Causes and Predictors of Death in Patients With Coronary Heart Disease (from the Heart and Soul Study)

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Although the prevalence of coronary heart disease (CHD) in the United States has increased during the past 25 years, cardiovascular mortality has decreased due to advances in CHD therapy and prevention. We sought to determine the proportion of patients with CHD who die from cardiovascular versus noncardiovascular causes and the causes and predictors of death, in a cohort of patients with CHD. The Heart and Soul Study enrolled 1,024 participants with stable CHD from 2000 to 2002 and followed them for 10 years. Causes of mortality were assigned based on detailed review of medical records, death certificates, and coroner reports by blinded adjudicators. During 7,680 person-years of follow-up, 401 participants died. Of these deaths, 42.4% were cardiovascular and 54.4% were noncardiovascular. Myocardial infarction, stroke, and sudden death accounted for 72% of cardiovascular deaths. Cancer, pneumonia, and sepsis accounted for 67% of noncardiovascular deaths. Independent predictors of cardiac mortality were older age, inducible ischemia on stress echocardiography, higher heart rate at rest, smoking, lower hemoglobin, and higher N-terminal pro-brain natriuretic peptide (all p values <0.05); independent predictors of noncardiac mortality included older age, inducible ischemia, higher heart rate, lower exercise capacity, and nonuse of statins (all p values <0.05). In conclusion, mortality in this cohort was more frequently due to noncardiovascular causes, and predictors of noncardiovascular mortality included factors traditionally associated with cardiovascular mortality. Published by Elsevier Inc. (Am J Cardiol 2017;119:27−34)

Heart disease has long been the leading cause of death in the United States. Coronary heart disease (CHD) accounted for over 375,000 deaths in the United States in 2011, or 1 of every 7 deaths.[1] Age-adjusted cardiovascular mortality rate, however, has decreased steadily since 1968, due both to advances in medical and surgical therapy as well as risk factor reduction.[2−6] As rates of cardiovascular mortality decrease and subjects live longer with CHD, understanding the noncardiovascular causes of morbidity and mortality in patients with CHD will be increasingly meaningful for clinicians who are caring for these patients and will inform screening and preventative measures. Rates, causes, and predictors of noncardiovascular mortality in patients with stable CHD in the United States, particularly as they reflect recent therapy, are not known. To our knowledge, only Dankner et al[7] have reported predictors of noncardiac versus cardiac mortality in patients with CHD. In that study, history of cancer was the only predictor of noncardiac (vs cardiac) mortality, whereas the presence of peripheral vascular disease was the only predictor of cardiac (vs noncardiac) death. However, Dankner's study used data from before 1996 and therefore does not reflect more recent advances in therapy for cardiovascular disease. We sought to: (1) quantify the rates of noncardiovascular and cardiovascular mortality among a well-studied ambulatory population with stable CHD in the current era and (2) define the predictors of noncardiac versus cardiac mortality among these subjects.

Methods

The Heart and Soul Study was a prospective cohort study of 1,024 ambulatory subjects with stable CHD at entry to the study who were recruited between September 2000 and December 2002 and followed for 10 years. Details regarding recruitment methods and study design have previously been published.[8,9] Eligible participants met 1 or more of the following criteria: (1) history of myocardial infarction (MI); (2) evidence of at least 50% diameter stenosis in 1 or more coronary arteries by angiography; (3) evidence of exercise-induced myocardial ischemia by treadmill electrocardiogram or nuclear perfusion stress imaging; or (4) previous coronary revascularization. We excluded subjects with a

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Table 1
Causes of death in 1,024 patients with coronary heart disease

Cause of Death	Number	Annual rate (%)
Sudden death	64	0.84
Heart failure	34	0.45
Myocardial infarction	24	0.32
Stroke	22	0.29
Peripheral artery disease	5	0.07
Severe dysrhythmia	5	0.07
Other (e.g. valvular)	9	0.12
Multiple	7	0.09
Total Cardiovascular	**170**	**2.2**
Cancer	79	1.04
Pneumonia	44	0.58
Sepsis	23	0.30
Kidney disease	12	0.16
Dementia/progressive neurological decline	10	0.13
Lung disease	10	0.13
GI or liver disease	9	0.12
Substance abuse	6	0.08
Accidents/trauma	6	0.08
Procedure-related	4	0.05
Suicide	3	0.04
Pulmonary embolism	3	0.04
AIDS	2	0.03
Other	7	0.09
Total Non-cardiovascular	**218**	**2.9**
Unknown	13	0.17
Lost to follow-up	1	
Total deaths	**401**	**5.2**

GI = gastrointestinal.

