Twenty-five-year cardiovascular disease incidence among middle-aged men. Disease burden, time shape, predictors, risk probabilities

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Cardiovascular diseases; Epidemiology; Risk.

Background. **This analysis aims at describing the 25-year experience in cardiovascular incidence in a sample of middle-aged men in rural Italy.**

Methods. **A total of 1712 men aged 40-59 years were examined in 1960 in two rural Italian cohorts belonging to the Seven Countries Study. Major risk factors were measured and a monitoring system for incidence of cardiovascular events was in operation for the next 25 years centered on the first event occurring within each subgroup of cardiovascular diseases. Data were modeled by the Weibull distribution incorporated in the accelerated failure time model.**

Results. **Among 1695 cardiovascular disease-free men at entry, 51.3% experienced at least one cardiovascular event, the first being a coronary heart disease (35.6%), a cerebrovascular disease (17.8%) or a peripheral artery disease (13.0%). Among all first events the most common was intermittent claudication (17.6%), followed by angina pectoris (16.6%). A proportion of 13% of all initial episodes was rapidly fatal, whereas 38% of subjects developing a cardiovascular event died within the 25-year deadline. Age, cigarette smoking, diabetes, corneal arcus, serum cholesterol, systolic blood pressure, and vital capacity fed into the accelerated failure time model showed a statistically significant association with cardiovascular disease incidence (inverse for vital capacity). The same model provided the shape of hazard during the 25 years with major events continuing to appear in an increasing exponential fashion, while soft criteria events were less likely to appear as a first event in the late phase of follow-up.**

Conclusions. **In middle-aged men 25-year incidence of cardiovascular diseases is high and more relevant compared to that of traditional hard criteria coronary heart disease that in the past has attracted almost exclusive interest.**

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Introduction

During the last few decades long-term population studies have allowed us to describe the natural history of cardiovascular diseases, including their frequency, prediction, possible causality, time occurrence, and risk probability[1].

At present there is great interest in preventive action, made possible by interventional procedures of hygienic and pharmacological nature. Some guidelines suggest estimating the multivariate probability risk for the occurrence of an event in order to select individuals carrying the highest levels of absolute risk[2,3]. Most of the so-called risk charts, however, limit their approach to coronary heart disease (CHD), neglecting the contribution to morbidity and mortality of other manifestations bound to the atherosclerotic process. This partly reflects the greater interest in prevention on the part of cardiologists, compared to other medical specialists, but also a relative lack of comprehensive information and data including other cardiovascular conditions, such as cerebrovascular diseases and peripheral artery diseases (PAD) studied in the same populations.

In principle, a comprehensive view of cardiovascular conditions bound to atherosclerosis and hypertension might represent a more rational approach towards selection of high-risk subjects for individual preventive action.

Within the Italian rural areas of the Seven Countries Study a 25-year follow-up, including a complex monitoring system for cardiovascular events, allowed us to collect data on the incidence of coronary and cerebrovascular diseases and PAD.

The purpose of this analysis was: a) to describe the comprehensive disease burden related to cardiovascular diseases of atherosclerotic-hypertensive origin in a population sample of middle-aged men followed-up for a quarter of century; b) to describe its time relationship; c) to produce predictive models as a function of some cardiovascular risk factors; d) to create a risk chart for these cardiovascular events.

Methods

Study population and data collection. In 1960, two Italian rural cohorts of men aged 40 to 59 years were enrolled and first examined within the Seven Countries Study on Cardiovascular Diseases[4]. They represented 98.8% (n = 1712) of defined samples belonging to the rural communities of Crevalcore in Northern Italy and Montegiorgio in Central Italy. Field surveys with measurement of risk factors and clinical evaluation were conducted at entry and then again every 5 years and a monitoring system was organized for the evaluation of mortality including causes of death, and incidence of cardiovascular diseases.

The material used for the analysis comprised several components, i.e. risk factors measured at entry examination, mortality and causes of death, and morbidity for non-fatal cardiovascular events over the 25 years. Mortality and morbidity were combined together to define incident cardiovascular events.

Fifteen risk factors or personal characteristics were initially considered but, after preliminary tests, only seven of them were used, on the basis of their predictive power for all cardiovascular disease manifestations considered together. They are:

• age in years, rounded off to the nearest birthday;

• right arm systolic blood pressure in mmHg, in supine position, at the end of a physical examination, measured by trained physicians, using mercury sphygmomanometers, following the procedure described in the WHO Cardiovascular Survey Methods Manual (WHO Manual)[5]; two readings, rounded off to the nearest 2 mmHg, were taken 1 min apart and averaged; diastolic blood pressure was also recorded but not used in this analysis;

• serum cholesterol in mmol/l, measured on casual blood samples using the method described by Anderson and Keys[6];

• smoking habits, elicited from a questionnaire allowing us to estimate the daily average consumption of cigarettes (n/day);

• vital capacity obtained using the best of two technically correct tests and expressed in deciliters of air; in the multivariate analysis it was expressed as deciliters of air/m^2 of height;

• corneal arcus, judged present or absent (code 1 or 0) by a physician's inspection;

• diabetes, whose diagnosis was derived from the evaluation of a medical history, the use of a specific diet and the presence of glucose in spot urine (code 1 or 0).

