The risk functions incorporated in Riscard 2002: a software for the prediction of cardiovascular risk in the general population based on Italian data

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Coronary heart disease; Epidemiology; Prevention; Risk factors.

Background. **The purpose of this analysis was to produce risk functions for the prediction of cardiovascular diseases based on Italian epidemiological data and suitable for the use in a PC program dedicated to the estimate of risk.**

Methods. **Three studies were used for the purpose: the Italian Rural Areas of the Seven Countries Study, the Gubbio Population Study and the ECCIS study, for a total of 9771 men and women aged 35 to 74 years and followed for a period lasting 5 to 6 years. The risk factors used for the prediction of cardiovascular events were sex, age, body mass index (derived from height and weight), mean blood pressure (derived from systolic and diastolic blood pressures), non-HDL cholesterol (derived from total and HDL cholesterol), HDL cholesterol, diabetes (yes-no), heart rate, and daily cigarette consumption. The endpoints were the first major coronary event, the first major cerebrovascular event, and the first major cardiovascular event (either one between the previous two plus major peripheral artery diseases). The model employed for the analysis was the accelerated failure time model.**

Results. **Having excluded those already presenting with a cardiovascular disease and those with missing values, a total of 9089 subjects were included in the models. In a period lasting 5 or 6 years, a total of 211 coronary, 64 cerebrovascular and 269 cardiovascular events occurred and were considered for analysis. Coefficients from the coronary model suggested a significant association of all risk factors except body mass index and diabetes (marginal significance). Coefficients from the cerebrovascular model suggested a significant association limited to age and mean blood pressure. Coefficients from the cardiovascular model suggested a significant association of all risk factors except body mass index. The discrimination between cases and non-cases was satisfactory with proportions of 37.0, 52.3 and 37.8% of observed cases in decile 10 of the distribution of the estimated risk for the three endpoints respectively.**

Conclusions. **The three models were used as a mathematical core for the construction of a PC software for the prediction of major cardiovascular events in Italy.**

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Introduction

During the last decade, physicians and cardiologists have become increasingly interested in the prevention of coronary and cardiovascular disease and in the use of practical tools for the probabilistic prediction of cardiovascular events[1-17].

On the other hand, it was definitely shown that tools based on risk functions derived from studies including Northern European and Northern American populations could not be properly used in Southern Europe and in Italy in particular. In fact, everything else being equal, they systematically over-predict the risk[18-21].

This prompted the need to produce, on the basis of national studies, practical tools for the primary prediction of cardiovascular diseases. The first of such tools was published in 1980[22], others were created between 1998 and 2001[23-26].

The latest tool created in this field is an interactive software called Riscard 2002, which derives from the same population studies and experience which have allowed the production of a chart for the estimate of cardiovascular risk[25,26]. Details on the chart and on the study populations from which it derived have already been published[26].

This report describes the innovative difference between the principles and procedures used for the elaboration of that chart and those employed for the construction of Riscard 2002.

Methods

Available material. The material available for the production of the models derived from three Italian population-based epidemiological studies. These were:
1) the Italian Rural Areas (IRA) of the Seven Countries Study, including 1712 male residents of the rural village of Crevalcore, Northern Italy, and of Montegiorgio, Central Italy, aged 40 to 59 years at the time of the initial evaluation and with an available follow-up lasting up to 25 years[27-29];
2) the Gubbio Population Study, run in the medieval town of Gubbio in Central Italy, where the available subgroup of the population with the required characteristics for the production of the predictive model, consisted of 3061 men and women aged 35 to 74 years and followed up for 6 years[30];
3) the ECCIS study (Epidemiology and Clinics of Silent Ischemic Heart Disease) run in occupational groups of Rome and Florence and including 4998 men aged 40 to 59 years and followed up for 5 years[31].

A total of 9771 subjects were thus enrolled and available for evaluation. Detailed information on the structure of these studies together with a description of the follow-up process can be found elsewhere[27-31].

The study of the IRA cohorts of the Seven Countries was started long before the era of the Helsinki declaration. Only after the initial examination, informed oral consent was obtained from all subjects. Informed oral consent was also obtained from all participants of the Gubbio and the ECCIS studies. The follow-up for the collection of data used in the present analysis was completed at the beginning of 1997.