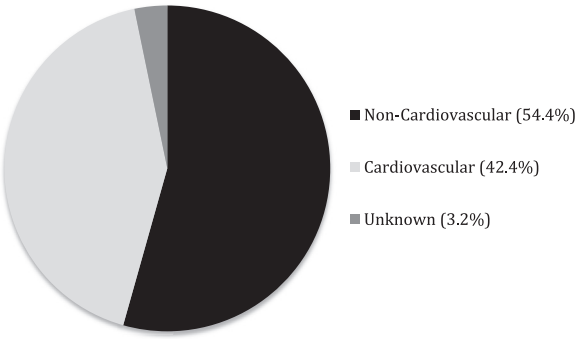

Figure 1. Causes of death in 1,010 patients with CHD.

history of MI in the previous 6 months, inability to walk 1 block, or plans to move out of the local area within 3 years.

Self-reported age, gender, ethnicity, medical history, and smoking status were determined by questionnaire. To tabulate medication use, participants were instructed to bring their medication bottles to the study appointment and study personnel recorded all current medications. Significant alcohol use was coded as an Alcohol Use Disorders Identification Test score of 4 or greater.[10] Levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and the amino terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP) were measured as previously described.[8,9] Estimated glomerular filtration rate was calculated using the CKD-Epi Cystatin equation.[11]

Participants underwent symptom-limited exercise stress testing according to a standard Bruce protocol (those unable to complete the standard protocol were converted to a manual protocol) with continuous 12-lead electrocardiogram monitoring. Before exercise, participants underwent complete 2-dimensional echocardiograms at rest. Standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views were obtained during held inspiration and were used to calculate the volumetric left ventricular ejection fraction. Diastolic dysfunction was defined as pseudonormal or restrictive filling on mitral inflow. At peak exercise, precordial long- and short-axis and apical 2- and 4-chamber views were obtained to assess wall motion abnormalities. We defined exercise-induced ischemia as the presence of 1 or more new wall motion abnormalities at peak exercise that was not present at rest.

We conducted annual telephone follow-up interviews with participants (or their proxy) and asked about death or hospitalization for "heart trouble." For all reported deaths, medical records, electrocardiograms, death certificates, and coroner reports were retrieved and reviewed by 2 independent and blinded adjudicators. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator. For deaths attributable to more than 1 cause, a fourth blinded physician adjudicator rereviewed all materials to assign the most plausible cause of death. Causes of death were categorized as cardiovascular versus noncardiovascular using standardized definitions.[12] Noncardiovascular deaths were subclassified as due to pulmonary embolism, cancer, suicide, accidents/trauma, acquired immunodeficiency virus, chronic obstructive pulmonary disease/asthma, pneumonia, other lung disease, natural causes, kidney disease, liver disease, or other causes.

Cardiovascular deaths were subclassified as due to MI, sudden death, stroke, heart failure, peripheral artery disease, severe dysrhythmia, or other cardiovascular causes. Deaths were categorized as MI if they occurred during the same hospitalization in which an acute MI was documented. Sudden death was defined as death within 1 hour of the onset of terminal symptoms not explained by other etiologies. Stroke deaths were defined as death after onset of a new neurological deficit not known to be secondary to brain trauma, tumor, infection, or other cause. Peripheral artery disease deaths were defined as death during hospitalization for peripheral artery disease.

