

# Exercise-Induced Silent Myocardial Ischemia and Coronary Morbidity and Mortality in Middle-Aged Men

Jari A. Laukkanen, MD,\* Sudhir Kurl, MD,\* Timo A. Lakka, MD, PhD,\* Tomi-Pekka Tuomainen, MD,\* Rainer Rauramaa, MD, PhD, MSc,† Riitta Salonen, MD, PhD,\*‡ Jaakko Eränen, MD,§ Jukka T. Salonen, MD, PhD, MScPH\*‡||

*Kuopio, Finland*

<b>OBJECTIVES</b>	We investigated the prognostic significance of exercise-induced silent myocardial ischemia in both high and low risk men with no prior coronary heart disease (CHD).
<b>BACKGROUND</b>	Silent ischemia predicts future coronary events in patients with CHD, but there is little evidence of its prognostic significance in subjects free of CHD.
<b>METHODS</b>	We investigated the association of silent ischemia, as defined by ST depression during and after maximal symptom-limited exercise test, with coronary risk in a population-based sample of men with no prior CHD followed for 10 years on average.
<b>RESULTS</b>	Silent ischemia during exercise was associated with a 5.9-fold (95% CI 2.3 to 11.8) CHD mortality in smokers, 3.8-fold (95% CI 1.9 to 7.9) in hypercholesterolemic men and 4.7-fold (95% CI 2.4 to 9.1) in hypertensive men adjusting for other risk factors. The respective relative risks (RRs) of any acute coronary event were 3.0 (95% CI 1.7 to 5.1), 1.9 (95% CI 1.2 to 3.1) and 2.2 (95% CI 1.4 to 3.5). These associations were weaker in men without these risk factors. Furthermore, silent ischemia after exercise was a stronger predictor for the risk of acute coronary events and CHD death in smokers and in hypercholesterolemic and hypertensive men than in men without risk factors.
<b>CONCLUSIONS</b>	Exercise-induced silent myocardial ischemia was a strong predictor of CHD in men with any conventional risk factor, emphasizing the importance of exercise testing to identify asymptomatic high risk men who could benefit from risk reduction and preventive measures. (J Am Coll Cardiol 2001;38:72-9) © 2001 by the American College of Cardiology

Exercise-induced myocardial ischemia is known to increase the risk of future coronary events not only in patients with coronary heart disease (CHD) (1-6) but also in individuals with no prior CHD (7). Some studies (2,4) have indicated that symptomatic ischemia is a stronger risk factor for future coronary events, whereas other studies (3,5,6) have suggested that silent ischemia has a similar prognostic value in these patients. However, there are few if any data showing that silent ischemia during and after exercise would have

the prognostic value of exercise-induced silent ischemia in high risk individuals. Therefore, we investigated the prognostic significance of silent myocardial ischemia during and after exercise with regard to the risk of acute coronary events and coronary death in a population-based sample of middle-aged men with no prior CHD. Furthermore, we explored if smoking, serum low density lipoprotein (LDL) cholesterol and systolic blood pressure (SBP) modify these associations.

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long-term prognostic significance with regard to coronary risk in persons without CHD (7). The likelihood to detect myocardial ischemia by exercise testing in asymptomatic individuals is known to rise with increasing pretest probability of CHD (7-10). Nonetheless, little is known about

## METHODS

**Subjects.** The subjects were participants in the Kuopio Ischemic Heart Disease risk factor (KIHD) study. This study was designed to investigate previously unestablished risk factors for cardiovascular disease (CVD), carotid atherosclerosis and related outcomes in a population-based sample of men from eastern Finland (11). Of the 3,433 men aged 42, 48, 54 or 60 years who resided in the town of Kuopio or its surrounding rural communities, 198 were excluded because of death, serious disease or migration. Of the remainder, 2,682 (83%) participated in the study. Baseline examinations were conducted between March 1984 and December 1989.

