Predictors of Cardiac and Noncardiac Mortality Among 14,697 Patients With Coronary Heart Disease

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The decrease in mortality from ischemic heart disease during the last 25 years may partly reflect improvement in diagnosis and treatment of patients with coronary heart disease. These patients, therefore, are experiencing morbidity and mortality due to other causes. The aim of our study was to describe the incidence and causes of cardiac mortality (CM) and noncardiac mortality (NCM) and to identify predictive factors. A cohort of 14,697 patients with coronary heart disease was merged with the Central Population Registry to identify mortality records from 1990 to 1996. Among the 1,839 deaths, 1,055 (57.4%) were cardiac, 626 (34.0%) were noncardiac, and 158 deaths (8.6%) were due to unknown causes as classified in the *International Classification of Diseases*–Ninth Edition (ICD). The 3 most significant predictors were age for a 10-year increment (odds ratios 1.75 and 2.25 for CM and NCM, respectively), chronic obstructive pulmonary disease (odds ratios 1.67 and 1.71), and current smoking (odds ratios 1.29 and 1.66). A history of cancer was a predictor of NCM, but not of CM, whereas peripheral vascular disease predicted CM but not NCM. As the number of predictive factors increased from none to ≥5, the risk of NCM gradually increased from 1.9% to 15.5%. Similar predictors expose subjects with coronary disease to CM and NCM, but smoking plays a more pronounced role in the prediction of NCM, whereas past myocardial infarction, lower levels of high-density lipoprotein cholesterol, and peripheral vascular disease are mainly associated with CM. Because of the similarity of antecedent predictors, treatment of risk factors among patients with coronary heart disease should prove valuable for the prevention of all-cause mortality.
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The age standardized mortality rates from heart disease in Israel decreased between 1984 and 1994 by 27% for men and 32% for women. The greatest decrease was in the standardized death rates from acute myocardial infarction.[1] This decrease may partly be due to improvement in diagnosis and treatment of patients with coronary heart disease, i.e., thrombolysis and revascularization procedures,[2] as well as use of aspirin, β blockers, and angiotensin-converting enzyme inhibitors. As a result, patients with coronary heart disease survive longer following a myocardial infarction,[3] and are increasingly exposed to morbidity and mortality from other diseases. A number of studies have examined predictors from the *International Classification of Diseases*–Ninth Edition (ICD) for cardiac mortality (CM) among cardiac patients.[4] Several other studies have examined cardiac[5] and noncardiac[6] mortality (NCM) in the general population. To the best of our knowledge, no study has yet quantitatively evaluated predictive risk factors for noncoronary death in patients with coronary heart disease. This study describes the incidence of CM and NCM in a large population of patients and delineates risk factors as possible predictors for cardiac and NCM.

METHODS

Study population: Between February 1990 and October 1992, 15,502 patients with coronary artery disease, aged 45 to 74 years, from 18 cardiology departments throughout Israel, were screened for participation in a randomized placebo-controlled, secondary prevention trial—The Bezafibrate Infarction Prevention (BIP) study. Of these patients, 3,122 fulfilled the inclusion criteria (included group) and took part in the trial,[7] which was aimed at evaluating the effectiveness of a lipid-modifying drug, bezafibrate, in decreasing the incidence of fatal and nonfatal coronary events. All 15,502 patients of the cohort underwent a screening medical interview followed by physical examination. Of the 15,502 subjects, 805 were lost to follow-up and therefore excluded, thus leaving a remaining cohort of 14,697 patients with known vital status. The mean ages for the latter group and the 805 subjects who were lost to follow-up were 60 and 61 years, respectively, with a distribution of 81% and 74% men, respectively. The frequencies of previous myocardial infarction were both 72%; current smoking was 9% and 11%, respectively. The present study included patients who died between the screening for the BIP study and October 1996 (mean follow-up 5.2 ± 1.3 years; range 2 days to 6.8 years) or those who survived until the end of follow-up period.