Data collection on vital status and mortality was complete for the 25 years and not a single subject was lost to follow-up. Causes of death were allocated reviewing and combining together information from several sources such as death certificates, hospital and medical records, interviews with physicians, relatives of the deceased and any other witness of the fatal event. Causes of death were determined by a single reviewer (AM) using the 8th Revision of the WHO-ICD[7] following defined criteria. In the presence of multiple causes a hierarchical preference was adopted with violence, cancer in advanced stage, CHD, stroke and others as mentioned in order.

Information on morbidity was obtained by the following procedures: a) *interim* quinquennial examinations including clinical history, ECG recordings and review of reported hospital or clinical records; b) information obtained in relation to causes of death as described above; c) periodic visits to local physicians and hospitals for identification of new cases; d) home visits to subjects suspected of having developed a new cardiovascular event, including medical history, physical examination and ECG recording; e) postal questionnaire and postal clinical records in a few cases.

Classification of incident cardiovascular events. Cardiovascular incident cases, corresponding to first cardiovascular events, included the following conditions, dealing with organ complication of atherosclerosis and hypertension:

• all CHD (CHD-A), manifested as sudden coronary death, definite fatal (non-sudden) myocardial infarction, non-sudden coronary death, definite non-fatal myocardial infarction, possible non-fatal myocardial infarction, angina pectoris, atypical non-fatal CHD manifested by heart failure (even initial or minor signs and symptoms) or arrhythmia;

• all cerebrovascular diseases (STR-A) manifested as fatal stroke, definite non-fatal stroke, and possible non-fatal stroke (including transient ischemic attacks);

• PAD, manifested as fatal and non-fatal PAD, including intermittent claudication and its consequences, and a few cases of aortic aneurysm.

Within CHD and cerebrovascular events, subgroups of hard manifestations were also defined as follows:

• hard criteria CHD (CHD-H), including sudden coronary death, definite fatal (non-sudden) myocardial infarction, non-sudden coronary death, definite non-fatal myocardial infarction;

• hard criteria cerebrovascular disease (STR-H), including fatal stroke and definite non-fatal stroke.

By subtraction soft criteria CHD (CHD-S) and soft criteria cerebrovascular disease (STR-S) were also considered for some analytical purposes.

Details on diagnostic criteria are reported elsewhere[8,9]. Each event was accompanied by a date.

During the 25-year follow-up, each subject could have been the target of one or more cardiovascular events. Some events, i.e. the occurrence of angina pectoris, the start of a chronic atypical CHD, or a chronic atypical cerebrovascular disease and the occurrence of intermittent claudication, were recorded only once, as well as any fatal event. All other events, such as definite and possible non-fatal myocardial infarction, non-fatal stroke and transient ischemic attacks could have been recorded more than once during the follow-up period.

For the purpose of this approach the event used for analysis, and determining the time distance from risk factor measurement, was the first ever occurred among those selected from each subgroup, independent of the possible occurrence of subsequent events of any type, even the fatal ones.

Baseline data were collected in the 1960's before the era of the Helsinki Declaration. Subsequently, oral informed consent was obtained in view of collecting follow-up data.

Statistical analysis. Data on baseline mean levels were descriptively reported as means and standard deviations.

Data on all-cause mortality (and some specific causes) were computed per 1000 over the 25 years.

First cardiovascular events, variously grouped, were computed as frequencies over the 25 years. Events were counted one by one (for each typology) and then in combination within the various groups, i.e. CHD-A, STR-A, PAD and cardiovascular disease, and separately for CHD-H and STR-H.

Multivariate analysis was based on a log-linear model incorporating the Weibull distribution, usually called accelerated failure time (AFT) model which has the advantage of providing a parameter which describes the shape of the hazard over time. The ATF model corresponds to the following formula:

$$p = 1- exp \{- exp[(ln (t) - (a+b_1x_1+ b_2x_2+ ... b_nx_n))/s]\}$$

where p is the probability to develop an event within time t; $ln (t)$ is the natural log of time elapsed between risk factor measurement and event (or censoring); a is a constant estimated by the model; b_1 , b_2 , b_n are coefficients estimated by the model for risk factors x_1 , x_2, x_n; s is a scale factor estimated by the model.

A peculiarity of the AFT model is that time is an explicit variable corresponding to the role of a risk factor. Moreover the algebraic sign of the coefficients is inverse, compared to the logistic or Cox models. This means that a factor whose coefficient has a positive sign is inversely associated with the event; in contrast a factor whose coefficient has a negative sign is directly associated, since a shorter time between risk factor measurement and events means an acceleration towards the occurrence of the disease.

Solutions of the AFT model were produced for CHD-A, STR-A, PAD events, CHD-H, STR-H and all cardiovascular events together. Hazard ratios and their confidence limits for arbitrary levels of differences in risk factor levels were computed and reported only for the solution of all cardiovascular events.