Deaths were classified as due to heart failure if they occurred during hospitalization for a clinical syndrome involving at least 2 of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, or cardiomegaly or pulmonary edema on chest radiography. These clinical signs and symptoms must have represented a clear change from the normal clinical status and must have been accompanied by either decreased cardiac output as determined by peripheral hypoperfusion (in the absence of other causes such as sepsis or dehydration) or peripheral or pulmonary edema requiring intravenous diuretic, inotropic agents, or

Table 2
Baseline characteristics of 1,010 participants with stable coronary heart disease

	Survivors (N=622)	Cardiovascular death (N=170)	Non-cardiovascular death (N=218)	P value		
Age (years)	64 ± 10	71.1 ± 11.1	70.9 ± 10.7	*	†	
Men	484 (78%)	147 (86%)	197 (90%)	*	†	
Race/ethnicity						
White	360 (58%)	101 (59%)	146 (67%)		†	
Black	107 (17%)	33 (19%)	27 (14%)			
Asian	75 (12%)	17 (10%)	21 (10%)			
Hispanic	59 (9%)	14 (8%)	16 (7%)			
Other	20 (3%)	5 (3%)	8 (4%)			
BMI (kg/m^2)	28.8 ± 5.4	28.3 ± 5.4	27.2 ± 4.8		†	‡
Waist-hip ratio	0.95 ± 0.08	0.97 ± 0.08	0.97 ± 0.07	*	†	
High school educated	552 (84%)	141 (83%)	185 (85%)	*		
Hypertension	432 (69%)	123 (72%)	157 (72%)			
Heart failure	87 (14%)	47 (28%)	42 (19%)	*		
Stroke	69 (11%)	41 (24%)	35 (16%)	*		‡
Diabetes mellitus	135 (22%)	57 (34%)	69 (32%)	*	†	
Myocardial infarction	311 (50%)	110 (65%)	123 (56%)	*		
Peripheral artery disease	40 (6%)	16 (9%)	27 (12%)		†	
Chronic lung disease	94 (15%)	32 (19%)	36 (17%)			
Atrial fibrillation	16 (3%)	15 (9%)	10 (5%)	*		
Revascularization	365 (59%)	102 (60%)	126 (58%)			
Cancer	98 (16%)	42 (25%)	61 (28%)	*	†	
LV ejection fraction	0.63 ± 0.08	0.58 ± 0.12	0.60 ± 0.11	*	†	‡
Diastolic dysfunction	57 (9%)	29 (17%)	27 (12%)	*		
Exercise capacity (METS)	8.2 ± 3.3	5.8 ± 3.0	3.9 ± 2.6	*	†	
Inducible myocardial ischemia	89 (14%)	62 (36%)	74 (34%)	*	†	
Systolic blood pressure (mm Hg)	132 ± 20	136 ± 23	133 ± 22	*		‡
Diastolic blood pressure (mm Hg)	75 ± 11	74 ± 13	73 ± 11		†	
LDL cholesterol (mg/dL)	104 ± 31	103 ± 35	106 ± 36			
HDL cholesterol (mg/dL)	47 ± 14	44 ± 15	45 ± 13	*		
Hemoglobin (g/dL)	14.0 ± 1.3	13.6 ± 1.3	13.5 ± 1.5	*	†	
Heart rate (beats/min)	67 ± 12	68 ± 11	69 ± 13			
NYHA Class III or IV	113 (18%)	52 (31%)	60 (28%)	*	†	
Log NT pro BNP (pg/mL)	4.8 ± 1.1	6.09 ± 1.49	5.7 ± 1.4	*	†	‡
Log CRP (mg/L)	0.6 ± 1.3	0.8 ± 1.3	0.9 ± 1.4	*	†	
Glycohemoglobin (%)	5.8 ± 1.0	6.2 ± 1.4	6.1 ± 1.2	*	†	
Estimated GFR (ml/min)	76 ± 19	61 ± 25	62 ± 21	*	†	
Log Urine Alb/Creat (mg/g)	2.1 ± 1.2	3.1 ± 1.7	2.8 ± 1.5	*	†	
Current smoker	116 (19%)	37 (22%)	46 (21%)			
Physically inactive	207 (33%)	73 (43%)	86 (39%)	*		
Medication non-adherence	51 (8%)	14 (8%)	15 (7%)			
Regular alcohol use	185 (30%)	41 (24%)	62 (28%)			
Anti-platelet	462 (74%)	112 (66%)	161 (74%)	*		
Statin	417 (67%)	108 (64%)	124 (57%)		†	

BMI = body mass index; CRP = C-reactive protein; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; METS = metabolic equivalents; NYHA = New York Heart Association.