Measurements. The risk factors used for the production of the predictive models were the following:
- sex, coded as female or male (0-1);
- age, in years, expressed as the difference between the year of examination and the year of birth;
- body mass index (i.e. weight in kg/height in m^2, derived from the measurement of the height and weight performed according to the rules given in the WHO Cardiovascular Survey Manual[32]);
- mean blood pressure, in mmHg, given by diastolic + 1/3 of (systolic - diastolic) based on measurements taken following the measurement technique described in the WHO Cardiovascular Survey Manual[32];
- non-HDL serum cholesterol obtained by computing the difference between total cholesterol and HDL cholesterol and expressed in mg/dl and mmol/l[33-36];
- HDL cholesterol expressed in mg/dl and mmol/l[36];
- diabetes, coded as absent or present as inferred from a diagnosis based on a history of known diabetes under medical treatment;
- smoking habits, expressed as the average number of cigarettes currently smoked per day, as derived from a questionnaire;
- heart rate, expressed in b/min derived in the IRA population from the resting ECG by averaging heart rates in lead I and lead V_6 whereas in the other two studies it was derived from the pulse count.

Since HDL cholesterol was not available in one cohort (IRA) corresponding to about 18% of the total population, it was decided to impute the unmeasured values using a regression equation computed from the other two populations and in which the HDL cholesterol was considered as a dependent variable and all the other risk factors as independent variables. Before proceeding with the production of risk functions including the imputed HDL cholesterol values, the following tests were made:
• solutions were computed for each endpoint, using the total cholesterol (together with the other variables, but excluding HDL cholesterol) separately for the IRA group and the pool of the other two groups; tests between each pair of coefficients for all risk factors did not show any statistically significant difference;
• solutions were computed for each endpoint using the imputed HDL cholesterol levels (and correspondingly the non-HDL cholesterol values) for the IRA group. Similar solutions were employed for the pool of the other two groups using their own original HDL cholesterol values, and correspondingly the non-HDL cholesterol levels; tests between each pair of coefficients for all risk factors did not show any statistically significant difference.

Compared to the risk chart[28,29], the models included non-HDL and HDL cholesterol levels (instead of total cholesterol), mean blood pressure (instead of systolic blood pressure), and heart rate (not used in the chart).

Endpoints. Three different endpoints were considered for the production of this software. They included hard criteria coronary heart disease (CHD) events, hard criteria cerebrovascular disease events and hard criteria cardiovascular events. In the risk chart, only a pool of major coronary or cerebrovascular events was considered as endpoint.

The first event occurring within its own category during the follow-up observation period was used as the index event independently of the occurrence of subsequent events.

Hard criteria CHD and cerebrovascular events were already defined for the production of the risk chart[25,26]; hard criteria cardiovascular events included any of the above hard criteria coronary or cerebrovascular events, or major peripheral artery disease manifested as fatal peripheral artery disease, or as fatal or non-fatal gangrene of the extremities, or as fatal or non-fatal aneurysm of the aorta in any anatomical site, or as sur-

gical procedures for aortic aneurysm or for lower limb artery disease, or as any other fatal cardiovascular event attributed to arteriosclerosis.

The diagnostic criteria for the definition of the above manifestations are reported elsewhere for the IRA[27-29] and Gubbio Population studies[30], while those of the ECCIS study were coherently re-coded.

Deaths were coded by a single investigator (A.M.) following the 8th revision of the WHO-ICD[37] for the IRA study, and the 9th revision for the other two studies[38]. The relevant cardiovascular codes were then homogenized to make them coherent. Causes of death were allocated by reviewing and combining the information derived from death certificates, hospital and medical records, interviews with physicians and relatives of the deceased, and with any other witness of the fatal event. In the presence of multiple causes, a hierarchical preference was adopted with violence, cancer in advanced stages, CHD, stroke, and others in that order.

Subjects with cardiovascular diseases at the beginning of the follow-up period were excluded.

Deaths other than the specific ones considered in each model were treated as censored cases.

