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Clinical Investigations

"Nonspecific" Chest Pain Associated with High Long-Term Mortality: Results from the Primary Prevention Study in Göteborg, Sweden

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Summary

Background: The syndrome angina pectoris with effort-related chest pain or discomfort is usually easy to recognize. However, vague and nonspecific symptoms may cause little reason for extensive evaluation. The prognosis of such patients in the general population has so far not been well described.

Hypothesis: The study was undertaken to investigate long-term prognosis in men with chest pain considered to be nonspecific in comparison with men with typical angina pectoris (AP) or prior myocardial infarction (MI), and men without chest pain.

Methods: At the second screening of the Göteborg Primary Prevention Study in 1974–1977, 6,488 men aged 51 to 59 years at baseline were available for the present analysis. Men who had responded positively to a postal questionnaire about chest pain during exercise or at rest were interviewed by a physician according to a Rose questionnaire at the screening examination. Those with typical or probable AP were further examined by a single experienced physician. The following four groups were formed: Group 1: men who did not complain of chest pain (n = 5,545). Group 2: men who had not consulted any doctor because of chest pain, but who had chest pain according to a questionnaire (n = 441); these men were not considered to have AP according to a three-step examination by experienced physicians. Group 3: typical AP (n = 232). Group 4: men who had suffered an MI (n = 134).

Results: During 16 years of follow-up, coronary heart disease (CHD) mortality for Groups 1–4 was 8.0, 19.5, 24.8, and 48.5%, respectively. Mortality from all cardiovascular diseases was 11.5, 24.5, 31.2, and 59.0%, respectively. Noncardiovascular disease mortality was 14.1, 17.7, 14.3, and 8.7%, respectively. Thus, the relative risk (RR) for CHD mortality among men with nonspecific chest pain (Group 2) was 2.77 [95% confidence interval (CI) 2.20, 3.50], for all cardiovascular disease mortality 2.46 (95% CI 2.00, 3.02), and for noncardiovascular disease mortality 1.60 (95% CI 1.28, 2.00). Total mortality in this group was as high (44%) as among those with typical AP (45%), but the highest mortality was found among men with a previous MI (68%). In men without chest pain it was 26%. Patients of Groups 2–4 had higher levels of cardiovascular risk factors than those in Group 1. Neither any specific questions in the Rose questionnaire, nor electrocardiographic changes at rest (uncommon) were of prognostic significance. Serum cholesterol, systolic blood pressure, diabetes, and smoking were significant predictors of outcome, both with respect to fatal CHD and to total mortality during the 16-year follow-up.

Conclusion: We found a high cardiovascular as well as noncardiovascular mortality among patients with chest pain who had not been considered to have AP at a three-step examination procedure. It is important to be suspicious of early CHD symptoms in men (and women?) with "nonspecific" chest symptoms and to analyze their cardiovascular risk factor pattern further because they are at considerably higher risk for future events than those in whom CHD is not suspected.

Key words: chest pain, angina pectoris, myocardial infarction, coronary disease, serum cholesterol, blood pressure, diabetes, smoking, population study

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Introduction

The syndrome angina pectoris (AP) with effort-related chest pain or discomfort often associated with dyspnea usually is easy to recognize from a typical history. In a study of a random population sample of 7,495 men aged 47 to 53 years, we found a prevalence of typical AP of 4.3%. However, an-

other 5.7% reported chest pain in a questionnaire, but the symptoms were not considered typical of AP at check-up.[1] A large autopsy series found that patients with atypical AP and typical AP had a prevalence of coronary artery disease of 58.9 and 92.0%, respectively.[2] More recent studies have shown by continuous electrocardiographic (ECG) Holter monitoring that ischemia during daily life is common in chronic stable angina and may also be seen in patients without typical anginal symptoms. In a series of patients below the age of 65 years, who had suffered a definite myocardial infarction (MI) (1,306 men and 557 women), we found that before the infarction many had experienced nonspecific chest symptoms, which had aroused no clinical suspicion of typical AP.[3,4] Based on these experiences, we have become more careful not to exclude coronary artery disease in patients with chest discomfort. The discomfort is often explained as breathlessness (dyspnea),[5] and we have found that dyspnea without other symptoms is associated with an adverse prognosis compared with persons without dyspnea.[6]

In previous studies it has been found that patients in whom acute MI could not be confirmed prognosis was worse than in the general population of the same age.[7–12] Furthermore, risk factors for mortality during up to 10 years of follow-up were previous MI or definite AP, as well as history of smoking, diabetes mellitus, and history of hypertension. Thus, these studies involved many patients with a previous definite history of coronary artery disease. We have analyzed the fate of a random population sample of men, who had not consulted any physician for chest pain, but responded positively to some questions on chest pain in a questionnaire. To our knowledge, this is the first time that the long-term prognosis of patients with chest pain not considered to be AP has been presented.