Baseline characteristics, medical history, and med-

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ications administered were recorded for all patients. Smoking status documentation included information on period of smoking (current/past/nonsmoker), and number of cigarettes smoked per day. Diagnosis of heart failure, according to New York Heart Association functional class,[8] was determined by the screening physician. Blood samples were drawn after fasting for 14 hours for lipid profile assessment and other biochemical and hematologic parameters in a central laboratory. Diagnosis of coronary artery disease was made on the basis of a documented myocardial infarction or angina pectoris with evidence of myocardial ischemia on ergometry, radionuclide stress test, or ≥60% stenosis in 1 major coronary artery on coronary angiography.

The study file was merged with the Israel National Population Registry and the Israeli Cancer Registry by identification number to identify the occurrence of cause-specific mortality cancer morbidity and mortality.

In Israel, mortality data are retrieved from the Israel National Population Registry, which maintains a registry of all citizens and permanent residents. Each Israeli citizen and each permanent resident has a unique 9-digit national identification number, facilitating record linkage. The registry includes several sociodemographic parameters, including identification number, gender, date of birth, vital status, and date, place, and cause of death. It is updated on a routine basis for births, deaths, and immigration (to and from Israel), and is corrected by linkage with census data. The underlying cause of death is assigned according to the ICD-Ninth Edition.[9] Information about cancer can be retrieved from the Israeli Cancer Registry, established in 1960, which maintains a registry of all malignant and some benign tumors. By administrative order, the registry receives notification of all malignancies from hospital discharge summaries, oncology and pathology departments, district chest clinics, and others. Ascertainment for most tumors is close to 95%.

When cause of death was unknown, death certificates and/or medical charts were reviewed.

Identification of underlying cause of death: Deaths that occurred among the 3,122 BIP trial patients were blindly reviewed by a mortality committee and assigned an underlying cause of death. The study cohort was linked to the Israel National Population Registry to identify mortality events and cause of death for the nonincluded 11,575 cardiac patients.

All deaths that occurred after the beginning of the BIP study and before October 1996 were categorized into cardiac or noncardiac causes of death. Cardiac death was defined as death coded with ICD codes: 402, 410 to 414, 416 to 429, or 785.51 (cardiogenic shock). All other causes of death were defined as noncardiac deaths and included: mortality from stroke (430 to 438), cancer (140 to 209, and 230 to 239), pulmonary embolism (415), sepsis (038,785.59), and traumatic causes (800 to 999). For each death with an unspecified cause, when the cause of death was coded as ICD code 799 (unknown), and/or when the cause of death was registered as "cardiorespiratory arrest," we reviewed the medical record or the death certificate, after obtaining a permission from the attending physician, in an attempt to obtain a more accurate description of the circumstances of death. After revision of these death certificates, only 158 deaths (8.6%) were considered due to unknown causes.

Statistical analysis: The SAS (SAS Institute, Cary, North Carolina) software[10] was used for statistical analysis. Differences between baseline means and percentages were assessed by 1-way analysis of variance and the chi-square test. The risks for NCM, for CM, and for total mortality were calculated by multivariate analysis, adjusting for differences in prognostically significant variables between the study groups compared with survivors. A stepwise Cox regression (proportional hazard regression procedure [PHREG][10] procedure) was used to estimate the hazard ratios of significant predictors for noncardiac (cardiac deaths were censored at the time of death) and of cardiac (noncardiac deaths were censored at the time of death) death and the corresponding 95% confidence intervals (CI). The model used stepwise selection of the variables with $p = 0.15$ for entry and $p = 0.10$ for removal. Hazard ratios were adjusted for the following covariants: age, gender, cigarette smoking (never, past, current), body mass index (weight in kilograms divided by the square of height in meters), total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, and pulse rate (beats per minute). Other dichotomized covariants were history of myocardial infarction, history of hypertension (assessed according to the information given by the patient during his/her baseline interview, regardless of the use of antihypertensive medication), history of angina pectoris, New York Heart Association functional class (I, negative; ≥II, positive), history of peripheral vascular disease, history of chronic obstructive pulmonary disease, history of cerebrovascular accident, and history of cancer diagnosed before date of inclusion into the study (according to Israeli Cancer Registry data as of December 1995). To examine the possibility of BIP inclusion being an effect modifier, inclusion in the placebo-controlled randomized trial was also used for adjustment of outcomes.

