

## Cardiovascular Risk Prediction: Fact or Fiction? Treat the Patients at Risk or the Population at Risk?

*Predicción del riesgo cardiovascular: ¿realidad o ficción?, ¿tratar al paciente de riesgo o a la población en riesgo?*

*You can cut all the flowers, but  
you cannot keep Spring from coming*

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### INTRODUCTION

Prediction is the act of announcing something that is irrevocably going to happen, as stated in Pablo Neruda's epigraph.

Since the beginning, Medicine shared with the sorcerers' omens the ability of pronouncing what the future has in store for us; for the physicians this meant predicting the course of a disease or make its prognosis.

For the current cardiologists, as for physicians in general, the prediction of the risk that a healthy person may develop a cardiovascular disease at a certain moment assumed a key role in the last decades with the development of increasingly sophisticated algorithms aimed at assessing the future risk and help to prevent it by changes in lifestyle or specific pharmacological treatments.

A basic review to understand the history and principles of risk prediction, something of its statistical basis and mainly its clinical implications, could help physicians to take apparently simple, but complex decisions.

Cardiovascular risk estimation through its risk factors (RF) fulfils three basic functions: 1) to promote the population acknowledgement of cardiovascular diseases that cause a significant morbidity and mortality load in current society, 2) to communicate risk knowledge to groups and individuals, and 3) to encourage adherence to changes in lifestyle or therapy. (1)

In clinical practice, algorithms for risk prediction have been directly used to attempt identifying individuals at high risk of developing cardiovascular disease in the short-term, in order to select them for preventive intervention, assuming that treatment intensity in the reduction of risk factors should equate to growing levels of absolute risk. To achieve this, arbitrary cut-off thresholds are employed in this continuum to establish, for most algorithms, three risk categories: low, intermediate and high.

Although we all know individuals who seem to have a high probability of developing and even dying from cardiovascular disease, perhaps for belonging to a high risk family, and others who seem destined to live a long life without cardiovascular disease and with optimal RF parameters, the extrapolation of this simple observation to quantitative disease probability requires the fulfilment of a series of conditions:

1) We should have at our disposal reliable data on the incidence of cardiovascular disease from a cohort of subjects during a defined number of years, as with the initial follow-up of a group of persons from the city of Framingham in the United States; 2) we should have a certain number of available risk markers to assess their association with the future incidence of the disease; 3) statistical methods should have been developed to quantify the prospective association between risk markers and disease occurrence, the potential improvement of one risk model over another and the value of adding an extra RF to the original model, and most importantly, to know how the model really behaves in the clinical setting where it is used according to the characteristics of the population and disease load and severity; 4) the existence of effective and safe interventions such as statins; 5) a favourable cost-benefit evaluation when applied to different population segments.

A RF (which may or may not be causal) must be strongly associated with the disease to be seriously considered as a possible screening test. For example, the risk ratio [relative risk (RR) or odds ratio (OR)] between 20% of the population with the highest and lowest risk needs to be 50 times or greater. There is practically no single RF with an OR (or RR) sufficiently high to qualify as cardiovascular disease predictor and screening test; however, this real fact is not widely acknowledged. (2)

Even RF of etiological importance, as blood pressure and serum cholesterol (or apolipoprotein B) which are undoubtedly important causes of cardiovascular disease, have too low OR to be of great value as single cardiovascular disease predictors.

The paradox that relevant causal RF are poor predictors of the disease they engender is because they are usually disseminated in our society, so that nearly

everybody is exposed to its causes, though not everybody yields to the clinical effect of the exposure. For example, in the society we live in, almost everyone increases their blood pressure during the course of their lives; due to the high salt consumption in the diet; however, most people do not suffer from stroke despite the existence of a probably much higher stroke risk in people with high blood pressure. (3)

That is why a person in particular does not have the uncertainty expressed as a probability of suffering the disease; he either suffers or not suffers the disease. Therefore, telling him that he has a risk probability of 6% is inappropriate and pointless. The correct form of stating it, since it is a probability, is to exemplify it with a reference group and tell him that given 100 similar individuals (only for the considered RF) it is expected that 6 of them will experience a cardiovascular event in the next 10 years. But in his particular case, the doctor's job is to consider other clinical characteristics he might have, as family history or an increased body mass index, for in this situation, in this particular person, the possibility will be significantly higher.