Men who had prevalent CHD at the baseline (n = 888) and for whom exercise stress test was not performed due to severe CVD or some other disease (n = 25) were excluded from the study. Prevalent CHD was defined as either a

From the \*Research Institute of Public Health, University of Kuopio, Kuopio; †Kuopio Research Institute of Exercise Medicine and the Departments of Clinical Physiology and Nuclear Medicine, University Hospital of Kuopio, Kuopio; ‡Departments of Public Health and General Practice, University of Kuopio, Kuopio; the §Department of Medicine, University Hospital of Kuopio, Kuopio, Finland, and the ||Inner Savo Health Centre, Suonejoki, Finland. Supported by grants from the Finnish Academy, the Ministry of Education of Finland, the Juho Vainio Foundation, the Aarne Koskelo Foundation, Helsinki, Finland.

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#### Abbreviations and Acronyms

AMI	= acute myocardial infarction
BMI	= body mass index
CHD	= coronary heart disease
CI	= confidence interval
CVD	= cardiovascular disease
ECG	= electrocardiogram
FINMONICA	= Finnish part of WHO-MONICA
HDL	= high density lipoprotein
ICD	= International Classification of Diseases
KIHD	= Kuopio Ischemic Heart Disease risk factor study
LDL	= low density lipoprotein
RR	= relative risk
SBP	= systolic blood pressure
WHO-MONICA	= World Health Organization-Monitoring of Trends and Determinants in Cardiovascular Diseases

history of myocardial infarction or angina pectoris, angina pectoris on effort based on the London School of Hygiene Cardiovascular Questionnaire (12), the use of nitroglycerin for chest pain once a week or more frequently or chest pain as a cause of stopping exercise stress test at baseline. Thus, the present study is based on 1,769 men who had complete data on electrocardiographic recordings during and after exercise.

**Exercise stress test.** A maximal symptom-limited exercise stress test was performed using an electrically braked bicycle ergometer between 8:00 AM and 12:00 AM. For 407 men (23%) examined before June 1986, the testing protocol comprised of a 3-min warm-up at 50 W followed by a step-by-step increase in the workload by 20 W/min (Tunturi EL 400 bicycle ergometer, Turku, Finland). The remaining 1,362 men (77%) were tested with a linear increase in the workload of 20 W/min (Medical Fitness Equipment 400 L bicycle ergometer, Mearn, the Netherlands). Maximal oxygen uptake was measured directly using a respiratory gas analyzer, as explained previously (13). Also, heart rate and blood pressure were registered during the exercise test.

The most common reasons for stopping the exercise test were leg fatigue (1,021 men), exhaustion (298 men), breathlessness (245 men), and pain in the leg muscles, joints, or back (77 men). The test was discontinued because of cardiorespiratory symptoms or abnormalities for 120 men. These included arrhythmias (60 men), marked changes in systolic or diastolic blood pressure (44 men), dizziness (9 men) or ischemic electrocardiographic changes (7 men). Exercise-induced ventricular conduction disorders were observed in 5 men, one of who also had silent myocardial ischemia during exercise but not during recovery.

**Exercise electrocardiography.** Electrocardiography was recorded continuously with the Kone 620 electrocardiograph (Kone, Turku, Finland). The Mason-Likar lead

system including  $V_1$ ,  $V_5$  and aVF lead connections was used (14). An electrocardiogram (ECG) was printed in 30-s intervals during exercise and at least 5 min during recovery while the subject was sitting on the bicycle. Exercise ECGs were coded manually by one cardiologist (J.E.).

Silent myocardial ischemia during exercise and after 5 min of recovery was defined as ischemia in the ECG without typical chest pain indicating CHD. The criteria for ischemia in ECG during exercise and recovery were horizontal or downsloping ST depression  $\geq 1.0$  mm at 80 ms after J point or any ST depression of  $>1.0$  mm at 80 ms after J point.

**Assessment of other risk factors.** The collection of blood specimens (15) and the measurement of serum lipids and lipoproteins (16) have been described elsewhere. Assessment of smoking, alcohol consumption and blood pressure was carried out as described previously (13,15). Body mass index (BMI) was computed as the ratio of weight in kilograms divided by the square of height in meters.

