A competing risk analysis of factors related to long-term incidence of CHD[1]

by

Gilbert MacKenzie[2], Mary Greig[3], Iris Hay and John Pemberton[3]

from

The Department of Community Medicine[4],

The Queen's University of Belfast

[1]This paper was drafted by the first author in September 1986, ten years after John Pemberton had retired from the department which he had led from his appointment in 1958.

[2] Corresponding author. Address: The Chalet, 85, Maryville Park, Belfast BT9 6LQ, Northern Ireland. Email: gilbert.mackenzie@ul.ie

[3] Deceased.

4 Formerly called the Department of Social and Preventive Medicine, The Queen's University of Belfast, Northern Ireland, UK.

.**Abstract**

Background

The 5-year follow-up results for the 1202 middle-aged men prospective study of CHD incidence were published in 1980. This paper extends the follow-up, relating the development of CHD to ten risk factors.

Methods

The population studied comprised all men born in aged 45-64 years at baseline who were registered in six group practices in Belfast. Some 1202 CHD-free men entered the study. Study endpoints included: (a) the development of CHD, (b) of myocardial infarction, (c) of angina pectoris (d) death from myocardial (d) death from other causes. The men were followed for an average of 6.9 years and the influence of ten risk factors was assessed by Cox's proportional hazards model in a competing risk framework.

Results

The analysis first major CHD event identified 4 risk factors – diastolic blood pressure, serum cholesterol, T wave abnormality and tobacco index. First myocardial depended on diastolic blood pressure, ST abnormality and tobacco index, while time to first angina pectoris depended on serum cholesterol, T abnormality, tobacco index and age at entry. These findings do not support the hypothesis of a common risk factor profile in the myocardial infarction and angina pectoris groups. The sensitivity of all models was poor.

Discussion

The study confirms the role of known risk factors in the development of first CHD event. It also suggests that the risk factors involved in developing myocardial infarction and angina pectoris differ. The poor sensitivity of models suggests the presence of unmeasured risk factors in the aetiology of CHD.

.**Keywords:** Competing Risks**,** Coronary Heart Disease, Prospective Study, Risk Factors

What is already known about this subject?

A great deal of evidence has been adduced by various prospective studies conducted in North America and in Northern Europe. However, there have been comparatively few UK-based studies. Classically, these studies have implicated elevated serum cholesterol, hypertension, smoking and lack of exercise as being among the most important determinants of increased risk of CHD.

What does this study add?

It employs modern statistical survival methods to analyse, in a competing risks framework, the variable time incidence data accrued in Belfast, UK. Overall, the results are largely consonant with the findings from the mainstream international studies. A novel finding is evidence suggesting that the development of myocardial infarction and angina pectoris depend of different sets of risk factors. The total amount of tobacco smoked is, however, a risk factor in common. The paper is also interesting from a historical perspective, as it is a 'lost' paper from, John Pemberton, one of the founders of our Society. Accordingly, it is truly a *prospective study in the past*.

Introduction

Greig et al (1980)[1] reported the results of a prospective study of CHD conducted among 1202 middle-aged men registered in six group practices in Belfast, Northern Ireland, who were followed for five years. This report extends that original work to include the analysis of events which occurred in subsequent years of follow-up using time to event methods. Although the prospective study is now formally closed, 85% have been followed for more than 5.5 years and 39% for more than 7.5 years. As in the earlier study the aim is to identify social and biological characteristics of middle-aged men which are predictive of the development of CHD.

2. Methods

These have been described elsewhere.[1] Briefly, the population studied comprised all men born in the 10 year period 1909-1918 (that is, those aged 45-64 years at the beginning of the study) who were registered in six group practices in Belfast, Northern Ireland. For the prospective study, men were free from angina of effort and free from a confirmed MI at the baseline examination. Some 1202 men entered and were followed up. Study endpoints included: (a) the development of myocardial infarction (MI), (b) the development of angina pectoris (AP), (c) death from MI and (d) death from other causes.