The statistical model and its management. The analysis was based on the use of the log-linear model incorporating the Weibull distribution of hazard, usually designated as accelerated failure time model[39,40].

The decision was taken to use a follow-up of 5 years instead of the 10-year period considered by many tools including the risk chart based on the same populations[25,26] in view of two considerations: from a cultural point of view it was felt that the notion of a strong preventive action on cardiovascular events based on individual treatments became evident in the 1990's as inferable from trials whose duration always approximated 5 years[41], and this was part of the message that reached physicians all over the world. Moreover, some experts in the field have suggested that a 5-year period may better motivate both subjects and physicians since the deadline for a possible event is closer[42,43].

Results

Table I shows that, in general, the mean levels of risk factors are, in the IRA group, higher for blood pressure and lower for total cholesterol as compared with the other studies, at least for men. The other factors did not differ too much among the studies except for a slightly smaller cigarette consumption in the ECCIS population and a higher prevalence of diabetes in the Gubbio population.

After exclusion of subjects with prevalent cardiovascular diseases and with missing data, 9089 subjects were available for the solution of the multivariate models, with a total of 211 first major coronary events, 64 first major cerebrovascular events, and 269 first major cardiovascular events.

The three models adopted for the prediction of hard criteria CHD, stroke and cardiovascular diseases are reported in tables II, III and IV respectively, together with the correspondent hazard ratios (for arbitrary differences in risk factor levels) and their 95% confidence intervals. In the model for CHD (Table II) all coefficients show a direct association with risk, except that for HDL cholesterol. All the correspondent hazard ratios have 95% confidence intervals not including 1, except those for body mass index and diabetes.

In the model for stroke (Table III) all coefficients are directly associated with risk except those for body

Table I. General characteristics and risk factors in the three study populations.

General characteristics and risk factors	Population groups			
	IRA men	Gubbio men	Gubbio women	ECCIS men
No. enrolled	1712	1361	1700	4998
No. used for analysis	1598	1300	1651	4576
Age range (years)	40-59	35-74	35-74	40-59
Age (years)	49.8 ± 5.1	53.6 ± 11.2	55.0 ± 11.0	49.6 ± 5.5
Body mass index (kg/m^2)	25.2 ± 3.7	27.1 ± 3.6	27.5 ± 4.7	25.9 ± 3.1
Systolic blood pressure (mmHg)	143.6 ± 21.0	135.2 ± 21.3	139.0 ± 24.1	130.9 ± 18.2
Diastolic blood pressure (mmHg)	85.4 ± 11.2	80.3 ± 10.6	79.9 ± 11.5	85.5 ± 10.4
Total cholesterol (mmol/l)	5.21 ± 1.06	5.66 ± 1.10	5.72 ± 1.09	5.83 ± 1.06
Total cholesterol (mg/dl)	201.6 ± 41.2	219.0 ± 42.7	221.3 ± 42.3	225.4 ± 40.9
HDL cholesterol (mmol/l)	1.20 ± 0.09	1.12 ± 0.29	1.31 ± 0.31	1.23 ± 0.32
HDL cholesterol (mg/dl)	46.3 ± 3.3	43.4 ± 11.3	50.6 ± 12.1	47.5 ± 12.5
Diabetes (%)	4.8 ± 0.5	8.4 ± 0.8	8.1 ± 0.7	3.8 ± 0.3
Heart rate (b/min)	71.3 ± 12.9	70.6 ± 11.0	73.6 ± 10.6	71.7 ± 11.2
No. cigarettes per day	8.7 ± 9.5	7.7 ± 11.0	2.4 ± 5.6	6.8 ± 10.9

Values are expressed as mean ± SD for continuous variables, and mean ± standard error for the prevalence of diabetes. IRA = Italian Rural Areas.

Table II. Solution of the accelerated failure time model for the prediction of first major coronary event.