Since a RF with extremely high RR (or OR) is not found in clinical practice, multiple independent risk factors must be combined, as used in the Framingham risk score or other similar ones, which have RR (or OR) between 1.3 and 4.0 and a ROC (Receiver Operating Characteristic) curve or C statistic ranging between 0.75 and 0.80 (Table 1)

Among continuous risk markers, the OR and RR can be calculated between the highest and lowest quintile (20%) or how it differs from 2 upper and lower standard deviations (SD), as in the Women's Health Study. (4)

It is intuitively thought that the combination of moderately strong RF may substantially improve screening. However, most RF used to predict cardiovascular events as serum cholesterol, blood pressure and others have a modest performance.

The addition of each RF decreases the discrimination power associated to risk, since as the number of RF increases the standard deviation (SD) also increases, partly offsetting the effect of separation between means. (5) Table 1 shows that with each additional RF, the discrimination ability decreases by half (in the ROC curve or C statistic).

## EVALUATION OF ABSOLUTE RISK PREDICTION EQUATIONS' USEFULNESS

Although a statistically significant association of risk scores is necessary (for example in logistic regression), this is, however, grossly insufficient to evaluate their usefulness. In general, risk prediction models must have the ability to discriminate future cases from non-cases (evaluated with the ROC curve or C statistic); they must be able to adequately calibrate, that is, the calculated value must be similar to what really happens (using the Hosmer-Lemeshow test), and in

addition they must assess model adequacy and information.

## The ROC (Receiver Operating Characteristic) curve or C statistic

The discrimination measurement of the most widely published model for the prediction of cardiovascular risk is the ROC curve or C statistic, which is a function of both model sensitivity and specificity (actually, 1-specificity) for all its values. It indicates the possibility that a randomly selected person has a higher score of developing a disease (case) than a non-case randomly selected person.

A 0.75 ROC curve would imply that the randomly selected cases will have a higher score than the randomly selected non-cases, in 75 out of 100 instances. The C statistic varies from 1.0 (perfect discrimination) to 0.5 (random chance, meaning that the applied score is not better than tossing a coin to select between case and non-case) (Figure 1).

The C statistic has flaws; for example, it describes how well the model can order cases and non-cases, but not how much higher is the estimated risk between the selected cases and non-cases. In a hypothetical situation in which the model assigns a value of 0.52 to all cases and 0.51 to all non-cases, there would be perfect discrimination, though the probability assigned would be of no clinical help.

## Calibration measurements

Calibration measurements assess the ability of model predicted risk to accurately reflect the absolute risk level in the population applied. Calibration can be seen in a graphic representation of the population divided in deciles (10%) with paired columns of calculated risk versus real risk. The most widely used test for model risk calibration is the Hosmer-Lemeshow  $\chi^2$  test, in which  $p < 0.05$  would indicate poor model calibration for the population to which it is applied.

## Measurements of model adequacy and information

Measurements, such as the likelihood ratio and the Bayesian information criteria, could indicate whether adding new model factors improves risk prediction compared to the basic model.

## Risk reclassification analysis

Among the newest concepts to assess the usefulness of risk prediction models are the measurements of the proportion of subjects that can be restratified from a risk level (based on the risk estimated with the first model) to a different risk level (based on a new model adding variables to the previous model). As some of the reclassifications can be accurate and appropriate and others may be incorrect and inappropriate, two indices that consider this situation are used, the "net reclassification improvement" and the "integral discrimination index" to attempt quantifying what is ap-

propriate and the amount of reclassification.

The clinical significance of such reclassification movements, usually small, greatly depends on the selected thresholds.