Independent risk factors were derived from the multivariate model for the prediction of noncardiac death versus survival. The average probability for occurrence of noncardiac death was computed according to the number of independent risk factors present. Because bezafibrate did not have a significant influence on death reduction compared with the placebo group,[11] we did not consider it as a potential predictor for death. Kaplan-Meier mortality curves for CM and NCM were produced separately using the LIFETEST procedure.[10]

RESULTS

Baseline and clinical characteristics: During the follow-up period, 1,839 subjects died. We analyzed the cohort according to 3 groups: survivors ($n = 12,858$), CM ($n = 1,055$), and NCM ($n = 626$). A separate group of 158 deaths (8.6%) was excluded from the analysis due to death from unknown causes. Mean

TABLE 1 Baseline Clinical and Biochemical Characteristics of Patients With Coronary Artery Disease

	Survivors (n = 12,858)	Noncardiac Deaths (n = 626)	Cardiac Deaths (n = 1,055)
Age (yrs) (mean ± SD)	60 ± 7	63 ± 6	62 ± 6
Men	10,426 (81%)	506 (81%)	859 (81%)
Women	2,432 (19%)	120 (19%)	196 (19%)
Body mass index (kg/mr^2) (mean ± SD)	27 ± 4	27 ± 4	27 ± 4
Systolic blood pressure (mm Hg) (mean ± SD)	134 ± 19	137 ± 20	137 ± 21
Diastolic blood pressure (mm Hg) (mean ± SD)	81 ± 10	82 ± 10	82 ± 11
Heart rate (beats/min) (mean ± SD)	71 ± 10	73 ± 10	74 ± 11
Current smoking	11%	15%	14%
Past smoking	53%	50%	51%
Angina pectoris	59%	59%	67%
Past myocardial infarction	71%	76%	84%
Diabetes mellitus	17%	27%	35%
New York Heart Association class II, III, or IV	27%	33%	39%
Systemic hypertension	33%	36%	38%
Chronic obstructive pulmonary disease	3%	6%	7%
Peripheral vascular disease	3%	6%	10%
Inclusion in BIP study*	22%	18%	15%
Cerebrovascular Accident	1%	4%	4%
Glucose (mg/dl)	112 ± 43	127 ± 62	134 ± 63
Total cholesterol (mg/dl) (mean ± SD)	224 ± 39	220 ± 44	228 ± 42
HDL cholesterol (mg/dl) (mean ± SD)	38 ± 10	38 ± 11	36 ± 10
LDL cholesterol (mg/dl) (mean ± SD)	154 ± 34	150 ± 38	157 ± 36
Triglycerides (mg/dl) (mean ± SD)	161 ± 93	165 ± 108	177 ± 97

*Inclusion in BIP study, in either the bezafibrate group, or the placebo group.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

follow-up for the CM group was 2.7 ± 1.7 years, for the NCM group, mean follow-up was 3.2 ± 1.7 years, and for the 12,858 survivors, mean follow-up was 5.5 ± 0.8 years.

Among the patients who died, 269 participated in the BIP study (n = 3,122), whereas the other 1,570 had been excluded at the screening phase. Among the 3 mortality groups, NCM occurred among oldest patients at baseline (62.9 ± 5.7 years), whereas the 158 patients with unknown causes of death had a similar mean age with CM group (61.6 ± 6.2 and 61.9 ± 6.3 years, respectively). The male to female ratio among these 3 groups did not differ significantly.