Solutions of the several models were used to construct curves describing the time shape of the hazard. This means that the hazards (the instantaneous annual probability of an event for a man carrying the mean levels of the 7 risk factors) were cumulated over the 25 years providing the time shape.

Results

Baseline risk factor levels. They are reported, for reference, in table I in terms of means and standard deviations. They were among the only ones available in the country in that period. These levels are different from those recorded in other Italian studies carried out in the 1980's and 1990's[10,11].

Table I. Mean levels of seven cardiovascular risk factors at baseline in the study population.

Age (years)	49.8 ± 5.1
Cigarettes (n/day)	8.7 ± 9.5
Diabetes (%)	4.8
Corneal arcus (%)	13.9
Vital capacity (dl)	45.7 ± 8.0
Cholesterol (mmol/l)	5.21 ± 1.06
Systolic blood pressure (mmHg)	143.6 ± 21.0

All-cause mortality. Over the 25 years, all-cause death rate per 1000 was 483. Rates per 1000 for subgroups of causes were as follows: 126 for CHD, 62 for stroke, 8 for PAD, 9 for other heart diseases, 24 for lung cancer, 126 for other cancer locations, 21 for chronic bronchitis, 8 for infectious diseases, 25 for violence, and 75 for all other causes.

Disease frequency and burden. After exclusion of a few subjects with cardiovascular diseases at entry examination, 1695 remained exposed to risk. Table II provides the frequency of events recorded over the 25 years, listed one by one (each independent of the other) and in groups. In the latter cases the first event only is recorded.

When each single event is listed independently, non-fatal definite artery disease, angina pectoris, and non-fatal definite stroke are those occurring more frequently.

In the area of CHD-H the most common manifestation was non-fatal definite myocardial infarction.

When CHD-A were selected, the most common first event was the occurrence of angina pectoris, followed by non-fatal atypical CHD and non-fatal possible and definite myocardial infarction.

In the area of STR-H the most common manifestation was non-fatal definite stroke.

Table II. Type of clinical manifestations occurring as first event in different groups of cardiovascular diseases.

Clinical manifestation	Absolute independent frequency	First CHD-H event	First STR-H event	First CHD-A event	First STR-A event	First PAD event	First CVD event
Coronary heart disease							
Non-fatal angina pectoris	205 (13.7%)	–	–	157 (26.0%)	–	–	144 (16.6%)
Non-fatal possible myocardial infarction	150 (10.0%)	–	–	104 (17.2%)	–	–	92 (10.6%)
Non-fatal definite myocardial infarction	155 (10.3%)	155 (47.8%)	–	101 (16.7%)	–	–	90 (10.3%)
Non-fatal atypical coronary heart disease	176 (11.7%)	–	–	132 (21.9%)	–	–	112 (12.9%)
Fatal myocardial infarction	93 (6.2%)	62 (19.1%)	–	46 (7.6%)	–	–	34 (3.9%)
Sudden coronary death	45 (3.0%)	43 (13.3%)	–	28 (4.6%)	–	–	23 (2.6%)
Fatal atypical coronary heart disease	72 (4.8%)	64 (19.8%)	–	35 (5.8%)	–	–	25 (2.9%)
Cerebrovascular disease							
Non-fatal TIA	78 (5.2%)	–	–	–	73 (24.2%)	–	51 (5.9%)
Non-fatal definite stroke	201 (13.4%)	–	205 (83.0%)	–	186 (61.8%)	–	112 (12.9%)
Fatal stroke	102 (6.8%)	–	42 (17.0%)	–	42 (14.0%)	–	29 (3.3%)
Peripheral artery disease							
Non-fatal definite artery disease	212 (14.1%)	–	–	–	–	212 (96.4%)	153 (17.6%)
Fatal artery disease	12 (0.8%)	–	–	–	–	8 (3.6%)	5 (0.6%)
Total	1501	324	247	603	301	220	870
Crude incidence per 1000	–	191	146	356	178	130	513

CHD-A = coronary heart disease, all criteria; CHD-H= coronary heart disease, hard criteria; CVD = cardiovascular diseases, all events; PAD = peripheral artery disease; STR-A = cerebrovascular disease, all criteria; STR-H = cerebrovascular disease, hard criteria; TIA = transient ischemic attack.

When the selection dealt with STR-A, definite non-fatal stroke was again the most common first event.

In the area of PAD, non-fatal definite artery disease (intermittent claudication) was the most common manifestation.

When all cardiovascular events were pooled together, the most common first event was represented by intermittent claudication, followed by angina pectoris and non-fatal atypical CHD.

Altogether 870 men out of 1695 had at least one cardiovascular event in the 25 years (first cardiovascular event), corresponding to an incidence of 51.3%. All possible events, as classified above, were 1501. Therefore, the average number of events for each subject was 1.73 among middle-aged men who showed any cardiovascular disease manifestation during the 25 years, whereas 825 (48.7%) remained free from cardiovascular events during the same period of time.