#### Collection and Classification of Follow-up Events

**Acute coronary events.** The collection of data on and the diagnostic classification of nonfatal and fatal coronary events by the end of 1992 were carried out as a part of the multinational World Health Organization-Monitoring of Trends and Determinants in Cardiovascular Diseases (WHO-MONICA) project, in which detailed information of all coronary events and strokes were collected prospectively (17). At baseline, all KIHD participants lived in the province of Kuopio, one of the monitoring areas of the Finnish part of the WHO-MONICA project (FINMONICA) (18). In the FINMONICA study, regional coronary register teams collected data on coronary events from hospitals and wards of health centers and classified the events, as explained in detail previously (18). The sources of information were interviews, hospital documents, death certificates, autopsy reports and medico-legal reports. The diagnostic classification of coronary events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings and history of CHD. Each suspected coronary event (International Classification of Disease [ICD]-9 codes 410-414 and ICD-10 codes I20-I25) was classified into: 1) a definite acute myocardial infarction (AMI); 2) a probable AMI; 3) a typical acute chest pain episode of  $>20$  min indicating CHD; 4) an ischemic cardiac arrest with successful resuscitation; 5) no acute coronary event; or 6) an unclassifiable fatal case. The FINMONICA coronary register data were annually cross-checked with the data obtained from the computerized national hospital discharge and death registers. Data on nonfatal and fatal coronary events from the beginning of 1993 to the end of 1997 were obtained by computer linkage to the national hospital discharge and death certificate registers. An internist (T.A.L.) collected and classified the coronary events using the same procedures as in the FINMONICA study (18). Definite AMIs, probable AMIs and

**Table 1.** Baseline Characteristics of the Study Population

	Men Without Silent Ischemia During Exercise (n = 1580)	Men With Silent Ischemia During Exercise (n = 189)	p Value for Statistical Significance
	Mean (SD)		
Age (yrs)	52.2 (5.3)	52.7 (5.2)	0.17
Body mass index (kg/m <sup>2</sup> )	26.8 (3.4)	26.0 (3.1)	0.002
Smokers (%)	30.2	27.1	0.36
Cigarette smoking (pack-years*)	7.99 (16.2)	5.91 (13.1)	0.05
Alcohol consumption (g/week)	76.3 (119.9)	63.9 (84.5)	0.07
Diabetes (%)	4.0	4.2	0.87
Serum LDL cholesterol (mmol/l)	3.99 (0.99)	4.15 (0.94)	0.02
Serum HDL cholesterol (mmol/l)	1.31 (0.30)	1.30 (0.27)	0.83
Systolic blood pressure (mm Hg)	133.6 (16.0)	137.3 (17.4)	0.006
Diastolic blood pressure (mm Hg)	89.1 (10.3)	88.6 (10.3)	0.6
Resting heart rate (beats/min)	62 (11)	62 (10)	0.78
Maximal heart rate (beats/min)	160 (21)	165 (17)	0.001
Maximal oxygen uptake (ml/kg/min)	31.8 (7.5)	32.1 (7.4)	0.61

\*Pack-years denotes the lifelong exposure to smoking which was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination (15).

HDL = high density lipoprotein; LDL = low density lipoprotein.

prolonged chest pain episodes were used as outcome events. All chest pain episodes lead to hospitalization. If a subject had multiple nonfatal coronary events during the follow-up, the first was considered the end point. The average follow-up time to the first coronary event was 10.2 years (range 0.7 to 13.8 years). Of all 174 coronary events, 91 were definite AMIs, 54 were probable AMIs and 29 were typical acute chest pain episodes leading to hospitalization and 8 of these typical chest pain episodes later led to AMI. **CHD deaths.** Deaths were ascertained by computer linkage to the national death registry using the patient's social security number. There were no losses to follow-up. All deaths that occurred by the end of 1997 were included. Cardiovascular disease and CHD deaths were coded using to the ninth ICD codes (390-459 and 410-414, respectively) or the tenth ICD codes (I00-I99 and I20-I25, respectively). The average follow-up time to CHD death or the end of follow-up was 10.5 years (range 0.3 to 13.8 years). In the present sample, there were 77 CVD deaths, 53 of which were due to CHD.