* $p < 0.05$ (CV death vs survival).

† $p < 0.05$ (non-CV death vs survival).

‡ $p < 0.05$ (CV death vs non-CV death).

vasodilator therapy. Supportive documentation of reduced cardiac output, elevated pulmonary capillary wedge pressure, decreased oxygen saturation, and end-organ hypoperfusion were noted when available.

The outcome was number of days until death or last follow-up interview (censor date February 1, 2012). The following comparisons of baseline characteristics were conducted using *t* tests for normally distributed continuous variables or chi-square for binary or categorical variables: (1) patients with cardiovascular death versus survivors, (2) patients with noncardiovascular death versus survivors, and (3) patients with cardiovascular versus noncardiovascular death. Continuous variables were log transformed if not normally distributed. Individual age-adjusted hazard ratios were computed for each covariate using separate Cox regression models, with continuous variables entered per SD change. Variables associated with death in age-adjusted models (at $p < 0.1$) were then entered in a multivariable Cox regression model to determine independent predictors. We evaluated potential interactions of age with gender, race/ethnicity or statin use, gender with race/

Table 3
Predictors of cardiovascular death (vs survival) in 1,010 patients with coronary heart disease

Covariate*	Age-adjusted		Multivariable-adjusted	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age (alone)	1.77 (1.50-2.09)	<0.001	1.68 (1.23-2.31)	0.001
Male	1.38 (0.89-2.15)	0.16	2.31 (1.00-5.31)	0.05
White	1.0 (reference)	–	1.0 (reference)	–
Black	1.63 (1.09-2.44)	0.02	0.75 (0.36-1.58)	0.45
Asian	0.83 (1.50-1.39)	0.48	0.93 (0.44-1.93)	0.84
Hispanic	0.91 (0.52-1.59)	0.74	0.69 (0.29-1.64)	0.41
Other	1.10 (0.45-2.71)	0.84	0.99 (0.26-3.93)	0.99
Body mass index (kg/m^2)	0.97 (0.82-1.16)	0.74	–	–
Waist-to-hip ratio	1.17 (1.00-1.37)	0.05	0.98 (0.74-1.30)	0.90
High-school educated	0.68 (0.46-1.02)	0.06	0.82 (0.43-1.56)	0.54
Hypertension	1.06 (0.75-1.48)	0.75	–	–
Heart failure	2.08 (1.48-2.91)	<0.001	0.85 (0.49-1.48)	0.56
Stroke	1.83 (1.29-2.61)	<0.001	0.83 (0.46-1.50)	0.53
Diabetes	2.04 (1.48-2.81)	<0.001	1.14 (0.61-2.12)	0.68
Myocardial Infarction	1.73 (1.26-2.37)	<0.001	1.14 (0.70-1.86)	0.59
Peripheral artery disease	1.41 (0.84-2.38)	0.19	–	–
Coronary revascularization	0.92 (0.68-1.26)	0.61	–	–
Chronic lung disease	1.27 (0.87-1.87)	0.22	–	–
Atrial fibrillation	2.09 (1.22-3.58)	<0.001	0.56 (0.11-2.79)	0.48
Cancer	0.92 (0.80-1.07)	0.27	–	–
LV ejection fraction (%)	0.68 (0.60-0.76)	<0.001	0.88 (0.70-1.11)	0.29
Diastolic dysfunction	1.98 (1.33-2.97)	<0.001	0.97 (0.50-1.87)	0.92
Exercise capacity (METS)	0.49 (0.39-0.61)	<0.001	0.70 (0.49-1.02)	0.06
Inducible ischemia	2.83 (2.03-3.95)	<0.001	2.28 (1.44-3.61)	<0.001
Systolic BP (mm Hg)	1.14 (0.99-1.32)	0.07	1.10 (0.84-1.43)	0.48
Diastolic BP (mm Hg)	1.09 (0.93-1.28)	0.26	–	–
LDL cholesterol (mg/dL)	1.05 (0.90-1.24)	0.51	–	–
HDL cholesterol (mg/dL)	0.81 (0.68-0.96)	0.01	0.91 (0.71-1.16)	0.45
Hemoglobin (g/dL)	0.83 (0.71-0.96)	0.01	0.78 (0.61-1.00)	0.04
Heart rate (beats/min)	1.21 (1.04-1.40)	0.01	1.42 (1.12-1.81)	0.004
NYHA Class III or IV	1.87 (1.35-2.59)	<0.001	1.09 (0.63-1.89)	0.76
Log NT pro BNP (pg/ml)	2.35 (2.00-2.76)	<0.001	1.55 (1.09-2.19)	0.01
Log CRP (mg/L)	1.31 (1.11-1.54)	<0.001	0.96 (0.77-1.21)	0.75
Glycohemoglobin (%)	0.83 (0.71-0.96)	<0.001	1.06 (0.84-1.34)	0.63
Estimated GFR (ml/min)	0.56 (0.48-0.67)	<0.001	1.10 (0.83-1.46)	0.51
Log Albumin/Creatinine (mg/g)	1.70 (1.50-1.93)	<0.001	1.24 (0.98-1.58)	0.07
Current smoker	2.41 (1.63-3.56)	<0.001	2.79 (1.55-5.02)	<0.001
Alcohol use	0.78 (0.55-1.10)	0.16	–	–
Physically inactive	1.65 (1.22-2.24)	0.001	1.05 (0.64-1.73)	0.84
Medication non-adherence	1.66 (0.95-2.91)	0.07	1.54 (0.60-3.92)	0.37
Anti-platelet	0.76 (0.54-1.05)	0.10	1.00 (0.59-1.70)	1.00
Statin	0.77 (0.56-1.07)	0.12	–	–