Crude incidence per 1000 over the 25 years (referred to first events) is given on the bottom line of table II showing the dominant role of CHD. In that period of time more than one third developed any CHD manifestation, a little less than one fifth developed a cerebrovascular disease while, overall, 51.3% had at least one episode of a cardiovascular disease manifestation.

After the 25 years 214 subjects died from a CHD, 105 from a cerebrovascular disease, and 14 from a PAD covering 41% of all-cause mortality and representing 38% of those who developed any cardiovascular disease manifestation.

Multivariate models. Models were solved with the 7 risk factors mentioned above, corresponding to those exhibiting statistically significant coefficients in the prediction of all cardiovascular diseases. There were 1582 subjects with all risk factors available; over the 25 years there were 774 cardiovascular events; 326 subjects died from other causes; there were 482 healthy survivors.

Six models were produced, one for each of the six end-points described above (Table III). Risk factors with statistically significant coefficients were age, and systolic blood pressure for all the considered end-points; cigarette smoking for all end-points except STR-A; diabetes for all end-points, except the two CHD end-points; corneal arcus for the two CHD end-points and all cardiovascular diseases; vital capacity for STR-A, CHD-H, and cardiovascular diseases; cholesterol for all end-points except the two stroke end-points. As expected, the magnitude of coefficients was larger for hard end-points compared to the others.

Hazard ratios derived from the model of cardiovascular disease for arbitrary levels of each risk factor (roughly corresponding to one standard deviation) are reported in table IV. All of them have narrow confidence intervals that do not include 1. Relatively simple alge-

Table III. Solutions of the accelerated failure time model for the prediction of first events as a function of seven risk factors.

Risk factor	CHD-H		CHD-A		STR-H		STR-A		PAD		CVD	
	Coefficient	T value	Coefficient	T value	Coefficient	T value	Coefficient	T value	Coefficient	T value	Coefficient	T value
Age	-0.0308	-3.69	-0.0281	-3.63	-0.0471	-5.17	-0.0471	-5.55	-0.0450	-3.27	-0.0401	-6.42
Cigarettes	-0.0101	-2.60	-0.0070	-1.89	-0.0038	-0.89	-0.0041	-1.02	-0.0276	-4.45	-0.0115	-3.95
Diabetes	-0.1231	-0.74	-0.2299	-1.45	-0.2066	-1.26	-0.3155	-2.16	-0.1000	-0.35	-0.3024	-2.47
Corneal arcus	-0.2509	-2.54	-0.2427	-2.44	-0.0980	-0.90	-0.0948	-0.92	-0.0671	-0.38	-0.1727	-2.15
Vital capacity	0.0485	2.86	0.0169	1.06	0.0567	3.18	0.0359	2.15	0.0272	0.98	0.0270	2.13
Cholesterol	-0.1431	-4.04	-0.1083	-3.22	-0.0387	-0.96	-0.0193	-0.51	-0.1392	-2.39	-0.0773	-2.92
SBP	-0.0082	-4.51	-0.0071	-3.86	-0.0093	-4.94	-0.0085	-4.64	-0.0064	-2.02	-0.0073	-4.94
Constant	9.4916	15.00	9.1350	15.59	9.8134	14.28	9.8297	15.35	11.0683	10.53	9.0710	19.54
Scale	0.6400	18.88	0.8294	25.68	0.5653	16.01	0.6074	18.24	0.8828	15.38	0.7949	31.67

SBP = systolic blood pressure. Other abbreviations as in table II.

Table IV. Hazard ratios for arbitrary amounts of differences in risk factor levels for the solution of the accelerated failure time model for cardiovascular diseases.

Risk factor	Delta for hazard ratio	Hazard ratio	95% CI
Age (years)	5	1.29	1.19-1.39
Cigarettes (n/day)	10	1.16	1.08-1.24
Diabetes	Yes - No	1.46	1.08-1.98
Corneal arcus	Yes - No	1.24	1.02-1.51
Vital capacity (dl/m^2)	2.5	0.92	0.85-0.99
Cholesterol (mmol/l)	1	1.11	1.03-1.18
SBP (mmHg)	20	1.20	1.12-1.29

CI = confidence interval; SBP = systolic blood pressure.

braic computations based on the AFT model formula allowed us to produce rough estimates of the impact of high levels of risk factor on cardiovascular disease incidence. For example an excess of 10 cigarettes per day, together with 1 mmol/l of cholesterol and 20 mmHg of systolic blood pressure corresponds to an excess risk of about 55%. The presence of diabetes alone, everything else being equal, produces an excess risk of 46%.

Time shape of cardiovascular diseases. The solutions of the AFT model were used to construct curves describing the time shape for the occurrence of the several disease manifestations. They relate, if not differently stated, to the instantaneous (yearly) cumulative risk over time for a subject with the average risk factor levels.