Table 1 lists the baseline clinical and biochemical characteristics of survivors, patients dying of noncardiac causes and those dying of cardiac causes. Mean age at baseline was close to 60 in all groups, although survivors were younger at baseline (59.5 ± 7.0 years) than the 3 mortality groups.

Means or proportions for systolic blood pressure, pulse rate, current smoking, angina pectoris, history of myocardial infarction, diabetes mellitus, severity of congestive heart failure, hypertension, and the prevalence of chronic obstructive pulmonary disease, peripheral vascular disease, and cerebrovascular accident, were all significantly higher among the 2 mortality groups than among survivors.

Blood biochemical markers of the cohort at baseline showed that fasting glucose and triglycerides were significantly higher in the NCM group compared with survivors, whereas low-density lipoprotein cholesterol was significantly lower.

A comparison between the CM and the NCM groups by *t* test (not shown in Table 1) revealed that the CM group was significantly younger at baseline and had higher total cholesterol, low-density lipoprotein cholesterol, triglycerides, and glucose levels. High-density lipoprotein cholesterol was significantly lower in the CM group and their baseline pulse rate was higher. A history of myocardial infarction, diabetes, angina pectoris, New York Heart Association functional class >I and peripheral vascular disease were significantly more prevalent at baseline among the CM group compared with the NCM group. All other baseline characteristics were similar in the 2 mortality groups.

At baseline (data not shown), β-adrenergic blockers and aspirin were used significantly less frequently in both mortality groups compared with the survivors, whereas nitrates, antiarrhythmic, oral hypoglycemic, antihypertensive, and diuretic drugs, potassium chloride, digitalis, and angiotensin-converting enzyme inhibitors were used significantly more often at baseline by those who subsequently died. Calcium channel blockers and anticoagulants were used with similar frequencies in the survivors and NCM group but significantly more frequently in the CM group.

Mortality: Table 2 shows the distribution of causes of death according to ICD-9, grouped into 10 large categories. Malignancy (16.2%) was the most frequent cause of death among the NCM group followed by stroke (5.4%), sepsis (3.8%), trauma (1.5%), and pulmonary emboli (0.6%).

Of the malignancies, those of the lung and bronchus (ICD-9 code 162) both contributed to 23.7% of deaths followed by colon (ICD-9 code 163) and prostate cancer (ICD-9 codes 179 to 181), which contributed 9.8% and 7.1% of the deaths due to malignancies.

TABLE 2 Classification of Cause of Death for 1,839 Patients, According to ICD-9

Cause of Death	ICD-9 Codes	Diagnosis	No. of Deaths (%)
Cardiac causes	402, 410–414	Coronary heart disease	1,055 (57.4)
	416–429	Other heart disease	
	785.51	Cardiogenic shock	
Noncardiac causes	430–438	Stroke	99 (5.4)
	140–209, 230–239	Neoplasia/malignancy	298 (16.2)
	038, 785.59	Sepsis	69 (3.8)
	800–999	Traumatic cause	29 (1.5)
	415	Pulmonary embolism	11 (0.6)
		Other causes*	120 (6.5)
		Total	626 (34.0)
Unknown	799	Unknown	158 (8.6)
Total			1,839 (100)

*Other causes included: diabetes (n = 20), gastrointestinal bleeding (n = 11), other diseases of the gastrointestinal tract (n = 10), aortic aneurysm (n = 8), infectious diseases (n = 7), renal failure (n = 11), other renal disease (n = 11), liver disease (n = 7), lung disease (n = 7), and several other causes with ≤2 subjects dying from each.

Predictors of mortality: MULTIVARIATE ANALYSIS: Analysis with the Cox proportional hazard model showed that in addition to previous diagnosis of cancer, age per 10 years increment, and a history of cerebrovascular accident, chronic obstructive pulmonary disease, current smoking, past myocardial infarction, elevated blood glucose level, congestive heart failure, pulse rate, and decreased levels of total cholesterol were associated with increased NCM (Table 3).

Although previous cancer was not found to be a risk factor for CM, past myocardial infarction, peripheral vascular disease, and total cholesterol were strongly associated with CM. High-density lipoprotein cholesterol was found to be protective against CM as expected.