The aim of the present study was to compare 16-year prognosis in a random sample of middle-aged men without chest pain, men with chest pain not considered to be AP, men with clinically typical AP, and men with a previous MI at a screening examination. Possible predictors for prognosis in the medical history as well as the importance of major coronary heart disease (CHD) risk factors were also analyzed.

Subjects and Methods

The Multifactor Primary Prevention study started in Göteborg in 1970 and was originally an intervention trial with interventions against smoking, hypercholesterolemia, and hypertension at predefined levels in an intervention group comprising 10,000 men, a random third of all men in the city who were born between 1915 and 1925, except those born in 1923. There were two control groups of 10,000 men each. A first screening examination took place between 1970 and 1973 and a second between 1974 and 1977. After 11.8 years of follow-up, serum cholesterol, smoking, and blood pressure had decreased in all three groups, but no significant differences in the pattern of risk factors or in outcome were detected within the intervention and control groups.[13] Any changes brought about by the intervention took place among the general population as well, and the present study group is considered to be representative of the background population in the city.

The present study deals only with men in the intervention group born between 1917 and 1925, for whom assessment of type of chest pain according to a three-step procedure was available. The second examination between 1974 and 1977 was used as the baseline examination. A postal questionnaire included questions on diseases in the family, physical activity, smoking habits, diabetes mellitus, and previous MI and diabetes mellitus. Simple questions on chest pain brought about by walking uphill or climbing stairs and whether these symptoms were relieved by rest, and questions regarding dyspnea were also included.

Smoking habits were coded as 1 = never smoked, 2 = former smokers of more than 1 month's duration, 3 = smoking 1–14 g of tobacco per day, 4 = smoking 15 g or more per day. One cigarette was considered to contain 1 g of tobacco, a cigarillo 2 g, and a cigar 5 g of tobacco.

Screening examinations were performed in the afternoon. Blood pressure was measured after 5 min rest to the nearest 2 mmHg with the subject seated. Body mass index was calculated as weight/height^2. Serum cholesterol concentration (from a sample taken after fasting for at least 2 h) was determined according to standard laboratory procedures.

A 12-lead ECG was registered in each individual and coded according to the Minnesota Code[14] by two observers who were blinded to the previous history or outcome of the men.

All men who, according to the postal questionnaire, had chest pain brought on by exercise were interviewed by a physician at the screening examination according to a more detailed questionnaire (17 questions).[1, 14] Men who were judged to have definite or suspected AP were invited to another examination by a single senior, well-trained physician (MH). This examination comprised another interview according to the detailed questionnaire and a clinical examination including another 12-lead ECG. In doubtful cases in which a decision could not be made solely on clinical grounds, an exercise test was also performed.

Altogether, data were available for 5,773 men. Group 1 consisted of 4,905 men who denied chest pain and prior MI. Group 2 included 441 men who responded positively to the questionnaire on chest pain walking uphill or while walking on level ground. These men had not consulted any physician because of chest pain or discomfort, and after careful consideration by at least two experienced physicians they were not considered to have AP (nonspecific chest pain). Because of the very low suspicion of CHD in these cases, no further investigations such as coronary angiography were considered. Group 3 comprised 266 men whose symptoms were considered to be AP, but none had had an MI prior to the examina-tion (= uncomplicated AP). In addition, there were 161 men who had suffered an MI prior to the screening examination (Group 4), and this diagnosis was checked against hospital files.

Since 1970, all cases of nonfatal MI in Göteborg have been recorded according to specific predefined criteria.[15] These criteria include admission to hospital with a clinical di-

agnosis of MI and fulfillment of at least two of the following criteria: (1) central chest pain, shock, syncope, or pulmonary edema suggesting an MI; (2) typical enzyme changes; (3) development of ECG changes with either development of Q waves or serial ST-T changes.