Figure 1 reports curves for CHD-A, STR-A, PAD and cardiovascular diseases, the latter representing the combination of the first three. The curves for the three basic conditions grow regularly over time with a similar shape but different levels, with CHD-A at a higher level, and STR-A and PAD at lower similar levels. However, the shape for STR-A tends to rise more steeply during the last few years of follow-up, while the other curves tend to slightly reduce their relative increase over time.

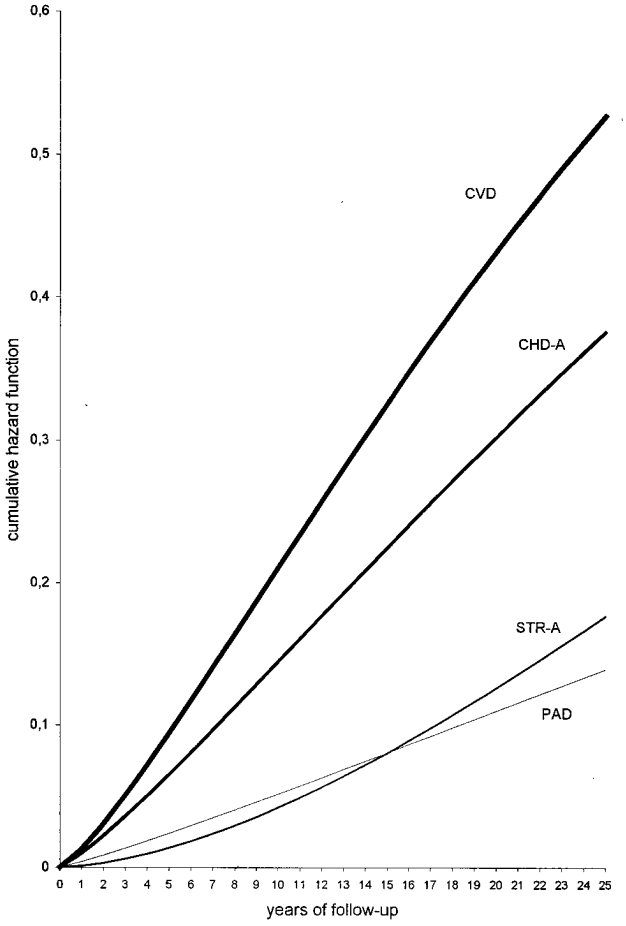

Figure 1. *Time shape of cumulated hazard for first cardiovascular event risk over the 25 years, following the Weibull distribution modeling. CHD-A = coronary heart disease, all cases; CVD = cardiovascular diseases, all cases; PAD = peripheral artery disease, all cases; STR-A = cerebrovascular accidents, all cases.*

In figure 2, curves for CHD and stroke have been split into subgroups of hard and soft events (again manifesting as first events). For both CHD-H and STR-H, curves tend to increase over time in an exponential fashion suggesting that hard events accelerate their occurrence during the late years of follow-up. Conversely, soft events are less likely to appear as a first manifestation of either CHD

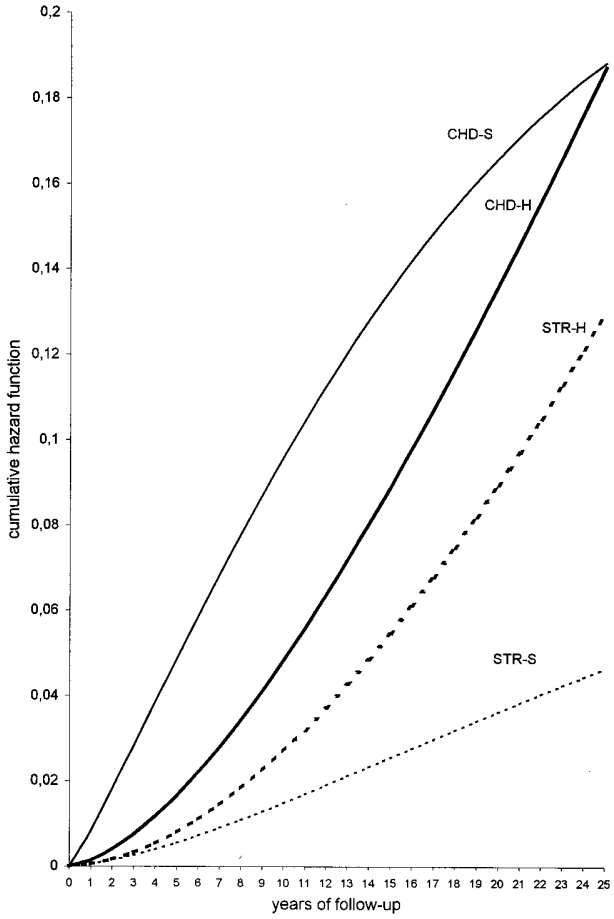

Figure 2. *Time shape of cumulated hazard for first cardiovascular event risk over the 25 years, following the Weibull distribution modeling. CHD-H = coronary heart disease, hard criteria; CHD-S = coronary heart disease, soft criteria; STR-H = cerebrovascular accidents, hard criteria; STR-S = cerebrovascular accidents, soft criteria.*

