

# Comparison of the Framingham risk function-based coronary chart with risk function from an Italian population study

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**Aims** The aim is to compare the coronary risk chart published by the European Task Force for Prevention of Coronary Heart Disease and produced using a Framingham risk function, with a risk function derived from an Italian population study.

**Methods and Results** Coronary risk function in this study was the result of longitudinal experience in an Italian middle-aged population of 1656 male subjects followed-up for 25 years. To comply with the Framingham equation the same risk factors (age, systolic blood pressure, total serum cholesterol and smoking habits), end-points (any possible coronary event including angina pectoris), and length of follow-up (10 years) were used, and the model (log-linear accelerated time failure model, accommodating the Weibull distribution) was similar. Comparisons were made computing the coronary risk for each cell of the coronary risk chart for men aged 40, 50 and 60 years. The Italian risk function produced highly significant coefficients for all four risk

factors. Forty-four out of a total of 120 cells had a coronary risk of 20% or more in 10 years following the coronary risk chart, whereas this was reduced to four while using the Italian risk function ( $P < 0.001$ ). The Italian risk function largely underestimated the corresponding levels produced by the coronary risk chart and vice versa.

**Conclusion** The Framingham risk function-based coronary risk chart overestimates absolute coronary risk in countries characterized by a lower incidence of coronary events and should be used with caution.

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**Key Words:** Coronary heart disease, prevention, prediction, risk factors.

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## Introduction

Since it is now possible to initiate primary and secondary prevention of coronary heart disease this has resulted in the production of many guidelines. Here we refer to those prepared by the Joint Task Force of the European Society of Cardiology, the European Atherosclerosis Society and the European Society of Hypertension. The first report was published in 1994<sup>[1]</sup>, the second in 1998<sup>[2]</sup>. The main reason for the publication of the joint Task Force report was to avoid the creation of separate guidelines on hypertension management and hyperlipidaemia management, and to use a multifactorial approach to risk assessment and preventive measures.

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One of the underlying features of these reports is the requirement to look at coronary risk as a whole, that is, the risk derived from a combination of several risk factors. For this purpose a coronary risk chart is included which allows graded categories of absolute coronary risk to be identified, based on a combination of several risk factors. The coronary risk chart is derived from Framingham risk functions published in 1991<sup>[3]</sup> and was created to emphasize this aspect and the importance of considering absolute risk. The appointment of the second Task Force was probably stimulated by the results of statin trials and some new hypertension trials.

The Task Force reports have, however, emphasized that although the Framingham risk functions predict absolute risk reasonably well in high-risk populations, they may overestimate it in low-risk populations. European physicians and cardiologists were, in fact, offered a system for the assessment of absolute coronary risk

derived from an American experience, instead of using risk functions derived from European prospective studies<sup>[4]</sup>.

Several European cohort studies had published risk predictions and some of them had also given coefficients for their risk function before 1994, but very few of them were available in an as easily available form as the Framingham risk functions and none of the European studies provided risk functions for women. Furthermore, it was clear that the Framingham risk functions problem would have to be faced with any European risk functions: large differences in coronary heart disease rates between European populations would, in any case, have led to problems in the assessment of absolute risk. The limitations of the Framingham risk functions, when applied to European populations, were mentioned in both the 1994 and 1998 recommendations.

The purpose of this paper is to compare the best of the available and accessible information: risk functions produced from an Italian population study with the risk probabilities obtained from the Framingham risk function-based coronary risk chart of the European Task Force recommendations.

## Methods

### *The European coronary risk chart*

The coronary risk chart in the 1998 version is a tabulation system allowing classes of absolute coronary risk in the next 10 years to be identified, based on the measurement of the following risk factors: sex (male and female), age (years), smoking habits (smokers and non-smokers), systolic blood pressure in mmHg (four classes, made up of levels of 120, 140, 160, 180 mmHg), and total serum cholesterol in  $\text{mmol} \cdot \text{l}^{-1}$  or  $\text{mg} \cdot \text{dl}^{-1}$  (five classes made up of levels of 4, 5, 6, 7 and 8  $\text{mmol} \cdot \text{l}^{-1}$  or about 160, 200, 240, 280 and 320  $\text{mg} \cdot \text{dl}^{-1}$ ). Five age groups (exact ages) are considered i.e. 30, 40, 50, 60 and 70 years.