MI was diagnosed when the subject had typical a history of chest pain and at least one of: serial changes in a follow-up ECG, indicative of MI (usually Minnesota[2] codes 1-3), or elevated serum enzymes. All diagnoses were made by consultant physicians. Angina of effort was diagnosed according to the criteria devised by Rose,[3] as provided for in the study follow-up procedures. Details of

the causes of death were obtained from the Registrar General of Northern Ireland[4].

Associated with each of the events was a corresponding ‘time to event’. For individuals who developed two or more events, the time to each event was recorded. The protocol permitted recurrent episodes of some types of non-fatal CHD events to be recorded.

The follow-up was by annual questionnaires, supplemented by GP visits (by Dr. Greig) and referrals to outpatient Departments where the diagnosis of angina pectoris or cardiac ischaemia was made by a consultant physician.[1] Information on Deaths was obtained from the Northern Ireland Registrar General[4].

Ten risk factors were studied. They were: diastolic blood pressure (mm Hg), height (cm), serum cholesterol (mg/100 ml), lipo-protein ratio (dimensionless), skinfold thickness (mm), Q/QS abnormality (present/absent), T wave abnormality (present/absent), ST abnormality (present/absent), tobacco index (lifetime grams/365) and age at entry. These data were complete.

The standard method of analysing prospective incidence data is based on the multiple logistic function[5]. Here, the data, being variable time incidence, were analysed within the competing risks framework using Cox’s PH model [6,7] . In this approach time is measured from baseline to the development of a CHD-related event or death. More general methods[8,9] have been developed to deal with the analysis of multiple episodes, but the incidence of these events was too low to warrant their application.

Four separate analyses were undertaken:

1. Time to first major CHD event, defined as the first of any of the events a) to c) above.
2. Time to first MI defined as the first of either of the events a) *or* c) ,
3. Time to first AP defined as the first occurrence of event b) above.
4. A competing risks analysis involving three mutually exclusive endpoints: first MI alone, first AP alone, and both conditions together. For individuals who developed both, time to the first event was used.

In all four analyses, individuals who died from other causes were treated as censored at their time of death.

3. Results

Of the 1202 men followed for an average of 6.9 years, 1047 (87.1%) were disease-free and 155 (12.9%) developed CHD. Among the developers, 52 (4.3%) developed MI alone, 62 (5.2%) developed AP alone and 41 (3.4%) developed both conditions. Among men who developed myocardial infarction, 43 (3.6%) died.

The annual incidence rate for first major CHD event rose from a minimum 0.84% in the first year of follow-up to a maximum of 3.67% in the last 10^{th} year. The low incidence in the first years suggests that the baseline examination was successful in excluding subjects with overt disease. There was a gradual increase in the incidence rate over time. These rates are high in comparison with other published studies[10].

The relationship between the incidence of the first major event and the ten factors was investigated using the PH regression model. As a first step the global null hypothesis (β=0) was tested and rejected (χ^2 =47.92, df=10, p<0.001) . Table 1 details the maximum partial likelihood estimates of the parameters in the PH model for: no adjustment, age-adjustment, and full adjustment (10 factors). The single factor analysis identified six factors which were individually positively associated with developing a major CHD event. Adjustment for age left these findings unaltered. However, simultaneous adjustment (final column) identified a subset of only four factors: diastolic blood pressure (DBP), serum cholesterol (SC), T abnormality and tobacco index (TI). The independent effects of these four factors were confirmed using a backwards elimination algorithm (Table 1). The magnitude of the effects of SC and TI were similar in the various analyses.

In relation to first MI the global null hypothesis was again tested and rejected (χ^2 =20.77, df=10, p<0.05). However, the pattern of contribution from the 10 factors studied singly differed from that observed in the previous analysis. In particular, the factors T abnormality and SC were not included in the model. Adjustment for age made no difference and details of the final 3-factor model which included: DBP, ST abnormality and TI are presented in Table 2.

Similar analyses were repeated for the time to first AP (χ^2 =37.16, df=10, p<0.001). The final (Table 3) contained SC, T abnormality, TI and age at entry. The absence of DBP and the entry of age at baseline examination should be noted (Table 2)..