BP = blood pressure; CI = confidence interval; CRP = C-reactive protein; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; METS = metabolic equivalents; NYHA = New York Heart Association.

* Continuous variables entered per SD increase unless otherwise indicated.

ethnicity or statin use, and ethnicity with statin use. Analyses were performed in R version 3.2.1.

Results

Of the total cohort of 1,024 subjects, 401 participants (39%) died during the 10 years of this prospective study. The mean follow-up for all subjects was 7.5 ± 2.8 years. Patients were more likely to die from non-CV than CV causes (21.3% vs 16.6%, p = 0.002). Of the 401 deaths, 170 (42.4%) were classified as due to cardiovascular causes (MI, heart failure, stroke, peripheral artery disease, sudden death, severe dysrhythmia, valvular, or other causes) and 218 (54.4%) were due to noncardiovascular causes (Table 1). The 3 most common causes of cardiovascular death were sudden death (38%), heart failure (20%), and MI (14%). The 3 most common causes of noncardiovascular death were cancer (36%), pneumonia (20%), and sepsis (11%). Six deaths were determined to be of unknown cause (e.g., patient found dead in bed and more than a week since last known contact), and 7 could not be classified due to missing medical records (Figure 1). One patient was lost to follow-up.

As compared with the 623 survivors, those who died from noncardiovascular causes were older, more likely to be

Table 4
Predictors of noncardiovascular death (vs survival) in 1,010 patients with coronary heart disease