From the reference in the Framingham paper quoted in the chart<sup>[3]</sup> it is possible to learn that:

- the population at risk is a mixture of fathers and mothers (first generation in the Framingham Study) with sons and daughters (offspring generation of the Framingham Study), who have reached the age of their parents when the study was started;
- people with cardiovascular manifestations present at entry examination were excluded from the analysis, which therefore deals with cardiovascular disease-free subjects;
- follow-up was approximately 12 years;
- coronary end-points are coronary events, as described in another paper<sup>[6]</sup> and comprise sudden and non-sudden coronary death, myocardial infarction, coronary insufficiency, angina pectoris;
- the model uses natural log-transformed variables, and the overall number of factors exceeds that of the chart;
- the model is a modification of the log-linear accelerated failure time model (accommodating the Weibull

distribution), which was specifically created for the Framingham data<sup>[5]</sup>.

The coronary risk chart is a reasonable adaptation of the Framingham risk functions and was printed in black and white (and reprinted and distributed in colour). Various blocks of the chart looked at the differences in sex, age and smoking class; a range of absolute risk over 10 years, subdivided into levels below 5%, from 5 to 10%, exceeding 10 to 20%, exceeding 20 to 40%, and exceeding 40% was also represented.

### *The Italian study population*

The material used in this analysis derives from the two Italian rural areas of the Seven Countries Study of Cardiovascular Diseases, which comprised men aged 40 to 59 years first examined in 1960<sup>[7,8]</sup>. The men represented 98.8% ( $n=1712$ ) of defined samples from the rural communities of Crevalcore in Northern Italy and Montegiorgio in Central Italy. Field surveys with measurements of risk factors and clinical evaluation were conducted at 5-year intervals for three decades. For the purpose of this analysis, only measurements taken at baseline are considered, together with follow-up information on incidence of coronary heart disease and mortality during the next 25 years of follow-up.

Risk factors considered in this analysis were: (1) age, expressed in years and rounded off to the nearest birthday; (2) systolic blood pressure, expressed in mmHg, and measured in the right arm in the supine position, at the end of a physical examination by trained physicians using a mercury sphygmomanometer (following the procedure described in the WHO Cardiovascular Survey Methods Manual)<sup>[9]</sup>; two readings, approximating to the nearest 2 mmHg, were made 1 min apart and averaged; diastolic blood pressure phase V was not used in this analysis; (3) serum cholesterol in  $\text{mmol} \cdot \text{l}^{-1}$  (and  $\text{mg} \cdot \text{dl}^{-1}$ ), measured in casual blood samples using the method described by Anderson and Keys<sup>[10]</sup>; (4) smoking habits elicited from a questionnaire; the daily average number of cigarettes was estimated.

Collection of data on vital status and causes of death were complete for the 25-year follow-up and no subjects were lost. Causes of death were allocated by reviewing and combining information from death certificates, hospital and medical records, interviews with physicians and relatives of the deceased and any other witnesses of the fatal event. Causes of death were determined by a single reviewer (A.M.) following defined criteria, employing the 8th Revision of the WHO-ICD<sup>[11]</sup>. In the presence of multiple causes a hierarchical preference was adopted: violence, cancer in advanced stages, coronary heart disease, and stroke in that order.

The end-point of this analysis was the first coronary event in subjects free from coronary heart disease at entry examination. Information was obtained by the following procedures: (a) interim quinquennial examinations including clinical history, ECG records and review of reported hospital or clinical records; (b) information

**Table 1** Solution of the LLATFM for the Italian population

Risk factor	Coefficients	S.E.	T value
Age, years	- 0.0216	0.0066	- 3.2879
Systolic blood pressure, mmHg	- 0.0054	0.0015	- 3.5727
Serum cholesterol, mg . dl <sup>-1</sup>	- 0.0023	0.0008	- 2.9808
Cigarette, n . day <sup>-1</sup>	- 0.0087	0.0032	- 2.7027
Constant	6.2502	0.3815	16.3816
Scale factor	0.6598	0.0290	—

obtained in relation to causes of death as described above; (c) periodic visits to local physicians and hospitals for identification of lost cases; (d) home visits to subjects suspected of being new coronary cases, based on medical history, physical examination and ECG recording; (e) postal questionnaire and postal clinical records.