For men with a history of MI either before 1970, or who had been treated elsewhere than in Göteborg, hospital records were scrutinized after the examination. Myocardial infarction was verified in cases meeting the same criteria as the register.

Follow-Up Procedure

All subjects in this study were followed up until December 31, 1993 (mean 16 years). The Swedish National Register on Deaths due to specific causes was matched against a computer file of the men in the study. In 1987, there was a change from the 8th to the 9th revision of the International Classification of Diseases, but for the broad groupings used in the present study this will have made no difference. The following fatal end points were analyzed:

(A) Coronary heart disease = ICD 9 codes 410–414.
(B) Cardiovascular disease = A + stroke (= ICD 9 codes 430–438) as well as other vascular disease and cardiac failure = ICD codes 427, 428, and 440–442.
(C) Noncardiovascular causes of death = all other ICD codes.

Statistical Methods

We used the SAS statistical package (version 6.11). Numbers, percentages, and relative risks (RR) with their 95% confidence limits (95% CI) are presented in the tables. Cox regression analysis was used to analyze the independent effect of any variable on outcome. Survival curves were constructed according to the Kaplan-Meyer method.

Results

Table I shows mortality for the four previously defined groups. The risk is set to 1 for men with no chest pain. It is seen that mortality from CHD as well as total cardiovascular disease was significantly increased for the groups with nonspecific chest pain, typical AP, and was highest among those with previous MI. Patients with nonspecific chest pain also had a significantly increased noncardiovascular disease mortality, whereas patients with typical AP and a previous MI did not. In fact, patients with nonspecific chest pain had mortality from CHD, all cardiovascular diseases, as well as total mortality as high as in those with typical AP.

The percentage cardiovascular disease mortality out of total mortality in the group with no chest pain was 45%, nonspecific chest pain 55%, typical AP 69%, and previous MI 87%, respectively.

TABLE I Number, percent of deaths, and risk ratio (RR, 95% CI) for death from coronary heart disease, cardiovascular diseases, noncardiovascular disease mortality, as well as total mortality during 16 years of follow-up among men with no chest pain (1), men with chest pain and no typical angina pectoris (2), typical angina pectoris (3), and previous myocardial infarction (4), respectively, at start of follow-up.

	Number of patients	CHD mortality	CVD mortality	Non-CVD mortality	Total mortality
1. No chest pain					
N	4,905	392	562	690	1,252
%		8.0	11.5	14.1	25.5
RR		1	1	1	1
2. Nonspecific chest pain					
N	441	86	108	87	195
%		19.5	24.5	17.7	44.2
RR		2.77	2.46	1.60	1.99
(95% CI)		(2.20, 3.50)	(2.00, 3.02)	(1.28, 2.00)	(1.71, 2.31)
3. Typical angina					
N	266	66	83	32	121
%		24.8	31.2	14.3	45.5
RR		3.57	3.16	1.18	2.07
(95% CI)		(2.75, 4.64)	(2.51, 3.98)	(0.85, 1.63)	(1.72, 2.49)
4. Previous MI					
N	161	81	95	14	109
%		48.5	59.0	8.7	67.7
RR		9.07	7.93	0.94	4.07
(95% CI)		(7.11, 11.57)	(6.38, 9.86)	(0.56, 1.60)	(3.34, 4.95)

Abbreviations: CI = confidence interval, CHD = coronary heart disease, CVD = cardiovascular diseases, AP =angina pectoris, MI = myocardial infarction, N = number of patients, RR = risk ratio.

TABLE II Prevalence and means ± SD for smoking habits, diabetes prevalence, serum total cholesterol, and systolic blood pressure for Groups 1–4 (see Table I) at start of follow-up

Group	Smoking		Diabetes		Serum-cholesterol (mmol/l)		Systolic blood pressure (mmHg)	
	N	%	N	%	Mean	SD	Mean	SD
Group 1	1,940	39.7	122	2.5	6.35	1.06	145	20
N = 4905								
Group 2	228	51.7	27	6.1	6.42	1.12	144	20
N = 441	p = 0.001		p = 0.001		NS		NS	
Group 3	127	47.7	20	7.6	6.55	1.22	149	22
N = 266	p = 0.01		p = 0.001		p = 0.01		p = 0.003	
Group 4	71	44.1	14	8.7	6.76	1.26	143	18
N = 161	NS		p = 0.001		p = 0.001		NS	

Abbreviations: SD = standard deviation, N = number of patients, NS = not significant.