#### Attempts to improve risk prediction by adding new markers or using new predictors

Essentially, all additional markers have produced very slight clinical benefit (in case it can be demonstrated) when considered throughout the whole risk spectrum. Since most new risk markers are correlated with traditional RF, they do not have a high enough independent OR (or RR) to substantially change the C statistic when they are included in traditional risk models.

This happens with different biomarkers, including CRP, the calcium score or vascular images.

Risk prediction models in use estimate short-term risk, not beyond 10 years. Most are based on multivariate regression equations derived from the Framingham cohort. Although Framingham-based equations are most widely used in clinical practice, there are other similar models, as the EuroSCORE (European Systematic Coronary Risk Evaluation) which only estimates death of cardiac and vascular origin, the PROCAM (PROspective Cardiovascular Munster model) estimating hard coronary artery disease (fatal coronary artery disease and non-fatal infarction), the ATP III estimator (2001) predicting hard coronary artery disease (coronary artery death and non-fatal myocardial infarction), the English QRISK assessing cardiovascular disease (coronary artery disease, stroke and transient ischemic attack), the Reynolds risk score, estimating overall cardiovascular disease (cardiovascular death, myocardial infarction, stroke and revascularization) and, finally the new 2013 AHA-ACC score assessing cardiovascular disease.

#### LIMITATIONS OF 10-YEAR RISK PREDICTION MODELS. RISK ESTIMATION THROUGHOUT LIFETIME

Although a 10-year risk estimation guide represents a substantial improvement on the subjective and variable clinical judgment, it nevertheless presents acknowledged limitations.

An example is age, which has the greatest weight on 10-year risk models. Considering only age, in people over 55 years, 86% would be detected to develop

events. To identify the same percentage with the Framingham score performed every 5 years, a score cutoff point <8% should be used. (6)

Due to the effect of age on risk, the youngest adults (men <45 years and women <65 years), with modest elevation of RF, have very little effect on the 10-year risk estimation (well under 10% and even 5%), though the remaining risk over the course of their lifetime may exceed 50% with the same risk factors. (1) This is not due to an inaccurate prediction of the 10-year scores, but to a nearer scope and because the imposed thresholds for decision-making do not reach those recommended to carry out prevention.

A solution for this problem in young individuals could be to lower thresholds, but, as we will see, they would not separate those at greater from those at lower risk. Another alternative is changing the scope of risk estimation, performing a long-term or lifetime risk estimation for cardiovascular endpoints.

The methods that estimate risk throughout lifetime take into account competitive risk (non-cardiovascular deaths, which become relevant in long-term follow-up) thus providing real life long-term risk prediction.

In the Framingham Heart Study, risk was estimated throughout lifetime in more than 8,000 50-year old persons free from cardiovascular disease, up to 95 years of age. Cardiovascular disease was developed in 51.7% of men (95% CI 49.3-54.2) and in 39.2% of women (95% CI 37.0-41.4).

Participants were stratified in five mutually exclusive categories, according to RF values (optimal, non-optimal, elevated, 1 major RF,  $\geq 2$  major RF) (Table 2). Compared with participants with  $\geq 2$  major RF, those with optimal levels at 50 years had substantially less risk throughout their lifetime: 5% vs. 69% in men and 8% vs. 50% in women. They also had a markedly higher median survival, more than 11 years in men and 8 years in women.

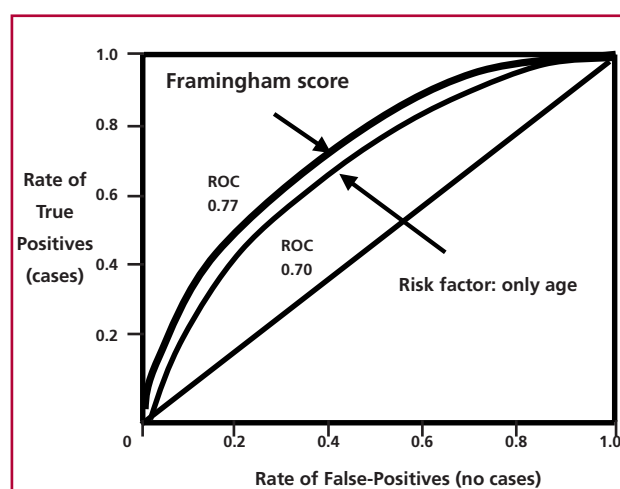
Based on usual recommendations, most people with an elevated RF, with risk estimations during the course of their lives between 40% and 69%, are not recommended to receive statins.