Except for total cholesterol and angina pectoris, the same predictors were found for total death as for CM. Total cholesterol was associated only with CM, and angina pectoris was found to be a predictor for total mortality, but not when separated from CM or NCM.

In addition to the data shown in Table 3, we found that, when controlling for other variables, fasting blood glucose of >140 mg/dl was associated with a 20% increased risk for NCM. When we substituted glucose levels with a history of diabetes mellitus in the multivariate model, the latter was associated with a 45% increased risk for NCM. Inclusion of reported diabetes instead of serum glucose tended to reduce the fit of the logistic model, although sharpness of discrimination was not affected.

Smoking was related to a certain increase in CM of 1.29 (95% CI 1.08 to 1.55) but was primarily associated with NCM of 1.66 (95% CI 1.33 to 2.08). As the level of smoking increased from nonsmoking to past smoking to current smoking, there was an increased age-adjusted NCM rate from 4.2 (95% CI 3.7 to 4.8) to 4.5 (95% CI 4.0 to 5.0) to 7.9 (95% CI 5.6 to 10.3), respectively. As the number of cigarettes currently smoked increased, the age-adjusted NCM increased from 7.9 (95% CI 5.6 to 10.3) for 1 to 20 cigarettes smoked per day to 9.2 (95% CI 6.7 to 11.8) for ≥21 cigarettes smoked per day.

MORTALITY ACCORDING TO NUMBER OF RISK FACTORS: To illustrate the incremental significance of risk factors for CM and NCM, we tabulated mortality as a function of the number of additional risk factors identified at baseline by the previously mentioned Cox model. Figures 1 and 2 show how the risks for CM and NCM "rise," as the risk profile for each of these fatal outcomes worsens. The risk factors chosen were the 11 risk factors for CM and the 10 risk factors for NCM identified as independent predictors in the Cox model. Figures 1 and 2 show how mortality for CM increased from 1.7% to 22.2% as the number of risk factors increased from 0 to ≥5. The corresponding risk for NCM increased from 1.9% to 15.5%.

KAPLAN-MEIER MORTALITY ANALYSIS: Two mortality curves are presented in Figure 3 and show that CM after 6 years was about 2 times more frequent than NCM in this population of patients with coronary heart disease.

DISCUSSION

Over the mean 5.15-year follow-up period of this cohort, 1,839 coronary patients died. This represents a death rate of 2,275/100,000/year, which is 2.2 times higher than the mortality rate of Israelis aged 44 to 74 years in 1994 (the mid follow-up year of the study), which was 1,104/100,000/year.[12] Because survival of patients with coronary heart disease following acute myocardial infarction has improved, these patients are increasingly exposed to other causes of death. Life expectancy at birth in Israel was 75.5 years for men and 79.5 years for women in 1995.[1] Although cardiac deaths accounted for the vast majority (about 2/3) of deaths among cardiac patients in this study, in the general Israeli population (aged 45 to 74 years), according to national data, only 1/4 of deaths were due to cardiac cause in 1995.[12] At the same time, malignancies and trauma accounted for only 16.2% and 1.5% of deaths in our study population, whereas in the general Israeli population of the same age group, 33% of deaths were attributed to malignancies and an additional 4.2% to traumatic causes. Competing risks certainly play a major role in determining the cause of death distribution among our patients. There are 2 main clinical implications to this finding: The first is that on an individual patient perspective, the treating physician should regard cardiac disease as the most likely cause of death; thus, the main consideration should be treatment and follow-up. The second is that from a public health preventive perspective, among cardiac patients, noncardiac causes are significant contributors to death (almost 40%). Because of the similarity of antecedent predictors, treatment of risk factors among coronary heart disease patients should prove valuable for the prevention of all-cause mortality.