Covariate*	Age-adjusted		Multivariable-adjusted	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age (alone)	1.72 (1.49-1.99)	<0.001	1.47 (1.17-1.86)	0.001
Male	1.87 (1.19-2.95)	0.006	4.43 (1.74-11.28)	0.002
White	–	–	1.0 (reference)	–
Black	0.94 (0.62-1.43)	0.78	0.70 (0.37-1.32)	0.27
Asian	0.70 (0.45-1.11)	0.13	0.67 (0.34-1.30)	0.23
Hispanic	0.81 (0.48-1.36)	0.43	1.03 (0.53-2.00)	0.94
Other	0.99 (0.49-2.02)	0.98	0.86 (0.32-2.33)	0.77
Body mass index (kg/m^2)	0.78 (0.66-0.92)	0.003	0.84 (0.67-1.06)	0.14
Waist-to-hip ratio	1.09 (0.95-1.26)	0.20	–	–
High-school educated	0.84 (0.58-1.22)	0.35	–	–
Hypertension	1.03 (0.76-1.38)	0.87	–	–
Heart failure	1.47 (1.05-2.06)	0.03	0.85 (0.50-1.46)	0.57
Stroke	1.29 (0.90-1.86)	0.17	–	–
Diabetes	1.76 (1.33-2.35)	<0.001	1.41 (0.83-2.39)	0.20
Myocardial Infarction	1.35 (1.03-1.77)	0.03	1.15 (0.79-1.67)	0.47
Peripheral artery disease	1.90 (1.26-2.86)	0.002	1.69 (0.96-2.98)	0.07
Coronary revascularization	0.88 (0.67-1.15)	0.34	–	–
Chronic lung disease	1.21 (0.85-1.74)	0.29	–	–
Atrial fibrillation	1.34 (0.71-2.54)	0.37	–	–
Cancer	1.02 (0.93-1.11)	0.74	–	–
LV ejection fraction (%)	0.82 (0.72-0.90)	<0.001	0.93 (0.77-1.12)	0.42
Diastolic dysfunction	1.34 (0.89-2.01)	0.16	–	–
Exercise capacity (METS)	0.53 (0.44-0.64)	<0.001	0.74 (0.56-0.97)	0.03
Inducible ischemia	2.19 (1.63-2.94)	<0.001	1.83 (1.24-2.70)	0.002
Systolic BP (mm Hg)	0.99 (0.87-1.14)	0.90	–	–
Diastolic BP (mm Hg)	1.02 (0.89-1.18)	0.74	–	–
LDL cholesterol (mg/dL)	1.14 (0.99-1.30)	0.06	1.06 (0.87-1.30)	0.55
HDL cholesterol (mg/dL)	0.84 (0.73-0.97)	0.02	0.94 (0.77-1.14)	0.52
Hemoglobin (g/dL)	0.77 (0.67-0.86)	<0.001	0.96 (0.80-1.17)	0.70
Heart rate (beats/min)	1.21 (1.06-1.39)	0.004	1.22 (1.01-1.46)	0.04
NYHA Class III or IV	1.79 (1.33-2.42)	<0.001	1.14 (0.70-1.86)	0.61
Log NT pro BNP (pg/ml)	1.78 (1.54-2.06)	<0.001	1.10 (0.87-1.39)	0.42
Log CRP (mg/L)	1.36 (1.18-1.57)	<0.001	1.16 (0.95-1.41)	0.14
Glycohemoglobin (%)	1.21 (0.67-0.89)	0.005	0.97 (0.75-1.26)	0.84
Estimated GFR (ml/min)	0.60 (0.52-0.70)	<0.001	0.80 (0.63-1.02)	0.08
Log Albumin/Creatinine (mg/g)	1.41 (1.25-1.59)	<0.001	1.19 (0.98-1.44)	0.08
Current smoker	2.21 (1.56-3.11)	<0.001	1.32 (0.78-2.24)	0.31
Alcohol score	0.97 (0.72-1.30)	0.83	–	–
Physically inactive	1.48 (1.12-1.94)	0.005	1.08 (0.73-1.61)	0.70
Medication non-adherence	1.10 (0.65-1.86)	0.73	–	–
Anti-platelet	0.98 (0.72-1.33)	0.89	–	–
Statin	0.58 (0.44-0.76)	<0.001	0.65 (0.43-0.98)	0.04

BP = blood pressure; CI = confidence interval; CRP = C-reactive protein; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; METS = metabolic equivalents; NYHA = New York Heart Association.

* Continuous variables entered per SD increase unless otherwise indicated.

men and white, had lower body mass index and higher waist-hip ratios, lower diastolic blood pressure, and lower hemoglobin levels (Table 2). Noncardiovascular death was associated with a history of cancer, diabetes, coronary artery bypass grafting, peripheral artery disease, higher NT-proBNP, C-reactive protein, and hemoglobin A1C levels, and greater urine albumin-creatinine ratio. It was also associated with lower left ventricular ejection fraction and exercise capacity, as well as the occurrence of inducible ischemia, and lack of statin use.