**Statistical analysis.** Differences in baseline variable between men with and without silent myocardial ischemia during exercise were analyzed using Student's *t* test. The associations of silent myocardial ischemia during exercise and recovery with the risk of acute coronary events and CHD death were analyzed using risk factor adjusted Cox proportional hazards models. The cumulative incidence of acute coronary events and mortality from CHD by the presence of silent myocardial ischemia was calculated using the Kaplan-Meier method. The modification of the prognostic value of silent myocardial ischemia by the major CHD risk factors was analyzed by comparing smokers and nonsmokers, men with higher ( $\geq 3.9$  mmol/l, median) and lower ( $< 3.9$  mmol/l) serum LDL cholesterol and men with higher ( $\geq 132.3$  mm Hg, median) and lower ( $< 132.3$  mm Hg) SBP. Four men who used cholesterol-

lowering drugs were excluded from the analyses comparing men with higher and lower serum LDL cholesterol levels, and 269 men who used antihypertensive drugs were excluded from the analysis comparing men with higher and lower SBP. If possible, confounding factors were entered uncategorized into the Cox models. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients for independent variables. Their confidence intervals (CI) were projected under the assumption of asymptotic normality of the estimates. All tests for statistical significance were two-sided. A *p* value of  $< 0.05$  was considered significant. All statistical analyses were performed using SPSS 9.0 for Windows (SPSS Inc., Chicago, Illinois).

## RESULTS

**Baseline characteristics.** Baseline characteristics in men with and without silent ischemia during exercise are shown in Table 1. Serum LDL cholesterol, SBP and maximal heart rate were higher and BMI was lower in men with silent myocardial ischemia during exercise. Similar differences were observed in men with and without silent ischemia after exercise except for maximal oxygen uptake ( $p = 0.01$ ) that was higher in men without silent ischemia after exercise.

**Strongest coronary risk factors.** The strongest risk factors for acute coronary events were smoking ( $p < 0.001$ ), diabetes ( $p < 0.001$ ), low maximal oxygen uptake ( $p = 0.002$ ), high serum LDL cholesterol ( $p = 0.003$ ), low serum high density lipoprotein (HDL) cholesterol ( $p = 0.004$ ) and elevated SBP ( $p = 0.01$ ). The strongest risk factors for CHD death were smoking ( $p < 0.001$ ), low maximal oxygen uptake ( $p < 0.001$ ), elevated SBP ( $p = 0.004$ ) and high BMI ( $p = 0.006$ ).

**Table 2.** Risk of Acute Coronary Events and Coronary and CVD Death According to the Presence of Silent Myocardial Ischemia in an Exercise Electrocardiogram in Men Without Prior Coronary Heart Disease

Risk Factor	Acute Coronary Events†		Coronary Death		CVD Death	
	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value
Silent myocardial ischemia during exercise*	1.71 (1.14-2.56)	0.009	3.51 (1.90-6.50)	<0.001	3.26 (1.93-5.52)	<0.001
Silent myocardial ischemia during recovery*	2.34 (1.31-4.19)	0.005	4.71 (2.09-10.6)	<0.001	3.67 (1.81-7.46)	<0.001

\*Each variable was entered separately into a Cox model with age, examination years, cigarette smoking, systolic blood pressure, alcohol consumption, body mass index, maximal oxygen uptake, diabetes and serum low density lipoprotein and high density lipoprotein cholesterol. †Included 91 definite and 54 possible acute myocardial infarction and 29 typical chest pain episodes (angina pectoris) of >20 min leading to hospitalization. CI = confidence interval; CVD = cardiovascular disease; RR = relative risk.

**Silent ischemia at baseline.** There were 189 (10.7%) men with silent ischemia during exercise and 54 (3.1%) men with silent ischemia after exercise. Silent ischemia during exercise was observed in 9.6% (n = 51) of smokers, in 12.3% (n = 110) of hypercholesterolemic men and in 12.4% (n = 107) of hypertensive men. Silent ischemia after exercise was found in 2.8% (n = 15) of smokers, in 3.3% (n = 30) of hypercholesterolemic men and in 4.0% (n = 35) of hypertensive men.