Table 1: Single and Multifactor analyses of factors influencing time to first major CHD-related event: MPL estimates and their standard errors (se) from the proportional hazard models.

Factor	Adjustment					
	None		Age		All	
	Estimate	se	Estimate	se	Estimate	se
Diastolic Blood Pressure	+0.194*	(0.062)	+0.195*	(0.062)	+0.133*	(0.065)
Height	-0.076	(0.058)	-0.076	(0.060)	-0.075	(0.064)
Cholesterol	+0.068*	(0.026)	+0.073*	(0.026)	+0.064*	(0.027)
Lipoprotein ratio	-0.020	(0.031)	-0.018	(0.031)	+0.003	(0.033)
Skinfold thickness	+0.025	(0.014)	+0.025	(0.014)	+0.016	(0.014)
Q/QS abnormality	+0.516	(0.264)	+0.542*	(0.265)	+0.162	(0.278)
T abnormality	+0.947*	(0.222)	+0.941*	(0.222)	+0.700*	(0.239)
ST abnormality	+0.798*	(0.281)	+0.789*	(0.281)	+0.449	(0.298)
Tobacco index	+0.049*	(0.018)	+0.047*	(0.019)	+0.052*	(0.018)
Age	+0.029	(0.024)	-	-	+0.026	(0.025)
NB: (a) * Exceeds 2 standard errors (b) continuous variables were re-scaled (z transformation).						

Table 2: Final models for CHD-related events and their sub-components: first major event, myocardial infarction and angina pectoris: MPL estimates and their standard errors.

Factor	Estimate	se	*t*
First Major Event			
Diastolic BP	+0.163	(0.061)	+2.7
Cholesterol	+0.065	(0.026)	+2.6
T abnormality	+0.824	(0.223)	+3.7
Tobacco index	+0.052	(0.013)	+2.8
First Myocardial Infarction			
Diastolic BP	+0.185	(0.082)	+2.3
ST abnormality	+0.772	(0.354)	+2.2
Tobacco index	+0.058	(0.024)	+2.4
First Angina Pectoris			
Cholesterol	+0.093	(0.032)	+2.9
T abnormality	+0.936	(0.266)	+3.5
Tobacco index	+0.044	(0.022)	+2.0
Age	+0.064	(0.030)	+2.2
NB: From the proportional hazards models.			

Table 3: Competing risks analysis: myocardial infarction alone, angina pectoris alone and both conditions: MPL estimates and standard errors.

Factor	Estimate	se	*t*
Myocardial Infarction Alone			
Diastolic BP	+0.249	(0.012)	+2.44
Angina Pectoris Alone			
Cholesterol	+0.096	(0.040)	+2.40
T abnormality	+1.074	(0.321)	+3.35
Age	+0.079	(0.037)	+2.11
Both MI and AP			
Tobacco index	+0.067	(0.035)	1.91

Finally a competing risks analysis was conducted. Table 3 shows the best fitting models in each of the three mutually exclusive groups analysed. In the MI alone group only DBP was formally statistically significant in multi-factor testing. The pattern in AP alone was more clear-cut with three factors identified: SC, T-abnormality and age at entry, significantly and positively related to outcome. In the subgroup of individuals who developed both conditions, TI was only factor to approach statistical significance. Although the numbers involved were small, these findings tend not to support the hypothesis that a common set of risk factors underpin the development of these two conditions.

The maximal estimated conditional probability of development of a major CHD event was 0.35 for men who were at highest risk. They had above average SC. a high DBP (100 mm Hg), smoked a lot (1000+) and had a T abnormality in their baseline ECG. By contrast men in the cell with minimum risk had an estimated conditional probability of developing of 0.03. Thus, the relative risk of development was approximately 11 showing that the risk factors graduated the relative risk well. However, regarding strength of association[11], a probability of 0.35 is not high. Thus, a man in the cell with the maximum risk has more chance of not developing CHD over the five-year period (1.00 - 0.35 = 0.65) and we conclude that the PH model is not a good predictor of individual risk. The distributions of estimated risk in the developed (a major CHD event) and non-developed groups were almost completely overlapping on the x-axis (Figure 1).