TABLE 3 Significant Predictors for Noncardiac Mortality, Cardiac Mortality, and Total Mortality Among Patients

	Noncardiac Mortality Hazard Ratio (95% CI)	Cardiac Mortality Hazard Ratio (95% CI)	Total Mortality Hazard Ratio (95% CI)
Previous cancer	3.35 (2.61–4.31)	1.30 (0.96–1.75)	2.07 (1.71–2.51)
Age, 10-yr increments	2.25 (1.96–2.50)	1.75 (1.59–1.94)	1.91 (1.76–2.07)
Cerebrovascular accident	2.19 (1.45–3.30)	2.05 (1.50–2.80)	2.09 (1.63–2.69)
Chronic obstructive pulmonary disease	1.71 (1.21–2.42)	1.67 (1.29–2.16)	1.66 (1.35–2.04)
Current smoking	1.66 (1.33–2.08)	1.29 (1.08–1.55)	1.42 (1.23–1.63)
Past myocardial infarction	1.26 (1.04–1.52)	2.10 (1.77–2.49)	1.69 (1.49–1.92)
Glucose (+40 mg/dl)	1.21 (1.14–1.28)	1.21 (1.16–1.26)	1.21 (1.17–1.25)
New York Heart Association class (class II +)	1.20 (1.01–1.43)	1.33 (1.20–1.59)	1.33 (1.19–1.49)
Pulse (increments of 10 beats/min)	1.15 (1.07–1.24)	1.28 (1.20–1.35)	1.23 (1.17–1.29)
Total cholesterol (40 mg/dl)†	0.88 (0.81–0.95)	1.09 (1.02–1.15)	—
Included in BIP study	0.81 (0.65–1.00)	0.69 (0.58–0.82)	0.73 (0.64–0.83)
Peripheral vascular disease*	—	1.83 (1.48–2.27)	1.63 (1.36–1.95)
HDL cholesterol*, (+10 mg/dl)	—	0.84 (0.78–0.90)	0.89 (0.85–0.94)
Angina pectoris	—	—	1.12 (1.00–1.25)

*Peripheral vascular disease and high-density lipoprotein (HDL) cholesterol were found to be significant predictors of cardiac but not of noncardiac death. Male gender, history of hypertension, past smoking, body mass index, and triglycerides were also examined in the models but were not found to be statistically significant predictors.

†Hazard ratio for noncardiac death was 12% lower for each 40 mg/dl increment in total cholesterol. Conversely for cardiac death, it was 9% higher for each 40 mg/dl increment in total cholesterol.

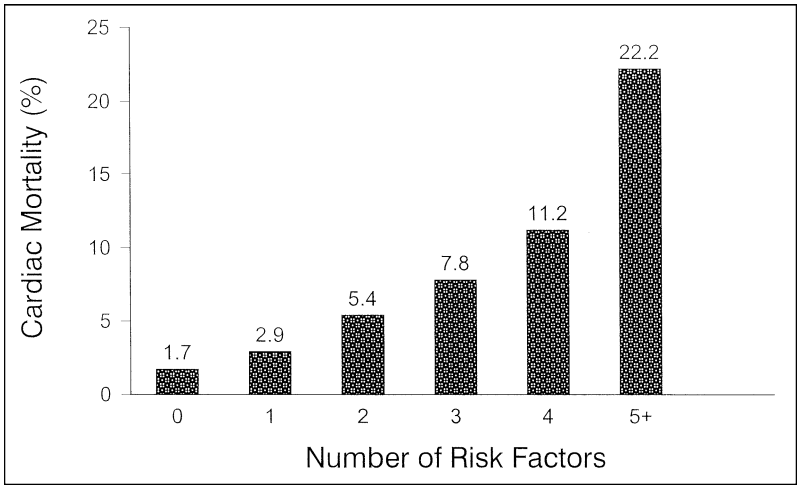

FIGURE 1. Rates of CM and NCM by number of independent risk factors. The list of independent risk factors for CM and NCM is: age (>65 years), past myocardial infarction, New York Heart Association class II, III or IV, peripheral vascular disease, chronic obstructive pulmonary disease, cerebrovascular accident, current smoker, total serum cholesterol (<200 mg/dl), serum glucose (>140 mg/dl), pulse rate (>80 beats/min). High-density lipoprotein cholesterol (<35 mg/dl) was included in the CM risk factors list only. All risk factors have been dichotomized.