**Number of coronary events during follow-up.** Twenty-nine (15.3%) of 189 men with silent ischemia during exercise and 145 (9.2%) of 1,580 men without silent ischemia had an acute coronary event during follow-up. The respective numbers (percentages) for CHD death were 15 (7.9%) and 38 (2.4%). Thirteen (7.5%) of 54 men with silent ischemia during recovery and 161 (2.6%) of 1,715 men without silent ischemia had an acute coronary event during follow-up. The respective numbers (percentages) for CHD death were 8 (15.1%) and 46 (2.7%).

**Relative risk of coronary events in men with silent ischemia.** Men with silent ischemia during exercise had a 1.7-fold risk of acute coronary events and a 3.5-fold risk of CHD death compared with men without silent ischemia after adjusting for conventional risk factors (Table 2). Silent ischemia after exercise was associated with a 2.3-fold risk of acute coronary events and a 4.7-fold risk of CHD death (Table 2). The cumulative hazard curves for CHD death continued to diverge during the follow-up period (Fig. 1). Silent ischemia during exercise and recovery were also statistically and significantly associated with increased CVD mortality (Table 2). In addition, milder silent ischemia (defined as horizontal or downsloping ST depression 0.5 to 0.9 mm) after exercise was related to the risk of acute coronary events (relative risk [RR] = 1.8, 95% CI 1.0 to 3.0, p = 0.047) and CHD death (RR = 3.8, 95% CI 1.8 to 8.0, p < 0.004) but not during exercise.

**Interactions of silent ischemia with conventional coronary risk factors.** Silent ischemia during exercise had a stronger association with the risk of acute coronary events in smokers, hypercholesterolemic men and hypertensive men than in men without such risk factors (Fig. 2A). Silent ischemia during exercise also had a stronger association with the risk of CHD death in these risk groups (Fig. 2B). Silent ischemia after exercise had a strong association with the risk of acute coronary events (RR = 3.5, 95% CI 1.6 to 3.5 for smokers, RR = 3.3, 95% CI 1.7 to 6.5 for hypercholester-

olemic men and RR = 3.4, 95% CI 1.8 to 6.4 for hypertensive men) and CHD death (RR = 5.0, 95% CI 2.1 to 11.9 for smokers, RR = 7.6, 95% CI 3.0 to 19.5 for hypercholesterolemic men and RR = 6.7, 95% CI 2.9 to 16.0 for hypertensive men) in men with any risk factor (Fig. 2C and D). All of these associations were statistically nonsignificant in men without any conventional risk factors, except for nonsmokers with silent ischemia after exercise who also had an increased risk of CHD death (RR = 2.7, 95% CI 1.1 to 6.3, p = 0.02).