Compared with those who died from noncardiovascular causes, participants who died from cardiovascular causes had higher body mass index and were more likely to have a history of stroke or atrial fibrillation. They also had lower left ventricular ejection fraction, higher systolic blood pressure, increased albumin-creatinine ratio, and increased NT-proBNP levels. Diastolic dysfunction and lower high-density lipoprotein levels were associated with cardiac but not with noncardiac mortality compared with survivors.

Age-adjusted predictors of both CV death and non-CV death are listed in Tables 3 and 4. In multivariate analyses, male gender, white race, peripheral artery disease, inducible myocardial ischemia, lower exercise capacity,

Table 5
Independent predictors of cardiovascular death

Covariate*	Hazard Ratio (95% CI)†	P value
Age	1.78 (1.30-2.42)	<0.001
Current smoking	2.78 (1.56-4.96)	<0.002
Inducible ischemia	2.23 (1.42-3.52)	<0.001
Heart rate	1.45 (1.14-1.85)	0.002
Hemoglobin	0.78 (0.61-1.00)	0.04
Log NT-proBNP	1.68 (1.20-2.35)	0.003

CI = confidence interval.
* Continuous variables entered per standard deviation increase.
† Hazard ratios adjusted for all variables in Table 3 multivariable model.

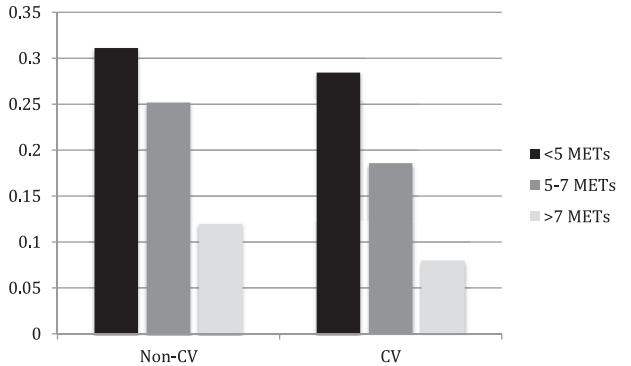

Figure 2. Proportion with death, stratified by exercise capacity. CV = cardiovascular.

and nonuse of statins were independently associated with noncardiovascular death (Table 4). Inducible ischemia, higher heart rate at rest, higher NT-proBNP level, lower hemoglobin, and current smoking were independently associated with cardiac mortality (Table 5). The effect of lower exercise capacity on mortality rates is shown in Figure 2. Patients with metabolic equivalents <5 had a 60% chance of dying from either cardiovascular or noncardiovascular disease over the 10 years of observation, whereas those with metabolic equivalents >7 had only a 20% chance of death during these 10 years. We found no evidence for interaction of age with male gender or race/ethnicity, or of race/ethnicity with age or statin use (all p for interactions >0.05). There was evidence of an interaction of age with statin use, but in stratified models, statin use was found to be protective in both older (age ≥65 years) and younger (age <65 years) patients (Table 6). Therefore, we elected to present the pooled model.

Discussion

In this study, we examined causes and predictors of cardiovascular and noncardiovascular death in 1,023 patients with CHD. During 7,680 person-years of follow-up, 401 participants died, representing an annual death rate of 5.2%. Patients were more likely to die from noncardiovascular causes (21.3%) than from cardiovascular causes (16.6%). Several predictors of cardiovascular mortality, including inducible myocardial ischemia and elevated heart rate at rest, also predicted noncardiovascular mortality. Statin use was protective against noncardiovascular mortality.

Table 6
Independent predictors of noncardiovascular death, stratified by age*

Covariate*	Hazard Ratio (95% CI)†	P value
Age	1.45 (1.22-1.73)	<0.001
Male	3.17 (1.65-6.05)	<0.001
Inducible ischemia	1.81 (1.30-2.52)	<0.001
Peripheral artery disease	1.63 (1.05-2.54)	0.03
Statin use	0.60 (0.43-0.70)	<0.001
Exercise capacity	0.56 (0.46-0.70)	<0.001

CI = confidence interval.
* Hazard ratios adjusted for all variables in Table 3 multivariable model.
† Continuous variables entered per SD increase.