	Coefficient	SE	t test	Difference for HR	HR (95% CI)
Sex	-0.9443	0.2567	-3.68	Male-Female	3.14 (1.71-5.78)
Age	-0.0742	0.0089	-8.36	5 years	1.57 (1.41-1.74)
Body mass index	-0.0205	0.0151	-1.36	3 units	1.08 (0.97-1.20)
Mean blood pressure	-0.0193	0.0042	-4.62	15 mmHg	1.42 (1.22-1.65)
Non-HDL cholesterol*	-0.0050	0.0020	-2.50	40 mg/dl	1.27 (1.04-1.54)
HDL cholesterol*	0.0275	0.0105	2.62	10 mg/dl	0.72 (0.56-0.92)
Diabetes	-0.3081	0.1860	-1.66	Yes-No	1.45 (0.93-2.26)
Heart rate	-0.0163	0.0045	-3.60	10 b/min	1.22 (1.09-1.36)
Cigarettes	-0.0250	0.0048	-5.22	10 cigarettes/day	1.35 (1.21-1.52)
Constant	19.2042	11.0385	17.40	–	–
Scale	0.8249	0.0558	–	–	–

Denominator = 9089; numerator = 211. CI = confidence interval; HR = hazard ratio; SE = standard error. * = the coefficients, in mmol/l, are -0.1933 for non-HDL cholesterol and +1.0634 for HDL cholesterol.

Table III. Solution of the accelerated failure time model for the prediction of first major cerebrovascular event.

	Coefficient	SE	t test	Difference for HR	HR (95% CI)
Sex	-0.1477	0.1887	-0.78	Male-Female	1.28 (0.69-2.37)
Age	-0.0657	0.0127	-5.16	5 years	1.73 (1.41-2.13)
Body mass index	0.0071	0.0190	0.37	3 units	0.97 (0.80-1.16)
Mean blood pressure	-0.0300	0.0059	-5.08	15 mmHg	2.12 (1.59-2.83)
Non-HDL cholesterol*	-0.0022	0.0021	-1.05	40 mg/dl	1.16 (0.93-1.52)
HDL cholesterol*	0.0133	0.0090	1.48	10 mg/dl	0.80 (0.60-1.08)
Diabetes	-0.2968	0.2132	-1.39	Yes-No	1.64 (0.82-3.30)
Heart rate	-0.0069	0.0062	-1.10	10 b/min	1.12 (0.92-1.37)
Cigarettes	-0.0016	0.0089	-0.18	10 cigarettes/day	1.03 (0.77-1.37)
Constant	17.6037	1.6010	11.00	–	–
Scale	0.5933	0.0733	–	–	–

Denominator = 9089; numerator = 64. Abbreviations as in table II. * = the coefficients, in mmol/l, are -0.0851 for non-HDL cholesterol, and +0.5143 for HDL cholesterol.

Table IV. Solution of the accelerated failure time model for the prediction of first major cardiovascular event.

	Coefficient	SE	t test	Difference for HR	HR (95% CI)
Sex	-0.5521	0.1415	-3.90	Male-Female	2.06 (1.43-2.96)
Age	-0.0670	0.0072	-9.25	5 years	1.55 (1.41-1.70)
Body mass index	-0.0051	0.0124	-0.41	3 units	1.02 (0.93-1.12)
Mean blood pressure	-0.0220	0.0034	-6.47	15 mmHg	1.54 (1.35-1.76)
Non-HDL cholesterol*	-0.0039	0.0012	-3.25	40 mg/dl	1.23 (1.06-1.39)
HDL cholesterol*	0.0097	0.0049	1.98	10 mg/dl	0.88 (0.78-1.00)
Diabetes	-0.2977	0.1520	-1.96	Yes-No	1.48 (1.00-2.18)
Heart rate	-0.0144	0.0037	-3.88	10 b/min	1.21 (1.10-1.33)
Cigarettes	-0.0209	0.0040	-5.18	10 cigarettes/day	1.31 (1.19-1.46)
Constant	18.2091	0.8994	20.24	–	–
Scale	0.7641	0.0457	–	–	–

Denominator = 9089; numerator = 269. Abbreviations as in table II. * = the coefficients, in mmol/l, are -0.1508 for non-HDL cholesterol, and +0.3751 for HDL cholesterol.

mass index and HDL cholesterol. The 95% confidence intervals of the correspondent hazard ratios do not include 1 only for age and mean blood pressure.