The concept of identifying younger individuals with low short-term (10 years) risk scores but with high risk during their lifetime has been validated with the subclinical atherosclerosis data in the images of the Coronary Artery Risk Development in Young Adults Study (CARDIA) and the Multi-Ethnic Study of Atherosclerosis (MESA). (8) More than 90% of participants between 37 and 50 years of age had a Framingham risk score <10% at 10 years. However, among this group, approximately half of participants presented with high risk during the course of their lifetime (from 39% to 69%). The risk was confirmed because this long-term high-risk group had higher load of carotid intima-media thickness and coronary artery calcification (CAC), which in the CARDIA study ranged from 6.8% to 19.5%, together with greater CAC

**Table 1.** Contribution of risk factors in the Women's Health Study

Variable	RR times 2 SD	ROC
Age	4.0	0.70
Age+ SBP	2.5	0.74
Age+ SBP+S	-	0.76
Age+ SBP+S+LDL	1.4	0.77

RR: Relative risk. SD: Standard deviation. ROC: Receiver Operating Characteristic. SBP: Systolic blood pressure. S: Smoking. LDL: Low-density lipoproteins.



**Table 1.** ROC (Receiver Operating Characteristic) curve

progression. Taken together, these findings provide a pathophysiological explanation of the marked risk difference found throughout lifetime in a population labeled as low risk in the short-term, and may have potential implications for clinical and public health.

The National Health and Nutrition Examination Survey (NHANES) from 2003 to 2006 revealed that most (82%) of the 87 million American adults (20-79 years old) present with low risk (<10% at 10 years) in the Framingham risk score.

But among that 82% at low short-term risk, more than 2 out of 3 subjects (55.5% vs. 26.5%) will have a high long-term risk. Finally, using both risks equations, most of the United States population (73.5%) has either high short- or long-term risk of cardiovascular disease.

Pencina et al. recently published an equation for predicting cardiovascular risk at 30-years. (10) They prospectively followed up 4,506 participants in the Framingham Offspring cohort, aged 20-59 years, free of cardiovascular disease and cancer, during 35 years of rigorous surveillance. The model offered excellent discrimination, C statistic 0.803 (95% CI 0.772-0.820), as well as calibration ( $\chi^2=3.98$ ;  $p=0.913$ ).

As Sniderman (11) points out, studies with shorter follow up-miss cases that would be revealed with an extended duration, behaving as false negatives, and thus “restrict our appreciation of the true importance of the modifiable factors that cause cardiovascular disease”.

# UNDERSTANDING THE PARADOX OF AGE. A MODIFIABLE RISK FACTOR?

We have previously shown that with the exception of age (and also gender), classical and causative modifiable factors of cardiovascular disease (such as LDL-cholesterol, blood pressure and smoking) appear to have little influence in the individual risk of clinical disease, if measured with the mathematical statistics of the discrimination C statistics index. However, we

have incontrovertible evidence of controlled clinical trials that show a substantial benefit with antihypertensive agents and statins, so it is unreasonable to think that they have little or no importance. Having a clearer idea of the age effect, i.e. the passing of time, will solve this paradox.

It is obvious that as well as higher LDL-C level poses greater risk than a lower LDL-C level, the exposure for 30 years to a given concentration of LDL-C would be expected to cause more cardiovascular disease than the same exposure in 3 years, probably 10 times more. Therefore, a conventional analysis does not distinguish between biological change over the years, due to causal RF (which are modifiable) and the real effects of tissue disintegration which are typical of aging and are unchanging.