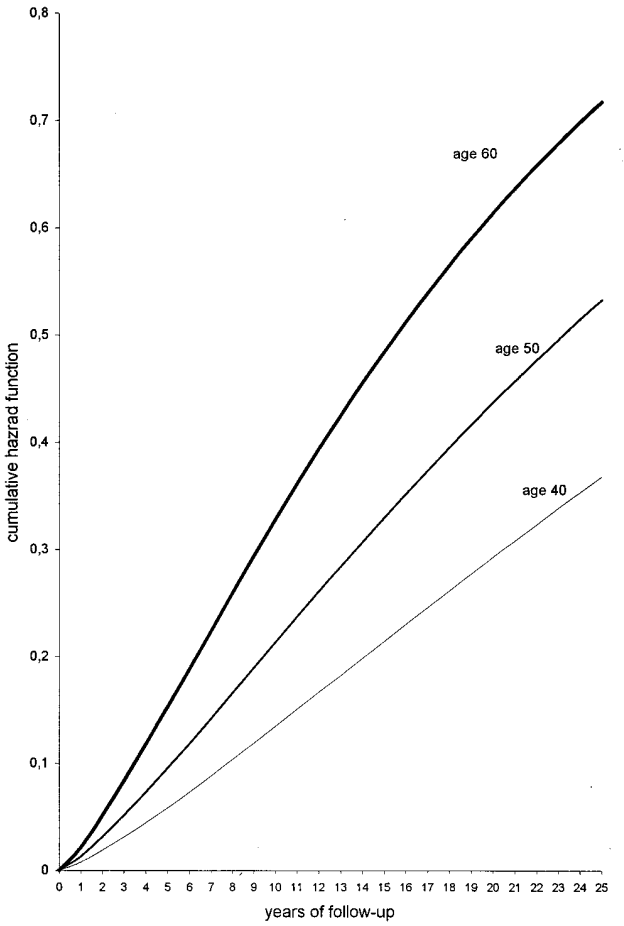

Figure 3. *Time shape of cumulated hazard for cardiovascular diseases in subjects with different ages and average levels of other risk factors.*

or cerebrovascular disease in the late years of follow-up, corresponding to older ages.

The impact of age on cardiovascular disease incidence in subjects carrying average levels of risk factors is shown in figure 3. Levels of hazard after the 25 years reach more than 0.7 if starting at age 60, about 0.5 when starting at age 50, and about 0.35 when starting at age 40. However, the acceleration of the hazard tends to decline in late years when starting from age 60.

The impact of combinations of risk factor levels is shown in figure 4. The hypothetical subjects are always aged 50 years and have an average level of vital capacity. The low risk subject is a non-smoker and non-diabetic, he does not have a corneal arcus, and has serum cholesterol levels of 4.65 mmol/l (180 mg/dl), and a systolic blood pressure of 120 mmHg. The medium risk subject is a non-diabetic and does not have a corneal arcus, but smokes 10 cigarettes per day, and has serum cholesterol levels of 5.70 mmol/l (220 mg/dl), and a systolic blood pressure of 140 mmHg. The high risk subject smokes 20 cigarettes per day, is diabetic, has a corneal arcus and has cholesterol levels of 6.70 mmol/l (260 mg/dl), and a systolic blood pressure of 160 mmHg. The three derived curves are largely distinct. The hazards for the low and medium risk subjects tend to grow regularly during the 25 years until levels of almost 40 and 50%; while the hazards for the high risk subjects tend to reduce its acceleration over time but reach very high cumulative levels of almost 90%. This means that the risk profile of a 50-year-old man with those characteristics corresponds to an almost sure occurrence of a cardiovascular event in the next 25 years.

Risk chart for all cardiovascular diseases. A risk chart was produced for the entire burden of cardiovascular diseases based on the solution of the AFT model for cardiovascular diseases. Only coefficients for age, systolic blood pressure, serum cholesterol, smoking habits and diabetes were employed, everything else being kept constant. This ensures a simple reading of the chart, whose structure is similar to those reported in the guidelines of the European Task Force for Prevention[2,3]. Two sections are reported, one for non-diabetic and one for diabetic men (Tables V and VI). This chart offers absolute risk probabilities related to the occurrence of any cardiovascular event over the 25 years among men