The consistency of the Belfast findings was examined by comparing them with the results of the Pooling Project,[10] in North America. Table 4 shows the numbers of observed and expected first major CHD events by quintile of expected risk based on the 4-factor multiple logistic function in Belfast and the multiple function

used in the Pooling Project. In Belfast the uppermost quintile of expected risk contained only 36% of the observed CHD events - exactly the same proportion as in the Pooling Project. Accordingly, overall, the results were not dissimilar.

4 Discussion

We have adopted new approach to the analysis of CHD incidence data. We have focussed on identifying risk factors associated with (first major) CHD event incidence in a prospective framework and on investigating whether the incidence of myocardial infarction and angina pectoris depends on the same set of risk factors. It was the proportional hazards regression survival model enabled the additional, variable time, follow-up information to be analysed. The use of the competing risks framework facilitated the investigation. These flexible methods will no doubt see future service in the analysis of longitudinal epidemiological data. Study Methods

Designed in 1963, the present study related measurements made at a single examination to the subsequent incidence of CHD among men who satisfied the common entry criteria for the prospective study. Accordingly, subsequent risk factor modifications, resulting from changes in life-style or from medication, were not evaluated. Diagnostic criteria for the surveillance of CHD-related events were modelled largely, but not exclusively, on contemporary American studies such as those conducted in Albany,[12] Los Angeles[13] and Framingham[14] thus permitting broad comparisons with many published series, especially in relation to myocardial infarction (c) Findings

Like many previous studies employing similar methods this study has shown that the risk of developing CHD was significantly related to a number of factors: SC,

DBP, T abnormality and TI. These results are broadly to similar to those presented in the final report of the Pooling Project which, however, excluded men who had definite ECG evidence of myocardial infarction, irrespective of history.

The analysis of component subgroups for first major event seemed mandatory since these sub-groups may contain valuable aetiological clues about the underlying disease process. Although the numbers involved are relatively small, any orthodox interpretation of the findings suggests that the incidences of first MI and first AP depended on different sets of risk factors. A common factor was TI, a finding also suggested by the competing risks analysis.

Overall, these results tend to support modern theories of pathogensis.[15] In the case of AP, the process appears consistent with chronic atherogenesis associated with elevated SC and increased tobacco consumption among older men who presented with evidence of ischaemia at initial examination. By contrast, for men in the myocardial infarction group the findings are consistent with a more acute process based, perhaps, on repeated haemodynamic stress resulting in increased thrombolytic activity.

Prospective studies of coronary events are limited in the information they supply and are seldom uniform with regard to methods employed. The relatively weak associations found here suggest that there are other, as yet unidentified, risk factors in play. The competing risks approach, found useful in this study, is relatively novel and so more detailed comparisons with other work are difficult [16].

Table 4: Comparison of numbers of first major CHD events by quintile of estimated risk in the 1202 men study in Belfast and in the Pooling Project.

Quintile of Estimated risk	Belfast		Pooling Project	
	Obs	Exp	Obs	Exp
I	5	10.5	21	21.2
II	15	14.8	27	29.8
III	15	17.1	39	38.1
IV	32	23.4	52	49.2
V	37	37.7	75	76.1
V/(I+II)	1.9	1.5	1.6	1.5
% in V	36	36	36	35
NB: I =lowest risk,…,V=highest risk				

5. Conclusions

Three decades of epidemiological research have identified associations between a number of risk factors and CHD. While these associations appear to satisfy many of Bradford Hill's criteria for causality[11] and can be regarded as having *aetiological significance,* they are nevertheless weak. The most succinct summary in shown in Figure 1 – important risk factors would have produced more separation. Perhaps such figures should be included routinely in the results sections of prospective studies as they quantify, forcefully, the magnitude of the identification task outstanding.