In the InterHeart Study, nine modifiable RF account for 90% of the population’s attributable risk, in which the apolipoprotein B/apolipoprotein A-I ratio is responsible for 50% of the risk. The Amoris (12) study compared that atherogenic ratio (apo B/apo A-I) between the lowest (10%) decile and the highest (10%) decile, evaluating the risk of myocardial infarction at 16 years. An 80% difference that would be attributable to the modifiable atherogenic factor was seen; however, only 20% could be attributed to true tissue destruction due to aging.

In addition to this evidence, there are others where Mendelian randomization was used to estimate the effect of exposure to lower LDL-C, beginning early in life and lasting a lifetime, on the risk of coronary heart disease.

To this end, a meta-analysis with Mendelian randomization was performed to determine the impact of 9 polymorphisms in 6 different genes in a group of people with lower LDL-C since birth which was compared with the clinical benefit associated with the same magnitude of LDL-C reduction during treatment with statins. (13) The 9 polymorphisms showed no evidence of heterogeneity on the effect; among the 312,321 participants, those randomly assigned to lower long-term exposure to LDL-C were associated with 54.5% (95% CI 48.8%-59.5%) coronary disease risk reduction. This represents a 3-fold decrease of coronary disease with 1 mmol/L (38.7 mg/dL) LDL-C reduction. The study concludes that prolonged exposure to low LDL-C since the beginning of life is associated with a substantially greater reduction than that achieved with the current practice of lowering LDL-C later in life.

Therefore LDL-C, as well as hypertension and smoking, are not merely markers but causal elements of vascular disease.

Sniderman and Furberg (11) conclude that “the natural history of coronary heart disease is like a three-act tragedy. The first act introduces and develops the main characters; namely, atherogenic dyslipoproteinemia, hypertension, and cigarettes, that appear as we mature and unless something is done, persist during our entire lifetime. In the second act, that takes



place during decades, these villains relentlessly attack and progressively deform the innocent arterial wall. Finally, the third act, which may be tragically short: in an instant the plaque breaks, the artery thromboses and the hero or heroine dies; frequently everybody is unaware of the drama that was represented in their arteries. One may wonder what the difference is. In the drama of coronary artery disease, the end is not established; if some of the characters are driven from the scene as fast as they appear, the third act is missing because it never takes place."

Since clinical risk cannot increase until an intramural extensive and advanced vascular disease is present, most subjects who would be eligible for prevention with statins based on the various 10-year risk calculations will have at least one moderately advanced diffuse atherosclerosis. Therefore it makes sense to identify and treat as early as possible known causes of vascular disease.

The "causal exposure paradigm" proposed by Sniderman et al. (14) aims to prevent advanced disease assessing vascular disease treatable causes and projecting its consequences at 30 years (from 40 to 70 years) and even to the remaining lifetime, so as to identify those who would gain the most from an early pharmacological intervention. "To test prevention strategies based on the paradigm of causal exposure would provide more information on the thresholds with which RF treatment is beneficial." (14)

### SHOULD STATINS BE USED ONLY IN HIGH RISK INDIVIDUALS OR IN THE POPULATION ACCORDING TO AGE IN ORDER TO PREVENT CARDIOVASCULAR DISEASE EPIDEMIC?

Previously in the eighties, Geoffrey Rose developed the provocative concept of "the prevention paradox", (15) where "a large number of people exposed to a small risk may generate many more cases (of cardiovascular disease) than a small number exposed to high risk." The paradox occurs because the causal RF (cholesterol, blood pressure and smoking) are a continuum. Each cardiovascular RF exhibits a linear-logarithmic association with no safety thresholds, while exposure to these same RF follows a normal distribution in the population.

As a result, the distribution of cholesterol and blood pressure openly overlaps between those who will or will not develop vascular events.

Therefore it could happen that focusing exclusively in the calculated absolute high risk population, we could overlook the load of events that will occur in the majority of the average population, i.e. low sensitivity to detect those who will have events.