Most of the noncardiovascular disease mortality was due to malignant diseases in all groups with no significant difference between those without chest pain (65% of noncardiovascular causes being cancer), those with nonspecific chest pain (60% cancer with no overrepresentation of cancer of the chest), AP (75% cancer), and previous MI (86% cancer).

Table II shows some characteristics of the four groups. Mean age was the same; smoking was more prevalent in Groups 2–4, and so was diabetes; serum total cholesterol increased from Group 1 to Group 4, and systolic blood pressure was highest in the group with typical AP.

The results mentioned above indicate a high mortality among patients who stated chest pain in the postal questionnaire, but was not considered to be AP (nonspecific chest pain). This group of men was further analyzed regarding possible indicators of a worse prognosis. First dyspnea according to responses in the postal questionnaire was tested. In univariate analysis it was found that men with dyspnea had a significantly higher risk of death from CHD; odds ratio 2.33 (95% CI 1.95, 2.78). However, this significance disappeared in multivariate analysis (see below). Then it was analyzed whether any answers to the 17 questions in the more detailed questionnaire contained any prognostic information. There were tendencies that CHD mortality was higher in men who complained about chest pain during exertion than in those who had it only at rest, in men with chest pain in cold weather, as well as localization under the middle or lower part of the sternum compared with other localizations (left part of the chest, etc.), but none of these comparisons were statistically significant.

Questionnaire data were available also from the first screening 4 years before the one used as entry for the present follow-up. Some of the men had had chest pain at both investigations but were still not considered to have typical AP at the second one. Table III shows mortality results for the group with chest pain at the second investigation according to presence or absence of chest pain also at the first screening examination. There was no significant difference between these two groups regarding any type of mortality.

The resting ECG coded according to the Minnesota code did not help in predicting prognosis in the Group 2 men, primarily because very few (6.4%) had any codable ECG changes at rest.

It is of practical importance that in the relatively large group with nonspecific chest pain, Group 2, there were 30% more deaths from CHD and 60% more total deaths than in the group with typical AP, and as many CHD deaths and 80% more total deaths than in the relatively small group with previous MI. The greatest number of deaths from all causes was recorded in the large number of men with no chest pain (Group 1).

Table IV shows results of multivariate Cox analysis among men with nonspecific chest pain. Age at entry, smoking, diabetes, serum cholesterol, and systolic blood pressure, but not dyspnea on exertion, were significant predictors for CHD mortality during 16 years of follow-up, and the same factors and, in addition, dyspnea were significant for total mortality.

TABLE III Number, percent of deaths, and relative risk[a] (RR, 95% CI) for death from coronary heart disease, cardiovascular diseases, as well as noncardiovascular disease mortality during 16 years of follow-up among men with chest pain but not typical angina pectoris at the second screening only (2A) and at both first and second screening (2B), respectively.

	N	CHD mortality	CVD mortality	Non-CVD mortality
2A. Chest pain at 2nd screening only				
N	207	42	51	29
%		20.3	24.6	14.0
RR		2.51	2.20	1.40
(95% CI)		(1.86, 3.38)	(1.69, 2.87)	(1.04, 1.88)
2B. Chest pain at 1st and 2nd screening				
N	170	36	46	38
%		21.2	27.1	22.4
RR		3.21	2.87	1.93
(95% CI)		(2.30, 4.47)	(2.14, 3.85)	(1.40, 2.66)

[a] Related to "no chest pain". See Table I.
Abbreviations as in Table I.

TABLE IV Cox regression analysis among men with nonspecific chest pain with fatal coronary heart disease and total mortality, respectively, as end points. Parameter estimates, as well as risk ratios with 95% confidence interval are given

	Dependent variable					
	Fatal CHD			Total mortality		
Independent variable	Parameter	RR	95% CI	Parameter	RR	95% CI
Age (years)	0.08	1.08	1.01, 1.15	0.06	1.06	1.02, 1.11
Diabetes, yes/no	0.89	2.44	1.73, 3.45	0.68	1.98	1.50, 2.60
Smoking, yes/no	0.36	1.43	1.13, 1.82	0.49	1.63	1.36, 1.94
Serum cholesterol, (mmol/l)	0.22	1.24	1.13, 1.37	0.10	1.11	1.03, 1.19
Systolic blood pressure (mmHg)	0.01	1.01	1.00, 1.02	0.01	1.01	1.00, 1.01
Dyspnea, yes/no	—	—	— —	0.23	1.26	1.05, 1.53

Abbreviations as in Table I.