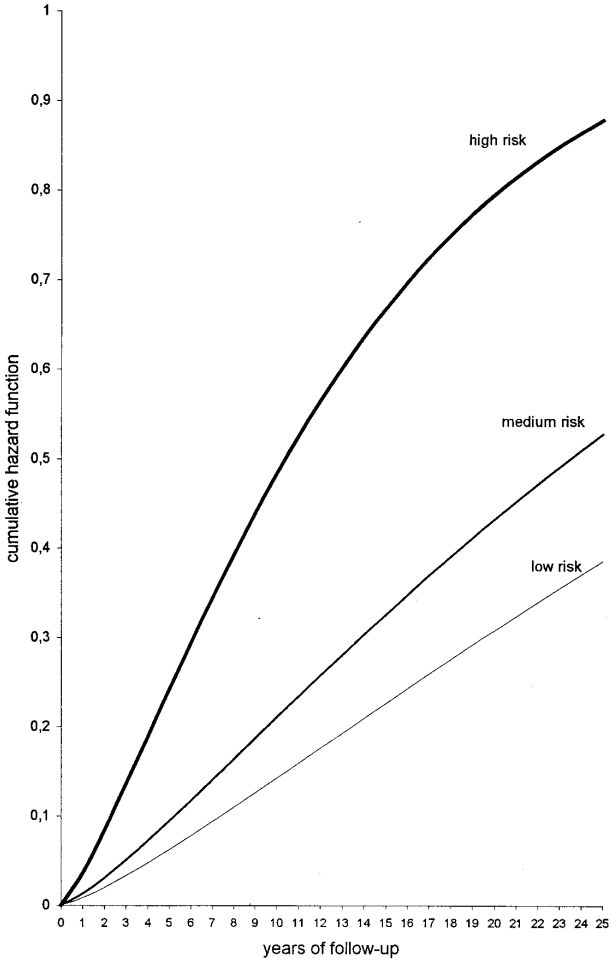

Figure 4. *Time shape of cumulated hazard for cardiovascular diseases in subjects aged 50 years at entry and with arbitrary levels of other risk factors as follows: low risk = cigarettes 0; diabetes, absent; corneal arcus, absent; vital capacity, average; cholesterol, 4.65 mmol/l (180 mg/dl); systolic blood pressure, 120 mmHg; medium risk = cigarettes 10; diabetes, absent; corneal arcus, absent; vital capacity, average; cholesterol, 5.70 mmol/l (220 mg/dl); systolic blood pressure, 140 mmHg; high risk = cigarettes 20; diabetes, present; corneal arcus, present; vital capacity, average; cholesterol, 6.70 mmol/l (260 mg/dl); systolic blood pressure, 160 mmHg.*

initially aged 40, 50 or 60 years. On the whole all probabilities are high since, in the cell with the best outcome (age 40, no smoking, no diabetes, systolic blood pressure of 120 mmHg, and serum cholesterol of 4 mmol/l) they are around 25%. Regularly increasing gradients are seen when moving from age 40 to 60, from low to high levels of systolic blood pressure and from low to high serum cholesterol levels. Systematic differences in risk are seen between smokers and non-smokers and between diabetics and non-diabetics with ratios between the two of about 1.5.

Among men aged 60, all cells show probabilities greater than 500 per 1000 (50%), with extremes over 90% among subjects who are smokers and diabetics and have high levels of cholesterol and blood pressure.

The relative risk computed between extreme cells is of about 4 on the chart for the non-diabetics and about 3 on the chart for the diabetics.

Discussion

This analysis deals with cardiovascular disease in initially healthy middle-aged men followed up for a quarter of century. The age range of 40 to 59 years at the beginning corresponded to 65-84 years at the end of follow-up.

For the fist time in this study, we included in the analysis cerebrovascular disease and PAD events together with CHD, which has been the most analyzed in the past in this as well as in other similar studies. The burden derived by combining different manifestations of the atherosclerotic process leading to different organ complications is remarkable since more than 50% of men experienced at least one event during the 25-year follow-up, and 38% of them died from one or another of the three major conditions, that is coronary, cerebrovascular or peripheral artery disease. The proportion of deaths could be considered high since it covers more than 40% of all deaths in the same period of time, or relatively low since less than two fifths of subjects starting with a history of a cardiovascular disease ended up with death during the same period of time. The fact is that fatality rates, figures to which physicians are accustomed, usually relate only to very severe disease manifestations such as an acute myocardial infarction. Moreover some of the minor manifestations reported here may suffer from limited specificity and diagnostic uncertainties due to the fieldwork conditions operating some decades ago. In any case the first event of CHD was fatal in 18% of cases; similarly, the first event of cerebrovascular disease was fatal in 14% of cases, and the first for any cardiovascular disease manifestation was rapidly fatal in 13% of cases.

Altogether 51.3% of cardiovascular disease incidence over the 25 years cannot be claimed as high or low since there are not comparable data available in the literature.

In determining the burden of the first cardiovascular event the role of age is fundamental as shown in figure 3. Ageing has a role also on the type of manifestations since the curves on figure 2 show that CHD-H and STR-H continue to appear at an exponentially increasing rate suggesting, by comparison with curves of soft events, that relatively minor components, such as angina pectoris, become less likely to represent the start of a disease process in late years.

The fact that PAD is the most common first manifestation of a cardiovascular disease was a surprise, but we are not aware of other studies that have taken this condition into account analyzed in the context of the time appearance together with other cardiovascular conditions. However the rate of appearance of angina pectoris, as representative of CHD, was not significantly different from that of PAD.