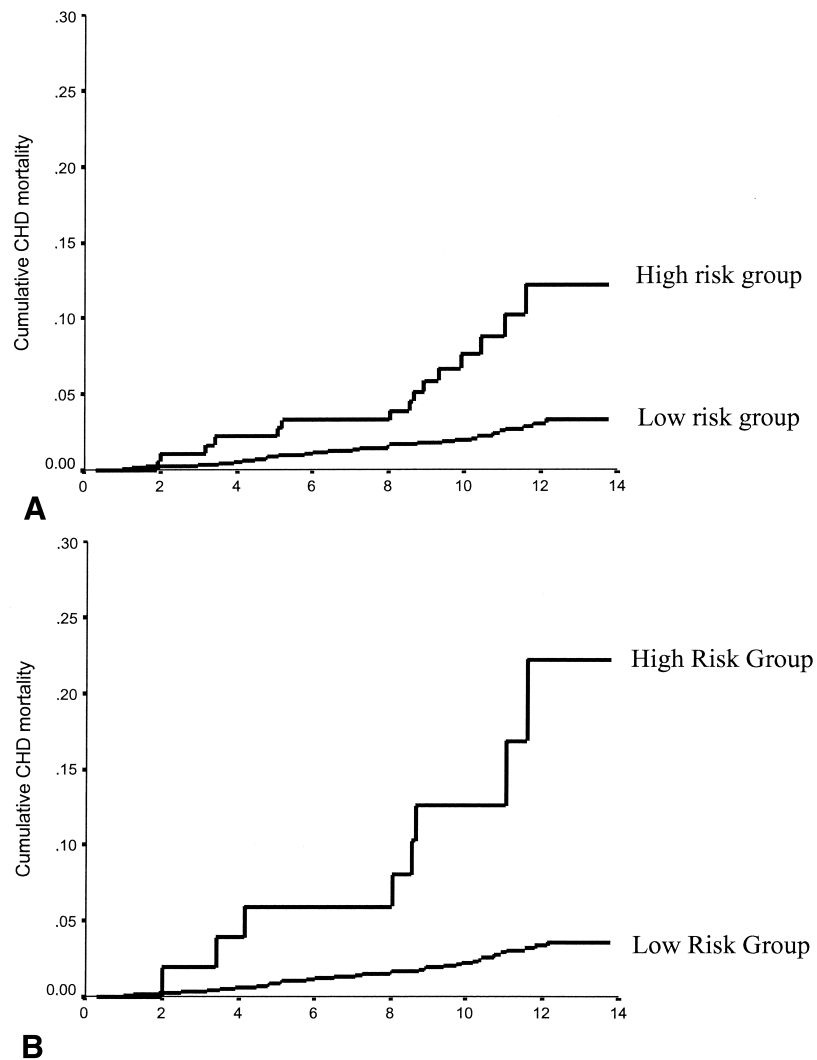
## DISCUSSION

**Principal findings.** The present prospective study demonstrates that silent myocardial ischemia during exercise and recovery, as indicated by ST depression in an ECG, predicts acute coronary events and CHD death in middle-aged men with no prior CHD. Our study emphasizes the independent prognostic value of exercise-induced silent myocardial ischemia with regard to coronary risk. A very important finding was that exercise-induced silent myocardial ischemia was a stronger predictor of CHD in men with an unfavorable coronary risk factor profile, i.e., in smokers, hypercholesterolemic men and hypertensive men.

**Previous studies and our findings.** Unrecognized myocardial ischemia is a common finding and increases the risk of future coronary events (19,20). In our study, we observed that painless myocardial ischemia during exercise was present in 10.7% of men. Ischemic ST depression in the absence of pain has been more common than ST depression with angina in daily life (20-22). Some studies have shown that the more frequent or progressive the anginal symptoms are, the poorer the prognosis will be in patients with CHD (2,4,23). Other studies have indicated that symptomatic and silent ischemia are related to a similar prognosis in patients with symptomatic (3,5,6) and mildly symptomatic CHD (5). As patients become increasingly selected toward a higher a priori likelihood of developing myocardial ischemia and CHD, there appears to be a tendency for chest pain to lose its significance as an additional predictive factor (23).

The prognostic value of silent myocardial ischemia, as indicated by exercise ECG findings, varies considerably in the published reports (2,7,10,24,25), most likely due to different selection criteria for the subjects. Most studies have included only patients with CHD (3,5,6), whereas few studies have included persons without prior CHD (10,26).





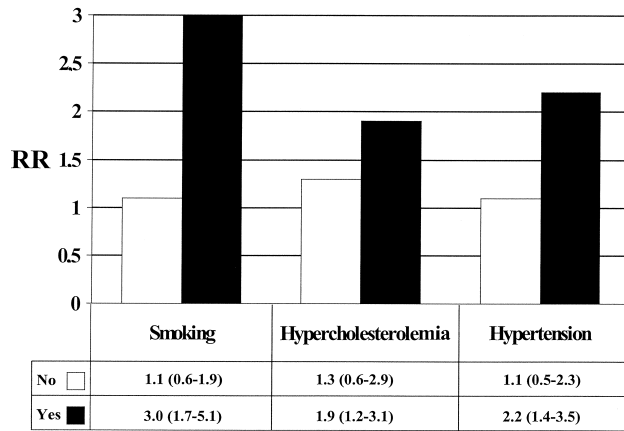
**Figure 1.** Cumulative hazards of coronary mortality in men with silent myocardial ischemia (high risk group) during exercise (A) and after exercise (B) versus all others (low risk group).

It has been argued that the prognostic value of exercise ECG is low in totally asymptomatic persons because of false-positive and false-negative responders. However, in healthy individuals with a high pretest probability of CHD (e.g., in those with major coronary risk factors), the frequency of false-positive test responses for myocardial ischemia is lower than in those without coronary risk factors, which diminishes the bias associated with false-positive responders (the Bayes' rule) (7,27). This could be one explanation for our finding that the association between silent myocardial ischemia with coronary risk was stronger in high risk groups.