Incident cases, corresponding to first coronary events, included the following conditions: 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. Details on criteria are reported elsewhere<sup>[8]</sup>. Each event was accompanied by a date; the first occurring during the follow-up period was taken for analysis. Data refer only to men aged 40 to 59, for a follow-up of 10 years. After exclusion for baseline coronary heart disease prevalence and missing values, 1656 men were used for analysis.

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

### The risk function used on Italian data

The risk function used in the Framingham Study, which represented the basis for the European chart, could not be used since it is not included in standard statistical packages. It was therefore decided to use the log-linear accelerated time failure model (LLATFM) accommodating the Weibull distribution, which is available in the **BMPD Statistical Package**<sup>[12]</sup>. This model is similar to the one used in Framingham<sup>[6]</sup>. Moreover, we have independently shown that: (1) the Italian data fit the proportionality assumption required for proportional hazards models; (2) an algebraic transformation of the LLATFM into a version complying with the proportionality assumption produced substantially similar coefficients. The LLATFM corresponds to the following formula:

$$P=1 - \exp \left( - \exp \left( \frac{\ln(t) - (a + b_1x_1 + b_2x_2 + \dots + b_nx_n)}{s} \right) \right)$$

where  $P$  is the probability of developing an event within time  $t$ ;  $t$  is the 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. One peculiarity of this model is that the algebraic sign of the coefficients is inverse compared to usual logistic or Cox models. This means that a factor whose coefficient has a positive sign is inversely related to the event, while a factor whose coefficient has a negative sign is directly related. Comparison with the coronary risk chart was made by computing coronary heart disease risk probabilities for each cell for ages 40, 50 and 60 years for males. The category of smokers was assigned an average daily consumption of 15 cigarettes.

## Results

### Presentation of the Italian solution

Mean ( $\pm$  SD) levels of risk factors used in the model were 49.8 ( $\pm$  5.1) years for age, 143.4 ( $\pm$  21.0) mmHg for systolic blood pressure, 201.5 ( $\pm$  41.0) mg . dl<sup>-1</sup> for serum cholesterol, while mean cigarette consumption was 8.6 ( $\pm$  9.5) cigarettes per day, corresponding to a prevalence of smokers of 62%. The solution of the LLATFM is given in **Table 1**. It is based on 435 events derived from a denominator of 1656 coronary free men at entry. Coefficients of all risk factors are highly statistically significant and all have negative signs indicating a direct relationship with events.

### Application of the Italian solution

The solution has been applied to arbitrary levels of risk factors, corresponding to the 120 cells of the coronary risk chart using the 10-year follow-up estimate of the Italian model related to ages 40, 50, and 60 years. They are reported in **Table 2**. These absolute risk probabilities are for reference only since they do not help in comparing the performance of the model against the coronary risk chart where only classes of risk are given.

### Comparison with the coronary risk chart

The estimated probabilities were therefore converted into classes comparable to the coronary risk chart and plotted into a similar drawing (**Fig. 1**). In this way the

**Table 2 Risk of first coronary event per 1000 in 10 years in males aged 40 to 60 years estimated by the Italian model in Table 1. Coronary events are sudden and non-sudden coronary death, definite fatal and non-fatal myocardial infarction, possible non-fatal myocardial infarction and angina pectoris**

Age 60 years										
SBP	Non-smokers (cholesterol)					Smokers (cholesterol)				
	160	200	240	280	320	160	200	240	280	320
180	128	146	166	188	213	154	175	198	224	253
160	110	125	142	162	184	132	150	171	194	219
140	94	107	122	139	158	113	129	147	167	190
120	80	92	105	120	136	97	111	126	144	163
Age 50 years										
SBP	Non-smokers (cholesterol)					Smokers (cholesterol)				
	160	200	240	280	320	160	200	240	280	320
180	94	107	122	139	158	113	129	147	167	190
160	80	92	105	120	136	97	111	126	144	163
140	69	79	90	102	117	83	95	108	123	141
120	59	67	77	88	100	71	81	93	106	121
Age 40 years										
SBP	Non-smokers (cholesterol)					Smokers (cholesterol)				
	160	200	240	280	320	160	200	240	280	320
180	69	79	90	103	117	83	95	108	123	141
160	59	67	77	88	100	71	81	93	106	121
140	50	57	66	75	86	61	69	79	90	103
120	43	49	56	64	73	52	59	68	77	88

SBP=systolic blood pressure in mmHg; cholesterol is total cholesterol expressed here in mg . dl<sup>-1</sup>.