Predictors of mortality by cause: Our findings are consistent with the American College of Cardiology/American Heart Association practice guidelines for acute myocardial infarction[13] regarding CM and other risk factors, i.e., blood total cholesterol, high-density lipoprotein cholesterol, previously established coronary artery disease, and smoking. Some of the known risk factors for coronary disease, such as smoking and diabetes, appear to be nonexclusive of death from cardiac causes, even among patients with coronary heart disease.

Our model predicts CM somewhat more accurately than NCM. This can be explained by the nature of the identified risk factors being more closely related to cardiovascular and metabolic diseases. Although angina pectoris was not predictive of CM in this study, other studies have found these 2 factors to be significantly associated.[4]

Elevated blood glucose levels were found to be a stronger predictor for NCM than a history of diabetes. This might reflect patients' tendency to negatively report regarding treated or controlled diabetes, or it might indicate an under-diagnosis of the disease.

Low cholesterol levels preceding mortality might mark some attrition process. In some previous studies, there was an excess risk of NCM for decreased total cholesterol levels.[14] There is a wide array of evidence associating spontaneously occurring lower cholesterol levels with a number of noncardiac causes of death,[15] such as suicide,[16] hemorrhagic stroke,[17] liver disease,[18] and cancer.[19] In the present study decreased levels of total cholesterol were associated with a slightly increased NCM, whereas increased levels were associated with increased CM. This U-shaped relation of mortality incidence with plasma total cholesterol levels is of interest in a sample of patients with coronary heart disease. It obscures the relation between total mortality and total cholesterol when entered into the model as a continuous variable. In the clinical setting, the physician of a patient who presents with spontaneously occurring low total cholesterol should be alert to the possibility

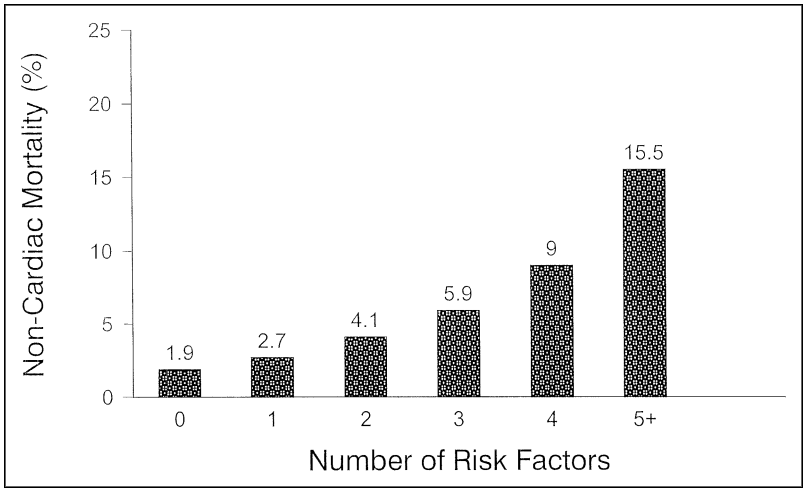

FIGURE 2. Rates of NCM by number of independent factors. The list of independent risk factors for NCM is the same as mentioned in Figure 1, except for high-density lipoprotein, which was not included among NCM risk factors.