The prognosis of the PAD condition does not seem particularly severe by itself, but the overlapping with other major cardiovascular events largely confounds the judgment. During the 25-year follow-up there was no decline in the hazard of the PAD appearance when con-

Table V. Risk of cardiovascular disease events per 1000 over the 25 years in non-diabetic men aged 40, 50 and 60 years, as a function of four other risk factors.

SBP (mmHg)	Cholesterol (mmol/l)									
	Non-smokers					Smokers				
	4	5	6	7	8	4	5	6	7	8
Age 60 years										
180	746	781	813	843	871	818	848	876	900	922
160	681	717	752	786	819	758	792	823	853	880
140	613	650	687	723	758	693	729	764	797	829
120	546	583	620	657	693	625	662	699	735	770
Age 50 years										
180	563	600	637	674	710	643	679	716	751	785
160	498	533	569	606	643	575	612	649	686	722
140	436	470	504	540	576	510	545	582	618	656
120	379	410	442	476	510	447	481	516	552	588
Age 40 years										
180	393	425	457	491	527	463	470	532	568	605
160	340	369	399	430	463	404	435	469	503	538
140	293	318	345	374	404	350	379	409	441	475
120	250	273	297	322	350	301	327	354	383	415

SBP = systolic blood pressure.

Table VI. Risk of cardiovascular disease events per 1000 over the 25 years in diabetic men aged 40, 50 and 60 years, as a function of four other risk factors.

SBP (mmHg)	Cholesterol (mmol/l)									
	Non-smokers					Smokers				
	4	5	6	7	8	4	5	6	7	8
Age 60 years										
180	866	891	914	934	950	917	936	953	966	976
160	812	842	870	895	918	874	899	921	939	955
140	751	785	817	847	875	822	852	879	903	924
120	685	722	757	791	823	762	796	827	857	883
Age 50 years										
180	702	738	773	806	837	778	810	841	869	895
160	635	672	709	744	779	714	750	784	816	846
140	568	605	641	678	715	647	684	720	756	790
120	503	538	574	611	648	580	617	654	690	727
Age 40 years										
180	519	555	591	628	665	597	634	671	707	743
160	456	490	525	561	598	531	567	603	640	677
140	397	429	462	496	531	467	501	537	573	610
120	344	373	403	435	468	408	440	473	508	543

SBP = systolic blood pressure.

sidered alone, independently of other cardiovascular diseases since the hazard curve seems to proceed in a straight fashion.

The predictive role of a small set of risk factors is that expected from previous similar analyses on the same material centered on CHD[12,13], but for the first time all cardiovascular disease manifestations were considered together for this purpose. Tables III and IV reveal that their predictive role is not very strong, but again minor and perhaps poorly specific diagnoses are included determining a dilution in the predictive power of these factors. On the other hand a combination of high levels of some of them, such as in the curve called “high risk” in figure 4, is still associated with a markedly increased risk for the occurrence of any cardiovascular event during the 25-year follow-up.

The structure of the risk chart, which for the moment is not proposed for practical use, is the same as those provided by the Second Joint Task Force of the European and other Societies on Coronary Prevention[2,3]. The basic differences are the wider range of end-points, represented by all possible cardiovascular disease events of an atherosclerotic-hypertensive nature and a dilution in the discriminating power of classical risk factors bound to the presence of soft, sometimes uncertain, events. However it reflects the outcome in terms of all cardiovascular disease incidence and risk in middle-aged men followed up for 25 years.

There are rare examples of information of this type from other population studies. Recently a comprehensive review has been published on the lifetime risk of developing a CHD in the Framingham study, covering both genders, ages from 40 to 90, for a total of over 100 000 person/year[14]. The lifetime risk of CHD ranged from 48.6% for men to 31.7% for women starting at age 40, and 34.9% and 24.2% respectively starting at age 70. After the exclusion of isolated angina pectoris as an initial event, the lifetime risk was 42.4% for men and 24.9% for women. These data can hardly compare with ours because our follow-up was much shorter, age range more restricted and no women were studied. The only figure of reference in our data is the risk of 19.1% for CHD-H events in men starting around the age of 50 and followed up for 25 years. From this figure one may cautiously conclude that there is a smaller incidence in CHD-H events in our population compared with the Framingham one, similar to what we have recently reported comparing Northern and Southern European cohorts of the Seven Countries Study[15]. This fact deserves scrutiny where differently derived charts are implemented or used with the aim at identifying high risk individuals for preventive action.

What really matters, from this experience, is the marked increase in the incidence of cardiovascular diseases when moving from CHD-H, which in the past has attracted an almost exclusive interest, to the comprehensive consideration of all possible manifestations of organ complication of the atherosclerotic and hypertensive conditions. From a clinical point of view this reminds us that the cardiovascular risk to which middle-aged men are exposed is not confined to hard CHD events but is much greater when considering also anatomically different or less severe manifestations of atherosclerosis.

Therefore a valuable public health effort in the direction of primary and even secondary prevention should also include attention to manifestations other than acute myocardial infarction and allied conditions although basically the same risk factors are implied.

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