistically significant for men (Table V), but the same trend is more pronounced and is statistically significant for women (Table VI).

TABLE V

AGE ADJUSTED CORONARY HEART DISEASE INCIDENCE
ACCORDING TO TRIGLYCERIDE AND HDL-C LEVELS
(14 YEAR RATE PER 1000)
MEN

	Triglyceride level (mmol/L)		
HDL-C Level	0.36-1.03	1.03-1.55	1.55-16.33
0.31-1.00	328	281	337
1.00-1.26	276	311	226
1.26-3.32	227	240	247

TABLE VI

AGE ADJUSTED CORONARY HEART DISEASE INCIDENCE ACCORDING TO TRIGLYCERIDE AND HDL-C LEVELS (14 YEAR RATE PER 1000)

WOMEN

HDL-C Level	Triglyceride level (mmol/L) 0.30-0.92	0.92-1.37	1.37-6.87
0.59-1.26	179	178	225
1.26-1.60	142	206	222
1.60-3.58	89	82	170

The associations of cigarette smoking and hypertension with coronary risk are shown in Tables VII and VIII respectively. In the former table, as smoking increases, coronary rates rise in younger (35-64 years) and older (65-94 years) groups. Coronary risk in men increases only after more than 10 cigarettes are smoked per day, and heavy smokers at all ages experience the greatest rates for CHD. Young women who smoke more than 40 cigarettes a day have coronary rates that are comparable to their male counterparts.

TABLE VII

AGE ADJUSTED INCIDENCE (PER 1000) OF CORONARY HEART DISEASE BY NUMBER OF CIGARETTES SMOKED PER DAY
30 YEAR FOLLOW-UP

Age Group (years)	Cigarettes per day 0	1-10	11-20	21-40	>40
Men					
35-64	10	10	16	17	20
65-94	25	21	21	23	29
Women					
35-64	6	5	6	6	32
65-94	16	14	18	2	-

Hypertension, as defined by the World Health Organization criteria, using repeated systolic pressures greater than 160 mm Hg and diastolic pressures greater than 95 mm Hg as the cutoff values for definite hypertension, shows a marked association with coronary disease rates. In these Framingham data, based on the experience of 1948-1978 when hypertension therapy was less common and not undertaken as early as current practice dictates, treatment is also associated with high coronary disease rates.

TABLE VIII

AGE ADJUSTED INCIDENCE (PER 1000) OF CORONARY HEART DISEASE BY HYPERTENSION STATUS

30 YEAR FOLLOW-UP

Age Group (years)	Hypertension Status			
	No	Mild	Definite	Treated
Men				
35-64	8	15	20	27
65-94	13	26	38	38
Women				
35-64	3	7	10	10
65-94	11	13	18	24

Factors such as cholesterol level, blood pressure level, and cigarette smoking can be combined in a logistic regression model to predict the development of coronary heart disease. An example of the effect of such factors, along with diabetes mellitus and left ventricular hypertrophy, are given in Table IX. The impact of each variable is shown for men and women 35-64 years over the 30 years of experience of the Framingham Heart Study. Statistically significant associations are present for each factor, but there are different relative weights for the factor's presence. Additionally, risk factors are multiplicative in determining risk of heart disease. For instance, if two men the same age are compared, and the first has no risk

factors, while the second individual smokes 10 cigarettes a day and has a blood cholesterol which is 0.25 mmol/L higher than the first man, the CHD risk for the second man will be 1.14 x 1.22 = 1.39, or 39% greater.

TABLE IX

PERCENT OF INCREMENTS IN CORONARY HEART DISEASE RISK ASSOCIATED WITH SPECIFIC RISK FACTORS ADULTS 35-64 YEARS

Factor	Women (%)	Men (%)
Cigarette smoking (effect of 10 per day)	22	15
Diabetes mellitus (effect of presence)	55	128
LVH on electrocardiogram (effect of presence)	35	39
Systolic Blood Pressure (effect of +10 mm Hg)	15	16
Cholesterol (effect of +0.50 mmol/L)	14	12

DISCUSSION

Coronary heart disease mortality has declined over the past two decades, but it is still responsible for more than half of the deaths of middle aged men and women in Europe and North America (11). While heart disease is uncommon prior to age 35, the rates increase dramatically in men after that age. The CHD rates are particularly associated with cholesterol level (Tables I and II). As a general rule, for every 1% increase in cholesterol level, there is a corresponding 2% increase in CHD rate over a six year follow-up (12).

While attention is often directed particularly at high cholesterol levels, the majority of heart disease victims in the MRFIT screenee follow-up, the Pooling Project, and Framingham have cholesterol levels that are not excessive, and lie in the approximately 5.2-6.5 mmol/L range, as demonstrated in the center columns of Table III (12,13).

Cholesterol measurements are important to determine heart disease risk, but recent data on the role of lipoprotein cholesterol and triglyceride improve the prediction of CHD. For instance, there is a gradient for CHD and HDL-C level: higher levels are associated with protection from CHD and myocardial infarction in men and women (Table IV) (14).

Triglyceride appears to be a risk factor for heart disease in most prospective studies of heart disease. When triglyceride and HDL-C levels are both available, a slightly different situation holds. In the latter instance, often triglyceride is no longer significant as a CHD risk factor, and HDL-C is seen to associated with the coronary outcome. Such is the case for Framingham men (Table V), but not for Framingham women (Table VI), where an independent association with CHD is seen for both triglyceride and HDL-C (15). There is much research interest in the triglyceride and HDL-C effects, and subgroups, such as individuals with high triglyceride, low HDL-C, hyperglycemia, and hyperuricemia may be at quite high risk for CHD (2).

Coronary risk for smoking appears not to apply to pipe and cigar smoking, but increases after more than 10 cigarettes a day are smoked (Table VII)(16). Although filter cigarettes are associated with lower rates of lung cancer than non-filter varieties, each type of cigarette has a similar effect to increase CHD rates (17).

Definite hypertension is a particularly strong risk factor for CHD in the 30 year follow-up data from the Framingham Study (Table VIII). Other analyses show that both systolic and diastolic pressure measurements are associated with CHD. Physicians tend to concentrate on the role of diastolic blood pressure, but systolic blood pressure levels are more highly correlated with CHD (18).

The impact of risk factors is guaged with a multivariate analysis (19). The relative importance of each factor can be assessed and tentative conclusions can be drawn as to the impact of change to a specific variable or group of variables. Such an example is shown in the results section where two men

are compared and the second has slightly higher cholesterol levels and blood pressure. The adverse effect of the two risk factor differences is multiplicative and increases the second individual's risk markedly for heart disease.

Several new risk factors are on the horizon for coronary heart disease. Examples include lipoprotein choleserol subfractions of HDL and LDL (20,21). The protein moieties of lipid particles, the apolipoproteins, are also being studied. Is it the apolipoprotein or the cholesterol associated with a particle that is key to determining coronary risk? Case control studies (22,23) have investigated this question for apolipoproteins AI and B, but prospective data from a large cohort are not available yet.

Factors other than lipids also hold promise as coronary risk factors. Framingham data on fibrinogen suggest that higher levels are a risk factor for cardiovascular disease over and above the standard factors (24).

The role of prospective studies in cardiovascualr epidemiology is now changing. Investigation has moved into the realm of subclinical disease. Whereas clinical events such as myocardial infarction and angina pectoris were the cornerstones of prospective studies in the past, techniques such as arrhythmia recording, echocardiography, and scanning doppler for plaque formation in major vessels are being used more and more. With better understanding of atherosclerotic events, we will be able to intervene earlier, more selectively, and improve care of the coronary disease.

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