The Belfast study suggests that different sets of risk factors underpin the development of MI and AP. Another novel finding is the identification of a ST-abnormality in the baseline ECG for MI. However, the study confirms the poor sensitivity and specificity encountered in other studies[10]. The implications for prediction for screening strategies have been discussed thoroughly elsewhere. [17-19]

Accordingly, either the final pathway by which existing risk factors co-operate to produce the disease is poorly understood (or poorly measured in this study) or there are other risk factors which remain to be discovered. This accounts, at least in part, for over-optimism about the usefulness of recent population-based multi-factor primary intervention studies.[20-22]

Acknowledgements

The authors wish to thank the participating GPs in Belfast without whose sterling co-operation, over many years, the project could not have been completed. We also thank Mr. J. Clint, The Department of Community Medicine, QUB, who assisted with the acquisition of the CHD literature. The paper is taken from the first author's PhD thesis entitled Regression Models and Medical Random counts, The Queen's University of Belfast..

The Nuffield Provincial Hospitals Trust, the Northern Ireland Hospitals Authority and the British Heart Foundation supported this study with generous grants over a number of years.

Licence for Publication

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd to permit this article (if accepted) to be published in JECH and any other BMJPGL products and sublicences such use and exploit all subsidiary rights, as set out in our licence (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

Competing Interests

None

REFERENCES

1. Greig M, Pemberton J, Hay I and MacKenzie G. A prospective study of the development of coronary disease in a group of 1202 middle-aged men. J. Epidemiol Community Health 1980; 34,1: 23-30
2. Rose G and Blackburn H. Cardiovascular Survey Methods. Geneva. WHO. 1968.
3. Rose G. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. Bull WHO 1962; 27:645-658
4. Registrar General NI, Chichester Street, Belfast.
5. Cox DR. The analysis of binary data. London: Methuen, 1970: 87.
6. Cox DR. Regression models and life tables (with discussion). J. R. Statist Soc 1972; B, 34:187-220.
7. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley, 1980.
8. Kay R. The analysis of transition time in multistate stochastic processes using proportional hazard regression models. Comm Statist 1982;11(15): 1743-1756.
9. MacKenzie G. A proportional hazard model for accident data. JRSS A (General) 1986; 149 (4): 366-375.
10. Pooling Project Research Group. Final report of the pooling project. J. Chronic Dis 1978; 31: 201-306.
11. Hill AB. Environment and disease: association or causation? Proc Roy Soc Med.1965; 58: 295-300.

12. Doyle JT, Heslin AS, Hilleboe HE, Formel PF and Korns RF. A prospective study of degenerative cardiovascular disease in Albany. I Ishaemic Heart Disease Am J Public Health 1957; 47, 4, 25-37.
13. Chapman JM, Goerke LS, Dixon W, Loveland DB and Phillips E. The clinical status of a population group under observation for two to three years. Am J Public Health 1957; 47, 4, 38-72.
14. Dawber TR, Moore FE and Mann EV. Coronary heart disease in the Framingham study. Am J Public Health 1957; 47: 4-24
15. Mitchell JRA. Prostaglandins in vascular disease: a seminal approach. Br Med J; 1982; 282: 590-594
16. Dyer AR. An analysis of the relationship of systolic blood pressure, serum cholesterol and smoking to 14 year mortality in the in the Chicago Peoples' Gas Company Study I and II. J Chronic Dis 1975; 28: 565-578.
17. Oliver MF. Should we not forget all about mass control of coronary risk factors. Lancet 1983; July 2nd : 37-38.
18. Oliver MF. Strategies for preventing and screening coronary heart disease. Br.Heart J 1985; 54: 1-5.
19. Lewis B, Mann JI and Mancini M. Reducing the risks of coronary heart disease in individuals and in the population. Lancet 1986; April 25th: 956-959.
20. Multiple Risk Factor Intervention Trial Research Group .Multiple Risk Factor intervention trial: risk factor changes and mortality. JAMA 1982; 248: 1465-1478.
21. World Health Organisation. European collaborative group. Multifactorial trial in the prevention of coronary heart disease 3. Incidence and mortality results. Eur Heart J 1983; 4: 141-147.

22. Hjermann I, Holme I, Byre KV, Leren P. Effect of diet and smoking intervention on the incidence of coronary heart disease. Lancet 1981; ii: 1303-1310.