In a hypothetical population sample of 500,000 subjects of 0-89 years of age, the sensitivity of the Framingham risk score was estimated compared with the use of only age as population screening. (16) Using the Framingham score every 5 years, with a threshold of 20% at 10 years, would detect 66% of the population; and only using as criterion those of 55 years would detect 86%, making it necessary to lower the Framingham threshold to 8% to detect a similar number. Likewise, with a cut-off point at 50 years, 91% would be detected and for a similar effectiveness the Framingham score should be lowered to 5%.

In real life, risk algorithms at 10 years have even worse performance. In a nested case-control study (252 cases of myocardial infarction and 499 controls) taken from 45,735 people in the Copenhagen City Heart Study and the Copenhagen General Population Study, the baseline Framingham risk score calculated within 4 years prior to the event only classified 38% of those who presented myocardial infarction as high risk, 13% women and 50% men. (17)

In a cohort of 355 consecutive patients with ST-segment elevation acute myocardial infarction, risk calculation with the Framingham score and 5 other known algorithms showed that high risk was identified in 41% of EuroSCORE, 28% of QRISK, 25% of PROCAM, 16% of Reynolds, 8% of ASSIGN and 6% of Framingham patients; i.e., more than 50% would be identified as low risk by 6 different scores and would not be chosen to receive statins in primary prevention. (18)

As Tunstall-Pedoe states: "It would be wrong, however, to suggest that a high-risk strategy would prevent more than a portion of cardiovascular disease, half or more of the disease occurs in those not labeled as high risk." (19)

**Table 2.** Five risk factor levels and estimated lifetime risk at 50 years of age.

Risk Factor	Optimal RF	≥1 non-optimal RF	≥1 elevated RF	1 major RF	≥2 major RF
SBP/DBP, mm Hg	<120/80	120-139/80-89	140-159/90-99	≥ 160/≥ 100*	≥ 160/≥ 100*
Total cholesterol total, mg/dL	<180	180-199	200-239	≥ 240*	≥ 240*
Diabetes mellitus	No	No	No	Sí	Sí
Smoking	No	No	No	Sí	Sí
Lifetime risk (♂), %	5%	36%	46%	50%	69%
Lifetime risk (♀), %	8%	27%	39%	39%	50%

(\*) It indicates that if they do not have these values but are "treated", a major risk factor should be considered. RF: Risk factor. SBP: Systolic blood pressure. DBP: Diastolic blood pressure.

One should not forget that statins are as effective in people in whom cardiovascular risk is mainly influenced by blood pressure, smoking and diabetes, as among those in whom the concentration of cholesterol is the most important risk determinant. (20)

Hingorani and Hemingway conclude, "In an era of safe, inexpensive generic statins, where new methods for risk assessment poorly discriminate cases of cardiovascular disease, the balance of evidence appears currently to favour wider eligibility for statins, as part of a broader population-based effort to reduce cardiovascular risk." (20)

Even if the threshold of 7.5% at 10 years of the new risk calculator of the American College of Cardiology and American Heart Association Guideline were used, it would demonstrate that 90% of men and 50% women over 60 years would have indication to receive statins. (21)

The critical issue to extend statins to the low-risk population is to know its efficacy and safety. In the new 2013 Cochrane meta-analysis of 18 clinical trials in primary prevention and 56,934 participants (22), statins significantly reduced all-cause mortality (-14%), fatal and non-fatal cardiovascular disease (-22%), coronary heart disease (-27%), stroke (-22%) and coronary artery revascularization (-38%). These benefits of risk reduction occurred in the absence of any increased risk of cancer, myalgia, rhabdomyolysis, elevated liver enzymes, renal dysfunction or arthritis. And what is even more important, both the statin and the placebo group discontinued treatment in the same proportion (12% in both groups). This means that adverse effects were really similar in both groups (statins and placebo) and not an artifact, because those with adverse events would have shown greater proportion of statin discontinuation.