**Table 3 Frequency distribution of score classes produced by the coronary risk chart and the Italian score**

	Score classes for probabilities in percent in 10 years					Total
	40+	20-40	10-20	5-10	<5	
Coronary risk chart	3	41	52	21	3	120
Italian score	0	4	65	49	2	120

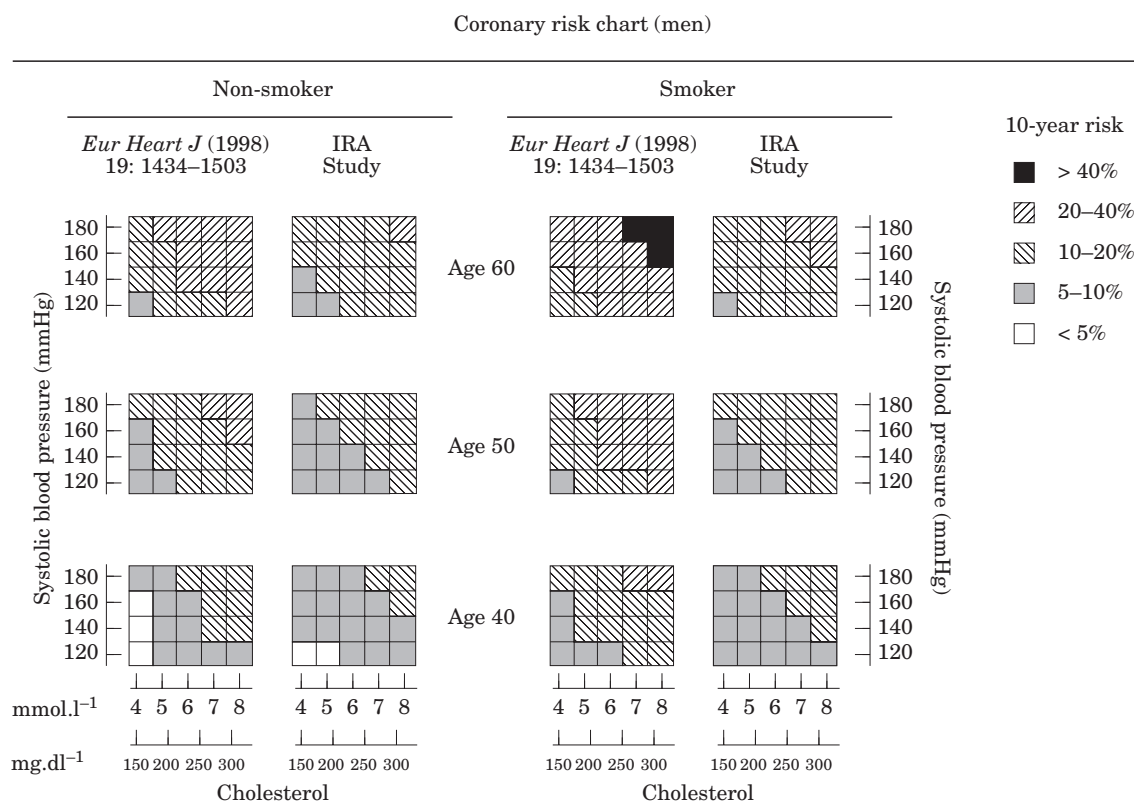
Chi-square=46.5 with 4 dof,  $P<0.001$ .

120 cells from the coronary risk chart can be compared with the 120 cells of the Italian risk function, both classified into five groups: probabilities of more than 40% or more; probabilities of more than 20-40%; probabilities of more than 10-20%; probabilities of more than 5-10%; probabilities equal to or smaller than 5%. The net result is provided by the distribution of the several classes given in Table 3. The two distributions are largely different, showing greater frequencies in the higher risk classes according to the coronary risk chart score compared to the Italian one and vice versa. The chi-square statistics is highly significant. Forty-four out of 120 cells have probabilities of 20% or more following the coronary risk chart, but only four following the

Italian score. Altogether, the Italian risk function produces lower probabilities for the same levels of risk factors.