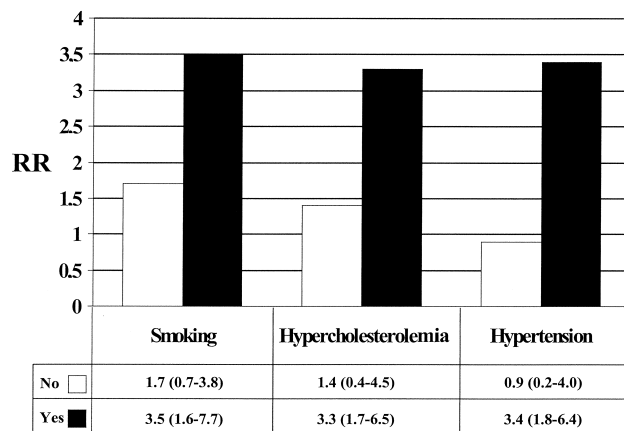
Electrocardiographic recordings not only during exercise but also after exercise may improve the sensitivity of exercise testing to detect myocardial ischemia. However, very few studies have provided evidence that ischemic ST depression after exercise would have an adverse prognostic value with regard to coronary events in apparently healthy men (28–

31). We found that silent ischemic ECG findings that prolonged or developed during recovery were associated with increased risk of both acute coronary events and CHD death. Interestingly, silent myocardial ischemia during recovery was even a stronger predictor of future events than silent myocardial ischemia during exercise, especially with regard to coronary death. This suggests that silent myocardial ischemia during the postexercise period could be of great clinical importance, and the prognostic value of exercise testing can be improved by assessing ischemic ECG changes during recovery.

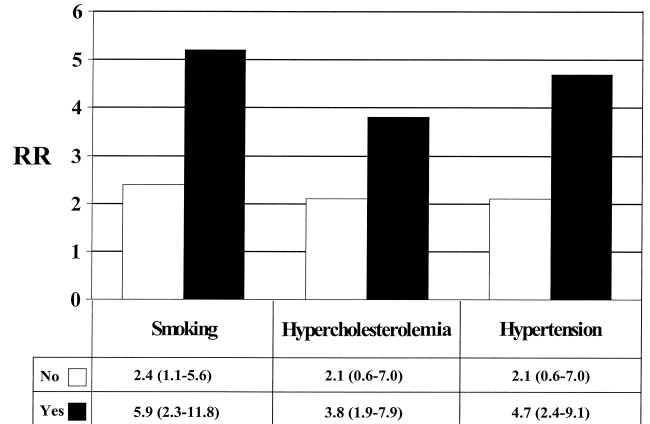
**Interactions with conventional risk factors.** It has been suggested that risk assessment for primary CHD is enhanced by the detection of abnormal exercise ECG findings only in those who had one or more conventional risk factor (7). However, there is no previous evidence that silent myocardial ischemia would have greater predictive value in high risk individuals. In the present study, men with silent