The Cholesterol Treatment Trialists' (CTT) meta-analysis at an individual level (23) performed in 2012, with 27 primary and secondary prevention clinical trials and 174,149 participants, confirmed the significant risk reduction both of major vascular events (-21%) and total mortality (-12%) for statin therapy independently of age, gender, baseline LDL-C or previous vascular disease.

An important observation is that greater RR reduction of major vascular events (including revascularization) was seen in those with 10% lower risk than in those with 10% higher risk at 5 years.

No increase in cancer incidence or mortality was observed at any level of major vascular risk events.

There is no doubt that statins are safe and effective when used in primary prevention.

We still need to know whether it is cost-effective to treat all subjects with age criteria or only those at high risk.

Macchia et al. (24) conducted a cohort study based on the population of the Italian region of Puglia, using administrative data from 920,067 individuals aged 40 to 65 years considered at low risk for not presenting

cardiovascular disease, cancer or treatment with statin, antihypertensive or antidiabetic drugs. During a 6-year follow up they identified 14,849 cardiovascular events, resulting in an incidence of 2.7% at 10 years (27.3 per 10,000 person-years).

Universal provision of statins would result in a significant decrease of risk from 27.3 to 17.5 per 10000 person-years (estimated from the Cholesterol Treatment Trial and the Heart Protection Study meta-analysis). Cost estimates (considering the real hospitalization and medication prices) show that provision of 20 mg simvastatin at the International Drug Price Indicator's price (€ 0.021 per tablet) would be both clinically effective and cost saving in men older than 44 years of age, but not in women, against the strategy of only treating high risk patients.

## CONCLUSIONS

All cardiovascular prevention guidelines, even the most recent, recommend that, except for people with diabetes or with extremely high LDL-C, the decision to start with statins should be based on the calculated risk of cardiovascular events in the next 10 years. However, we have seen that they are poor predictors of actual short and long-term events.

There is still age to consider, the strongest predictor of cardiovascular risk. But not because age itself causes cardiovascular events, but because the progressive and relentless lesion on the arterial wall due to LDL-C, blood pressure and smoking cause complex atherosclerotic lesions that anticipate and are precursors of cardiovascular events, which will increase exponentially after the age of 60 years.

This limitation in the use of risk at 10 years has led to acknowledge the high incidence of long-term events at 30 years or over lifetime, starting at the age of 50 years, unless they present with optimal or not high LDL-C and blood pressure values, no smoking or diabetes (which occurs in a small percentage of the population). The rest of the population will present a cardiovascular risk throughout lifetime ranging between 40% and 69%.

Mendelian randomization with genetic polymorphisms that decrease LDL-C levels showed a 3-fold greater reduction in cardiovascular events than the same decrease with statins, confirming that initiation is delayed or length of treatment not satisfactory.

Faced with the danger of unaffordable health expenditure, if the provision of generic statins is extended to the population according to age, studies show that costs could be reduced due to the decrease in hospitalizations for cardiovascular diseases.

The argument to be considered is a possible medicalization of the population, but some authors argue that receiving statins after a risk assessment, even though not an illness, makes the recipient feel ill compared with the rest of the people. On the other hand, if the entire population received it as a general preventive measure, similar to vaccines, it would not be

regarded as a disease. This discussion should be settled with a controlled experiment that could give us an answer.

Although the paradigm of causal exposure to RF is intuitively appealing, in a current population its average puts the majority at risk, so preventing the advanced disease that produces clinical events would be a more effective prevention strategy. However, this strategy has not been studied in controlled clinical trials, and given the extended time that would be required to demonstrate clinical benefit, such evidence would not be available in a short time, if it were ever feasible. It is possible that for the time being, studies of population dimensions with multiple observations with the best possible controls are needed.

Although the benefit of early interventions in the population can be estimated imperfectly, we could define more specifically how to start treating suboptimal or high RF, even with a low 10-year risk, since we have enough evidence that they affect long-term cardiovascular events. The analysis and clinical judgment should be essential in this process.

We must make an effort to test prevention strategies based on the paradigm of causal exposure, to provide information about the real thresholds, if any, upon which the treatment of RF would be beneficial.

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