

Cardiovascular Risk Functions, and Their Practical Relevance: To Be Trusted or Not To Be Trusted

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Abstract

The practical reliability of the 20% risk threshold is examined, as fixed by the Italian Health Ministry using the European Joint Task Force (JES) 'chart of coronary risk'. Two different risk functions, one derived from the Framingham study and one from the PROCAM study, are compared. The comparison has been carried out in a homogeneous way. The data base is represented by 4584 Italian subjects (2067 males, 2517 females) on primary prevention, who participated in the RAI (Registro ANCE Ipertensione) study.

The results show that there are 131 subjects (out of 271; 48.3%) who have a larger than 20% risk using the JES/Framingham algorithm, but are below threshold using the PROCAM one.

Although any cut introduces a subjective measure, the choice of different risk functions is relevant in a high percentage of borderline cases, thus changing the status from 'high risk' to lower risk and vice versa.

1. Introduction

The Joint European Societies Recommendations [1] state that "the overall objective of Coronary Heart Disease (CHD) prevention, ... in high risk individuals is ... to reduce the risk of major CHD, or other atherosclerotic disease It is important to estimate absolute risk ... by taking into account all the major risk factors. ... An absolute CHD risk which exceeds 20% over the next 10 years, ... and which is sustained despite professional lifestyle interventions, is sufficiently high to justify the selective use of proven drug therapies."

These recommendations have been fully accepted by the Italian Ministry of Health (January 2001), which states that "subjects having an absolute CHD risk which exceeds 20% over the next 10 years, ... should receive professional lifestyle interventions as well as a pharmacological treatment (with statins) which will be fully reimbursed by the National Health System." It is furthermore stated that the absolute risk should be assessed using the above mentioned "chart of coronary risk" (CCR).

2. The problems

2.1. The epidemiological problem

Years of epidemiological studies have led to the identification of "risk factors" of Cardiovascular diseases (CVD), which act in a multiplicative way. Guidelines have been worked out for individuals who have already undergone a CV event as well as for "high risk" individuals. In order to evaluate the concrete risk, CV risk functions have been constructed, and on these are based the "risk charts". The most used risk functions have been derived mainly from two epidemiological studies: the Framingham study (Mass., USA) and the PROCAM (Munster, Germany) one. The latter considers only males aged 35-65 years.-

2.2. The pharmacological problem

The so called 'pharmacological problem' is not only a pharmacological one, but also an economical and health policy one. As already stated, in January 2001 the Italian Health Ministry gave a particular economic relevance to the European "chart of coronary risk". It stated that "all individuals ... who present a CV risk higher than 20% must be considered at high risk to develop a CV event in the next 10 years, ... and [those] who furthermore present a total cholesterol value higher than 190 mg/dL, can be prescribed statins free of charge". Many considerations derive from this statement, three of which will be mentioned. It emerges clearly that for the high risk individuals (as defined by the Ministry), the state is ready to invest money in pharmacological prevention. We must not forget that these free statins are paid for by the National Health Service. Secondly the statement insists (the text is not quoted here) that the medical doctor (be it the General Practitioner or any other doctor) should invest time and effort in a proper education of the patient.

Finally there are at least three surprising numerical elements. First of all there is the choice of the European "chart of coronary risk" (CCR) as a kind of golden standard. Secondly there is the even more surprising element of the cholesterol double weighting. In fact in the European CCR cholesterol is taken into account both as

Total Cholesterol as well as HDL Cholesterol. In the statement of the Italian Health Ministry two requirements must be fulfilled at the same time: a CV risk higher than 20%, and furthermore a total cholesterol value higher than 190 mg/dL. Total cholesterol is therefore at least doubly counted. Finally there is the 20 % risk threshold. Although this (mandatory) threshold value derives from the Joint European Societies Recommendations [1], its implementation in a regulatory and economic context is at least overemphasized.

2.3. The computational problem, and its ‘analytical continuation’

Although some numerical elements have already been mentioned in the previous paragraph, the core of the computational problem depends on the cardiovascular risk functions (CRF) and their coefficients. As is well known, these risk functions are derived multivariate mathematical functions which assign weights to major CHD risk factors. The determination of the coefficients is based on a minimization process, which applies the (chosen) mathematical function to a given set of data. The set of data derives from epidemiological studies, two of which are the best known and used, namely the Framingham (Mass., USA) study and the PROCAM (Munster, Germany) one. From both studies many functions have been derived. In this paper two functions of each study have been primarily considered[2-5].

Under ‘analytical continuation’ two extrapolation processes are here considered. The first is related to the so called absolute CHD risk. The computations using any of the functions give a precise value. But in fact this value, due to its derivation, is affected by an indetermination (an error) which can be estimated at any desired level. It would of course be cumbersome to specify this kind of error for the single subject, but it has to be considered. Secondly it should be remembered that the cited epidemiological studies (Framingham (Mass., USA) and Munster, Germany) reflect among other things the genetic background and the life style of the populations considered. They cannot be extrapolated, at least without any caveat, to other populations. Two recent studies [6,7] emphasize that, at least in some cases, recalibrations are needed.