In the model for cardiovascular diseases (Table IV) coefficients are directly associated with risk except that for HDL cholesterol. All the correspondent hazard ratios have 95% confidence intervals that do not include 1, except that for body mass index.

Overall, the largest hazard ratios are seen in the model for CHD, except that of blood pressure whose highest level is seen in the model for strokes. In general, the hazard ratios for cardiovascular diseases are

greater than those for stroke but smaller than those for CHD.

The discriminating power of these risk functions were tested by applying back the constant, the coefficients and the scale factor to the individual levels of the risk factors of each subject involved in the analysis and the estimated probabilities were ranked and distributed in decile classes. In the solution for CHD, the proportion of cases located in the upper decile of the estimated risk was 37.0% with a relative risk versus the lowest decile of 78.7. In the solution for cerebrovascular diseases, the proportion of cases located in the upper decile of the estimated risk was 52.3%, while no cases were found in deciles 1 and 2. In the solution for cardiovascular diseases, the proportion of cases located in the upper decile of the estimated risk was 37.8%, with a relative risk versus the lowest decile of 94.5.

For the three models, the correlation coefficient between the proportion of observed versus expected cases in decile classes of estimated risk was 0.99.

The ROC curves, describing the relationship of false positive with false negative cases derived from the individual estimated risk, gave areas of 76% for coronary and cardiovascular events, and of 83% for stroke events.

The three models were then used as mathematical core of a software for PC called Riscard 2002 that is now being distributed in Italy.

Structure of the software. The software is loaded on a CD-ROM and can run on a medium powered PC. Detailed instructions are given in the Manual of Operations of the software. The program runs in a series of screen pages allowing the user to feed data and to obtain findings and services of different types.

The first screen page gives the title of the software and an index of its contents. It includes an introduction and presentation of the software, the scientific bases, the characteristics of the model and the access to the operative sections.

The second screen page deals with the loading of general information of the examined subject which is then retained in a permanent file.

The third screen page deals with the loading of data on risk factors and separately offers the option to load information on prescribed preventive treatments of hygienic or pharmacological type. Arbitrary lower and upper limits in risk factor levels were identified. The program does not accept values outside these limits.

The fourth screen page invites the user to choose the estimate for one of the three endpoints, i.e. hard criteria CHD, or hard criteria cerebrovascular disease or hard criteria cardiovascular disease.

Once the choice is made, the fifth screen page produces numerical and graphical findings of the estimated risk, the theoretical risk and the ideal risk; then of the ratios of the estimated to the theoretical risk (called relative risk). It also provides a comparison between the estimated and expected risks and, separately, between the estimated and ideal risks and finally the so-called coronary, cerebrovascular or cardiovascular biological age.

The *estimated risk* is the probability, expressed per 1000, that the studied individual experiences an event within 5 years.

The *theoretical risk* is the probability, again expressed per 1000, that a person of the same age and sex, who carries the mean Italian levels of the other risk factors, experiences the event within 5 years. Information on this issue derives from tabulations of risk factors published by the Italian RIFLE Pooling Project which included 52 population samples of men and women studied in the early 1980's in Italy[44].

The *ideal risk* is the probability, expressed per 1000, that a person of the same age, sex, height and weight, who carries low levels of the other risk factors, that is 120/70 mmHg for blood pressure, 170 mg/dl for total serum cholesterol, 55 mg/dl for HDL cholesterol, absence of diabetes, the condition of non-smoker, and a heart rate of 60 b/min, experiences the event within 5 years.

As said above, the ratio of the estimated to the theoretical risk is here conventionally termed the *relative risk*.

Comparisons between the estimated and theoretical risks and, separately, between the estimated and ideal risks are presented as the percent difference between the components of each pair.

The so-called coronary or cerebrovascular or cardiovascular biological age is the estimated age of a person who carries the average Italian levels of risk factors and has the same estimated risk as the investigated subject. This age can be equal to, greater or smaller than the actual subject's age.