Discussion

To our knowledge, this is the first time that the long-term prognosis of patients with chest pain not considered to be AP has been demonstrated to be nearly as poor as among those with typical AP. Our present findings also concur with a previous publication on the increasingly higher risk among men with no chest pain than among those with typical AP and among men with a previous MI in this population sample.[16] Diabetes, smoking, serum cholesterol, and elevated systolic blood pressure were predictors for CHD mortality and, in addition to these factors, dyspnea on exertion was a predictor for total mortality in the subset of patients with nonspecific chest pain. Thus, our results indicate that men with chest pain, even if it is not considered to be typical AP, are at increased risk of dying during long-term follow-up, especially if they are afflicted with the above-mentioned risk factors.

There are obviously several limitations in this study of a population sample followed for 16 years. More exact diagnostic methods for CHD by use of maximal exercise testing, myocardial imaging, or coronary angiography were not used. However, in a clinical setting these investigations would have been used in men with typical or suspected AP, but not in all of those with chest pain according to the questionnaire, and consequently in few, if any, of the Group 2 men of the present study. It should be emphasized that these men never had consulted a physician for chest pain and thus they would not spontaneously appear in a consulting room. The frequency and severity of chest pain were carefully considered during the interviews with experienced physicians at the screening examination and during follow-up, and only very few of these men would have been further examined in a purely clinical situation.

As shown in a previous report from this population sample, a history of CHD such as MI or AP increased the risk for future fatal events at each level of serum cholesterol,[17, 18] at each level of blood pressure,[18] and in the presence of a history of smoking[18] and of diabetes mellitus.[19] The present results emphasize the importance of a high level of suspicion of CHD in patients with chest pain, especially in the presence of CHD risk factors.

The practical implications of these findings are seen in Table V, which is based upon mortality from CHD during 16 years by chest pain group, smoking habits, and serum total

TABLE V Incidence of fatal coronary heart disease during 16 years of follow-up in relation to type of chest pain, smoking habits, and serum total cholesterol

	No chest pain		Nonspecific chest pain		Typical AP		Previous MI	
	Total N	CHD %	Total N	CHD %	Total N	CHD %	Total N	CHD %
Nonsmokers								
S-chol, mmol/l								
≤5.80	975	4	62	6	39	10	19	47
5.81–6.67	908	5	77	16	45	16	12	50
≥6.68	1,058	8	70	24	56	34	27	48
Smokers								
S-chol, mmol/l								
≤5.80	584	8	67	21	41	20	1	(100)
5.81–6.67	635	9	51	20	31	26	3	(33)
≥6.68	718	15	110	26	57	39	20	45

Percentages within patenthesis denote that they are based on very low numbers.
Abbreviations: S-chol = serum cholesterol. Other abbreviations as in Table I.

cholesterol tertile (third) at entry. No adjustments are made for slight differences in age, which would not materially affect the risks and no confidence limits are given because the statistical calculations are given in Table IV. It should be emphasized that the number of men in some of the cells is very low, especially for those who had suffered an MI, where mortality was about 50% for all subgroups. Secondary preventive measures regarding, for example, smoking had been given between the MI and the screening examination to several of these men. In the other groups, it is seen that mortality increases with smoking and elevation of serum cholesterol. With the exception of nonsmoking men with unspecific chest pain in the lowest cholesterol tertile, men with nonspecific chest pain or typical AP had a considerably higher risk at any level of smoking and cholesterol. With that exception, only those with cholesterol values in the highest tertile among men without chest pain had as high a risk as nonsmoking men with cholesterol in the middle tertile. This fact again emphasizes the risk associated with typical or atypical chest pain.

In the general population there are many men with nonspecific chest pain. Among them, as many or more deaths from CHD (as well as total deaths) are recorded as among those with typical AP and a previous MI. In the clinical setting it is important to be suspicious of early CHD; in particular, those with a high coronary risk factor profile should be evaluated further with regard to their coronary arteries in order that appropriate preventive action may be taken.

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