3. Materials, methods and results

A sample of 4584 Italian subjects (2067 males, 2517 females) on primary prevention, who participated in the RAI (Registro ANCE Ipertensione) primary prevention study, has been considered. In order to make the full comparison both at 10 and at 8 years with 2 Cardiovascular Risk Functions (CRF) [3,4], only male

subjects, with all the relevant data explicitly present, and in the age range of 35-65 years, were considered. There were 553 subjects left. These 553 males, a little more than 25% of the male population, are in any case fully representative, as far the common parameters are concerned, of the whole male population. Only two out of the four possible functions were chosen, in order to consider in both cases the same risk factors.

Because the 2 CRF are in fact optimised for a risk computed at 10 (JESRF/Framingham) and at 8 (PROCAM) years, the main results are presented (with the number of subjects) in the 2 following tables for these time intervals.

Table 1. Males, 35-65 yrs., CV risk at 10 yrs (%).

	PROC =< 20%	PROC > 20%
JES Risk Fct (FRAM) =< 20%	269	13
JES Risk Fct (FRAM) > 20%	131	140

Table 2. Males, 35-65 yrs., CV risk at 8 yrs (%).

	PROC =< 20%	PROC > 20%
JES Risk Fct (FRAM) =< 20%	337	26
JES Risk Fct (FRAM) > 20%	88	102

Let us consider the first table, which presents the ‘absolute risk’ at 10 years, therefore the one relevant for the reimbursement of pharmacological treatment in Italy. It should be borne in mind that the 553 male subjects are fully representative of the total number of males in this primary prevention study. The figures imply that there are 131 subjects (out of 271; 48.3%) who have a larger than 20% risk using the JES/Framingham algorithm, but are below threshold using the PROCAM one. This amounts to about half of the subjects being above threshold following the JES/Framingham, and therefore eligible for reimbursement of treatment. What is also remarkable, although not relevant for the subsequent discussion, is that about 50% of the male subjects of this

study have a higher than 20% risk according to the JES/Framingham risk function, as compared to about 28 % according to the PROCAM one.

The scenario is slightly different for the risk at 8 years (table 2), but the difference (88/190; 46.3%) is not statistically significant. The situation would be less dramatic, if the PROCAM algorithm were the golden standard. For the absolute risk at 10 years, only 13 subjects (out of 153; 8.5%) would be reimbursed, and only in the PROCAM case.

These results imply that, at least for our Italian male population, the JESRF/Framingham presents a higher absolute risk than the PROCAM one. As expected, this situation applies not only above the 20% threshold, but also in the whole risk range, as shown in Figure 1.

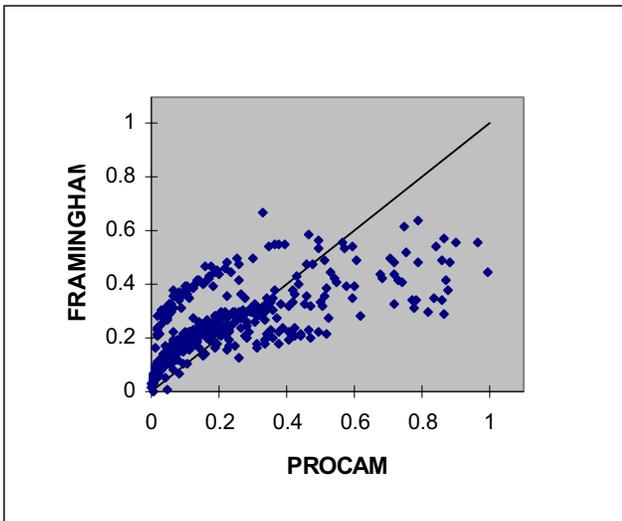


Figure 1: Absolute risk at 10 years, Framingham vs PROCAM.

4. Discussion

The Recommendations of the Joint European Societies [1] quoted at the beginning, state that “An absolute CHD risk which exceeds 20% over the next 10 years, ... and which is sustained despite professional lifestyle interventions, is sufficiently high to justify the selective use of proven drug therapies.” The wording of the statement is very clear, as is, nonetheless, the avoidance of an absolute order: “is sufficiently high to justify”.

Numerical Indices of the Cardiovascular Risk (NICR) as well as the related Risk Charts are a very useful tool both in the hands of the researcher as well as of the clinician. But both of them are usually well aware of the (statistical) limitations connected with the single number.

To state this in a crude and simple way, two of the objectives of statistics are to summarize many data with few data, and to extrapolate some results from one sample to other samples. Therefore the Cardiovascular Risk Index, computed for single subjects, represents on the one hand the summary of many risk factors by means of one single number, and on the other represents the extrapolation of the data of (many) other subjects, used for determining the coefficients of the multivariate mathematical functions.

In this case the application of two different functions, derived from different populations, give quite different results. Everybody is aware that the introduction of any threshold introduces a subjective measure. But in this case there is at least one further source of indetermination, namely the primary population studied. Therefore the choice of different risk functions is relevant in a high percentage of borderline cases, thus changing the status from “high risk” to lower risk and vice versa.

If an answer to the explicit question in the title is given, the results and the discussion point to the fact that Cardiovascular Risk Functions are relevant, that they have a practical relevance, and that they can be trusted. It should nonetheless be kept in mind that their results are a summary, and, like all summaries, they do not contain all the information of the original work. Therefore thresholds based on these (particular) summaries should be very carefully considered.

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