The sixth screen page describes, in a table, the dates, the estimated risk and the relative risk for each available examination, while a graph provides the changes over time of the relative risk. The choice has been made to use, for this purpose, the relative risk since it is relatively free or less influenced than the absolute estimated risk, from the effect of aging. In fact absolute risk grossly increases on a yearly basis with aging even for stable levels of the other risk factors.

The third, fifth and sixth pages can be printed on request. Special functions can be activated from the first screen page, including the possibility to view and print some selected data and findings, to look at and to export the archive constructed using the program, with all the available properly coded information and suitable for any kind of statistical analysis.

Discussion

The three models adopted for the construction of the software used 11 classical risk factors, compressed into 9 variables by combining some of the data. They pro-

vided significant coefficients for the factors that are typically associated with CHD, stroke, and all cardiovascular diseases of atherosclerotic origin. The coefficients of some factors did not reach statistically significant levels but this can be easily attributed to the small numbers involved and to the short follow-up period chosen for this software. On the other hand, the discriminating power was satisfactory for all the three models, as shown by the distribution of observed cases in decile classes of estimated risk and by the ROC curves.

In the production of this tool there are several limitations that should be kept in mind. They derive from the typology of the material employed and from some unsolved analytical issues.

The overall number of subjects involved in the analysis is not very large, in spite of the fact that the studied population is almost double that of the Framingham study[45] which has been used as the epidemiological basis for the production of most tools in cardiovascular prediction.

In our material, the proportion of females is relatively small (not exceeding 20%) and this is the reason why separate models for males or females were not computed. However, with this short-term follow-up we did not find any risk factor-sex interaction and therefore it was legitimate to use sex as a dummy variable.

The geographic distribution of the several populations located in 5 regions of the country is not the ideal for representing the country itself, but, at the time being, this was the material available for this purpose. Plans are in due course to involve other studies for the computation of future functions and for the construction of new tools based on a larger representation of the national population.

The three population groups are somewhat heterogeneous since they were studied in different decades (the 1960's and the 1970's for the IRA population; the 1980's for the Gubbio study; and the 1990's for the ECCIS study). Moreover, the ECCIS population was recruited on the basis of occupational groups which, in part, reflect different situations. However, everything else being equal, the analysis of models including dummy variables identifying the different studies showed only a slightly lower cardiovascular incidence for the ECCIS study. This lower incidence could be partly expected on the basis of the so-called "healthy worker effect". There are good reasons to believe that the material of the present study quantitatively represents the incidence of the cardiovascular events occurring in Italy during the last few decades.

Beyond the technical limitations described above, a tool of this type can give approximate estimates and therefore caution should be adopted when using it. Details are given in the operative manual of the software.

When producing single risk estimates using the software, the different role of the so-called relative risk compared with the estimated risk may not be sufficiently clear. In this context, the relative risk is the ratio of the estimated risk to the theoretical risk, that is to the risk of a person of the same sex and age and carrying the average national levels of the other risk factors[44]. In particular, relatively young people with high levels of risk factors are still at a relatively low absolute risk, although being at a high relative risk. On the other hand, relatively old people are at high absolute risk even in the presence of relatively low levels of risk factors. This means that, on the basis of a single threshold for the absolute risk, most older people would be eligible for treatment whereas almost no younger subject would be in this condition. On the other hand, considering only the relative risk, whatever the choice of the threshold, almost only younger people would be selected and treated.

Compared to the cardiovascular risk chart derived from the same population studies[25,26], this tool allows to use more risk factors and to use them as precise values instead of ranges or classes. Moreover, it allows the production of estimates for three different endpoints instead of only one, giving estimated probabilities in 5 years instead of ranges of probabilities. Different types of risk are estimated and compared to one another; repeated estimates can be produced and compared and all the information fed in the computer and all the estimates are retained in a permanent file.

The production of this tool was necessary in order to offer a new computer aid for the estimation of the cardiovascular risk on the basis of Italian data. The hope is that the use of similar computer programs derived from Northern European or North American populations[12,14,17], which has unfortunately been widely promoted in this country, would be discouraged.

This tool may help the Italian medical profession to be more motivated in selecting and treating high-risk individuals and, more in general, in its attitude towards cardiovascular prevention.

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