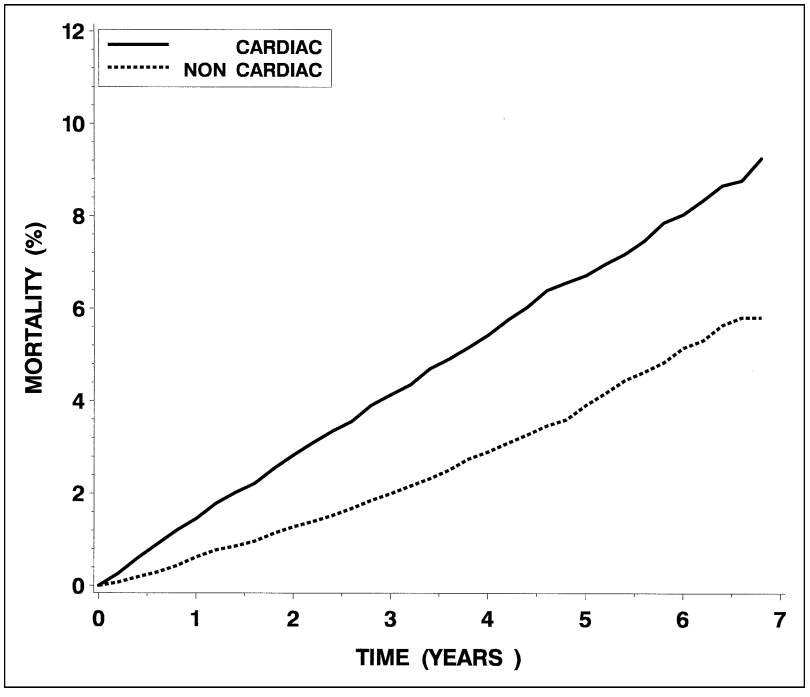

FIGURE 3. Kaplan-Meier mortality curves for cardiac and noncardiac causes of death.

of an underlying medical condition other than a cardiac one. Nevertheless, one should not hesitate, on these grounds, to implement statin therapy. Statins, as is shown in most clinical trials, do not increase the risk of death from any cause.[20]

A 10 mg/dl increase in high-density lipoprotein cholesterol was associated with a 16% reduction in CM. Recently, it was shown that gemfibrozil therapy increased high-density lipoprotein cholesterol levels and decreased triglyceride levels, and decreased fatal and nonfatal myocardial infarction in patients with coronary disease.[21]

Smoking is a well-established risk factor for cancer,[22] pulmonary diseases,[23] and stroke.[24,25] We found a positive correlation between smoking and the risk for NCM. Former smokers exhibited almost similar risk for noncardiac death as did patients with coronary heart disease who never smoked. Current smokers were at increased risk of NCM, depending on their level of exposure: the higher the number of cigarettes smoked, the greater the risk. In some previous studies, smoking cessation was paradoxically found to increase the risk for noncardiac morbidity and mortality, probably because persons usually stop smoking as a result of a medical problem.[26] This might cause a "quitting ill" effect, i.e., "smokers often quit as a result of developing symptoms of a life threatening disease or immediately following diagnosis."[27] This quitting ill effect has been seen for the first 2 to 5 years following cessation of smoking in a number of studies.[28] For that reason, several studies excluded former smokers who had stopped smoking $\leq$5 years before their study.[29] In our study, we did not know the cause for smoking cessation or the duration of smoking in the patients screened for the BIP study.

Our analyses have several potential limitations. First, we used death certificates to verify the cause of death. The relatively low accuracy of diagnosis on the death certificates, the worldwide decrease in autopsy rates, and competing risks between number of severe conditions complicates the interpretation of mortality data. Nevertheless, in our study, about 30% of those death certificates in which cause of death was unknown were individually reviewed to ensure the accurate underlying cause of death. Although death certificates represent the basis for mortality analysis in most epidemiologic studies, in some studies between 11.7% and 44.0% of death certificates were found to be lacking the underlying cause of death.[30] However, only 8.6% of deaths were due to unknown causes in our study (Table 2).

Inclusion of all screenees for the BIP clinical trial in this study might cause a selection bias as well as a surveillance bias. Inclusion in the trial was therefore entered as a confounder in the model. We repeated the main analysis for only those 11,575 patients not included in the BIP clinical trial and found similar estimated hazard ratios with those obtained for the entire group.

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