The findings in this study underscore the efficacy of advances in therapy for CHD, which has allowed patients with CHD to live long enough to die from noncardiovascular causes. In a review of trials enrolling patients with a history of MI, the proportion of annual mortality attributed to noncardiac etiologies varied from 42% to 53%.[13] Studies enrolling patients in the early 1990s reported that noncardiovascular causes were responsible for 30% to 48% of deaths in patients with CHD.[14,15] More recent studies, including the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial and the Suivi d'une cohorte de patients CORONariens stables en région NORd-pas-de Calais study, found that most deaths in patients with CHD were due to noncardiovascular causes,[16,17] but patients who enroll in clinical trials tend to be healthier than the typical ambulatory patient with CHD.

The primary predictors of cardiovascular mortality were as expected from previous Heart and Soul cohort studies (age, inducible ischemia, smoking, and NT-proBNP level).[18,19] Lower hemoglobin levels were an additional predictor of cardiovascular death, as were high heart rates at rest. High heart rate at rest has been previously shown to be a risk factor for morbidity and all-cause mortality in both healthy patients and those with coronary artery disease and has been proposed as a modifiable risk factor target.[20–22] High heart rate at rest increases cardiac morbidity and mortality through promotion of atherosclerosis through pulsatile shear stress and an increase in myocardial ischemia through an imbalance of oxygen supply and demand.[21,22]

Along with a higher heart rate at rest, the primary predictors of noncardiovascular mortality were older age, male gender, statin nonuse, decreased exercise capacity, and inducible ischemia. NT-proBNP level—a strong predictor of cardiovascular death—was not associated with an increased risk of noncardiovascular death, although elevated levels of NT-proBNP have also previously been found in patients with cancer.[23] Each 1 metabolic equivalent increase in exercise capacity was associated with a 26% lower risk of death from noncardiovascular causes (hazard ratio 0.74, 95% CI 0.56 to 0.97, p = 0.03). The significance of decreased exercise capacity in predicting noncardiovascular death suggests that exercise testing can be interpreted more as a measure of overall fitness than as an evaluator of cardiovascular disease severity. Furthermore, we have shown that inducible ischemia, a well-established marker of

cardiovascular morbidity, also predicts noncardiovascular death. These results highlight an interplay between cardiovascular and noncardiovascular disease, as well as the inadequacy of using chronological age alone as a marker of morbidity in an aging population.[24]

We also observed that statin use was associated with a 35% decrease in noncardiovascular mortality. In subjects with cancer, studies have recently found that use of statins is associated with a decreased risk of prostate, hepatocellular, gastric, and esophageal cancer.[25] Two independent meta-analyses have challenged this potential benefit, finding neither increased nor decreased risk of mortality due to cancer in randomized control trials of statin use.[26,27] However, the mean follow-up time for these studies was around 4 years, which does not capture the length of time our patients were likely to have been taking statins.

Some observational studies have reported reduced mortality in patients with life-threatening infections, including pneumonia and sepsis,[28] although other studies have found no effect.[29,30] However, these studies initiated statin therapy in patients who were already ill. It is possible that long-term therapy in patients with CHD could improve mortality outcomes from subsequent serious infections.

The "healthy user effect" is a potential source of bias in studies that report protective effects of statins. In the Heart and Soul Study, patients on statins did indeed exhibit elements of the healthy user effect, as they were less likely to be current smokers ($p = 0.001$) and more likely to be adherent to medications ($p < 0.001$) than nonstatin users. However, the large protective effect of statins in our study is likely not fully explained by the healthy user effect, as statin use remained significant even when medication nonadherence and smoking were included in the multivariate model.

Our study was strengthened by comprehensive follow-up and careful adjudication of medical records for cause of death. A potential limitation to our study was a predominantly male population. The study also only adjusted for characteristics at baseline; it is likely that changes in participant characteristics over time could better predict causes of mortality.

Disclosures

The authors have no conflicts of interest to disclose.

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