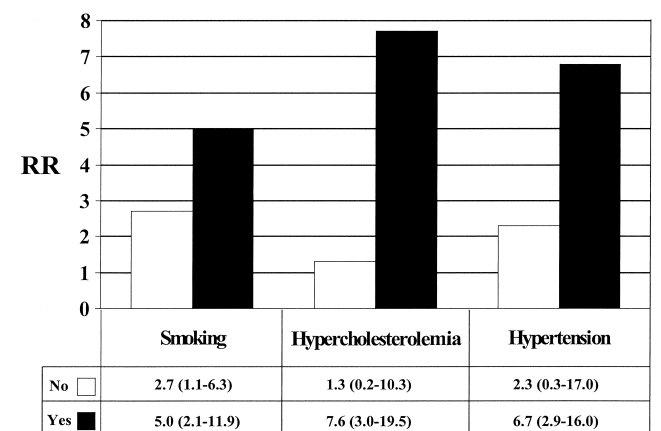
**A**



**C**



**B**



**D**

**Figure 2.** The relative risks (RR) (95% confidence intervals) of acute coronary events (A) and coronary death (B) in men with silent myocardial ischemia during exercise, and the RRs of acute coronary events (C) and coronary death (D) in men with silent ischemia after exercise according to conventional risk factor levels. Men without myocardial ischemia were a reference group. Cut-off for systolic blood pressure was 132 mm Hg and for serum low density lipoprotein cholesterol 3.9 mmol/l. Adjusted for age, examination years, alcohol consumption, body-mass index, maximal oxygen uptake, diabetes, cigarette smoking, systolic blood pressure and serum low density lipoprotein and high density lipoprotein cholesterol, except the risk factor of interest.

myocardial ischemia had a substantially increased risk of CHD, especially if they had any conventional risk factor. Interestingly, coronary mortality was very high in men with silent ischemia during recovery and any of these risk factors. These findings emphasize the importance of exercise testing in screening individuals free of clinical CHD but who have any of the major coronary risk factors and treated with therapeutic preventive measures.

**Mechanisms.** Our findings suggest that exercise-induced silent myocardial ischemia is a stronger predictor of fatal than nonfatal coronary events or any coronary event in healthy middle-aged men with no prior CHD. Consistent with these findings, some previous studies have suggested that silent myocardial ischemia is a pathophysiologic mechanism through which exercise increases the occurrence of sudden death (9,22,32). One explanation for this could be that painless ischemia increases the susceptibility to myocardial infarction, left ventricular dysfunction and, ultimately fatal ventricular arrhythmias. The transient impairment of coronary flow during and after exercise may be

caused by dynamic coronary stenosis as a result of epicardial coronary constriction, endothelial dysfunction, spasm and thrombosis (21,22,33). Such brief episodes may be painless because the stimulus is either inadequate or the pain usually appears quite late after the onset of ischemia (20,23). One mechanism for silent myocardial ischemia after exercise is the rapid decline in diastolic blood pressure during recovery, which reduces the myocardial perfusion pressure gradient and transiently impairs subendocardial blood flow (29,31). Furthermore, ischemic ST depression during recovery may be due to elevated levels of plasma catecholamines during the postexercise period, which could enhance myocardial oxygen demand (30,34,35).

**Methodologic considerations.** One of the explanations for the stronger associations between silent ischemia and coronary risk in men with conventional risk factors may be that ST depression is more likely due to true ischemia in these men than in those with no risk factors. Better quality of ECG recording after exercise may be one reason for the stronger association of silent ischemia after exercise with

coronary risk. Although we observed that milder silent ST depression after exercise may increase the risk of CHD, our main findings are based on conventional criteria for ischemia, as false-positive test results may lead to psychological and work disability as well as unnecessary medical expense (27,36). The use of a smaller ST depression tends to attenuate the specificity of the ischemic findings since factors other than myocardial ischemia, such as hyperventilation, electrolyte abnormalities, anemia, ventricular hypertrophy and increased sympathetic activity, are known to cause ST depression (10,24). One limitation of the present study is that we were able to study only middle-aged men and, thus, our findings may be not generalized to elderly and female populations. Furthermore, there are more accurate methods for assessing silent myocardial ischemia than exercise ECG, such as exercise and pharmacologic echocardiogram, myocardial perfusion imaging, positron emission tomography and ambulatory ECG monitoring (27,37), but as an easily available and inexpensive method exercise ECG is suitable for population studies and in everyday clinical practice.

**Implications.** The present findings are important from the public health and preventive cardiology viewpoint. Silent exercise-induced myocardial ischemia was common in middle-aged men with no prior CHD, and it was associated with a greater increased risk of CHD, especially in smokers, hypercholesterolemic men and hypertensive men. This study emphasizes the importance of identifying high risk persons (by exercise testing) in greatest need of preventive measures. The main clinical implication of our findings is that painless myocardial ischemia is of significant additional prognostic value when any conventional risk factors are present in men clinically free of CHD.

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**Reprint requests and correspondence:** Prof. Jukka T. Salonen, Research Institute of Public Health, University of Kuopio, P.O. 1627, 70211 Kuopio, Finland. E-mail: Jukka.Salonen@uku.fi.

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