## Discussion

The net result of this exercise is that the Italian estimates do not fit the estimates produced by the coronary risk chart derived from the Framingham Study. Everything else being equal, the expected incidence rates in Italy are much lower, although the same risk factors, end-points and length of follow-up were used. The reasons for the different performance of the two models is probably bound to factors not measured in these population



**Figure 1** Graphical comparison of coronary risk classes for men aged 40, 50 and 60 years, following the Coronary Risk Chart [Eur Heart J (1998); 19: 1434–1503] and the IRA study (Italian Rural Areas).

studies or simply unknown. The traditional experience in comparing population groups belonging to different cultures says that the relative risk bound to different levels in one or more risk factors is similar across cultures, while the absolute risk can be very different<sup>[13]</sup>. This means that an excess of people would be treated by drugs, in Italy (and probably in other Southern European countries), using the Framingham risk function as transformed into a coronary risk chart by the European Task Force. This statement is based on the notion that the great interest for practising cardiologists, in terms of prevention, is largely linked to the use of statins which also involves endless discussion on the level of coronary risk above which the approach is declared 'ethical' and 'accepted' by the National Health Service in terms of financial coverage of this treatment.

Another problem arises from the search for an absolute risk of 20% in 10 years (as suggested by the European guidelines and widely quoted at national levels) which has an entirely different meaning if we refer to hard coronary heart disease events, or to any coronary heart disease manifestation. If hard events are considered, the proportion of subjects to be treated would be much smaller both following the coronary risk chart and the Italian model. The 20% target is an arbitrary figure suggested by the European Task Forces<sup>[1,2]</sup> to try to define high risk. High risk takes into

account important factors which indicate the need for intensive lifestyle change and, if the high risk status remains, the need for proven drug treatment. This latter was not a dogmatic statement but was to promote discussion at national level. It has probably been overlooked for prevalent economic reasons, linked to the prescription of expensive hypo-cholesterolaemic drugs. However, it is not clear whether the Italian National Health Service (or similar bodies elsewhere) has ever considered the large difference, when taking as an end-point hard coronary cases vs all coronary cases.

The correct definition of the end-point, to which the chart refers, is provided in the 1998 Task Force Report. Usually physicians and cardiologists tend to identify coronary events as the major events that represented the outcome of the early statin trials<sup>[14–16]</sup>, although softer end-points were considered in a more recent trial<sup>[17]</sup>. It is felt that the positive results of the recent statin trials have enhanced interest in preventive cardiology guidelines, although the first European Task Force was appointed in 1993, before the publication of the 4S trials results<sup>[14]</sup>. The need to emphasize the choice of the end-point, or the option to offer more than one end-point (with the related charts) seems an important issue considering the large difference in absolute incidence and risk, bound to different definitions of coronary events.

This option, to reach a risk of 20% in 10 years (or any other target) before starting drug treatment in high-risk individuals, can be viewed from a different angle. This approach is somehow artificial since a given target can be easily obtained by adding the role of other non-modifiable risk factors, such as carriers of strong relative risk. For example, the role of corneal arcus if present (as it is in about 15% of the male population aged 40–59) adds a relative risk of about 1.80 or more, everything else being equal<sup>[18]</sup>. Similar operations can be made using a family history of heart attack, early onset coronary heart disease or other vascular disease, minor ECG abnormalities and so forth, as emphasized in the instructions for the use of the coronary risk chart<sup>[2]</sup> listing a number of risk modifiers, which lead to higher risk than that obtained from the chart.

The possibility that different predictive coefficients may result from more recent studies, as a consequence of changing trends in populations mean risk factor levels and coronary heart disease incidence rates should also be considered. However, in Italy, the most recent studies producing short-term prediction for coronary heart disease deaths<sup>[19–21]</sup> showed coefficients which were not basically different from those produced earlier by the Seven Countries cohorts.

The main message of this analysis is that the Framingham risk function-based coronary risk chart included in the European Task Force recommendations, compared with the functions obtained from the middle-aged Italian male population of the Seven Countries Study, markedly overestimated the absolute 10-year coronary heart disease risk.

The findings of this analysis emphasize the need for further work to develop risk functions which would be better suited for use in different parts of Europe. Intensive work is being done in this field, mainly by the research group of the SCORE project, funded by the European Union. The challenges are to find suitable population studies in each country or geographical-cultural area; to make systematic comparisons of risk functions derived from different populations; to stimulate the use of national risk functions, or to identify procedures so as to adapt general European functions for use in single countries or areas, based on proper correcting coefficients; to identify procedures so as to transform risk probabilities produced with coronary heart disease deaths as end-points into estimates for coronary heart disease incidence of fatal plus non-fatal manifestations of the disease.

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