Beyond Cardiovascular Prevention
The Road to Health Promotion

INTRODUCTION

The development of thrifty genes during genetic evolution in the paleolithic period results –together with our current lifestyle– in a burst of chronic conditions (cardiovascular disease, diabetes, cancer, and lung disease) that cause more than 60% (35 million) deaths all over the world. But most importantly for us, more than 80% of those deaths occur in middle-income and low-income countries, including ours. (1) That is, 19 million people all over the world die of cardiovascular disease and diabetes (32%); out of them, at least 15 million deaths occur in underdeveloped countries, and what is even worse, age-standardized mortality rate is 54% and 86% higher in men and women respectively compared to men and women of the same age who live in high-income countries.

WHAT WE KNOW ABOUT CARDIOVASCULAR PREVENTION WHEN WE INTERVENE IN RISK FACTORS

Here and now we will list several assumptions we identify, together with the most important experimental demonstration that corroborates them.

1. ***Prevention of vascular events is "proportionally" similar in both primary and secondary prevention.***
   In the Cholesterol Treatments Trialists (CTT) meta-analysis, (2) per 38.6 mg/dl reduction in LDL cholesterol a similar reduction in any major vascular event was observed, 22% (16-26%) for patients with prior myocardial infarction and 28% (10-34%) for those with no prior vascular disease. Since patients with previous disease have higher absolute risk, they benefit more, because 48 major vascular events per thousand patients were prevented, as opposed to 25 per thousand patients with no previous disease.
   Additionally, in the Antiplatelet Trialists' Collaboration (ATC), (3) the risk for a new vascular event was reduced by 25% with antiplatelet agents, either in patients with prior myocardial infarction or stroke, or in high risk patients with no disease.
2. ***It is corroborated by the fact that secondary prevention on a vascular territory results in a similar primary prevention on another different vascular territory.***
   When the Antiplatelet Trialists' Collaboration (ATC) (3) analyzes the subgroup of 20,000 patients who were admitted due to prior myocardial infarction, non-fatal myocardial reinfarction is lowered by 29% (6.5% with placebo as opposed to 4.7% with aspirin); at the same time, primary occurrence of non-fatal stroke decreases significantly, but with a lower absolute incidence (from 1.4% to 0.9%). Therefore, 18 non-fatal myocardial reinfarctions and 5 new strokes can be prevented per 1,000 patients treated over 2 years.
   In the subgroup analysis of 18,270 patients with a prior stroke, prevention of the target territories in which further events can occur is inverted. Risk reduction is similar, 26% for recurrent stroke ((10.8% versus 8.3%) and 27% for a new AMI (2.3% versus 1.7%), but this time, per 1,000 patients treated with aspirin, 6 new AMIs and 25 recurrent strokes are avoided.
   The same happens with the use of statins to lower LDL cholesterol levels. In the Cholesterol Treatment Trialistis' (CTT) (2), in which most patients were included due to coronary heart disease, vascular event reduction was similar for any major coronary event (RRR 23%) or any ischemic stroke (RRR 19%), but incidence decreased from 9.8% to 7.4% in coronary events (24 per 1,000 patients), and 3.4% to 2.8% in ischemic strokes (6 per 1,000 patients). In turn, the SPARCL, (4) which included stroke or TIA patients, also showed significant reduction of fatal or non-fatal stroke relapse (RRR 16%), and the new major coronary event (RRR 35%), which avoids 19 stroke relapses per 1,000 patients, and 17 new coronary events per 1,000 patients.
   We may conclude that when secondary prevention of a vascular territory is performed, the occurrence of a new event in another so-far-unaffected vascular territory is also prevented *in the same proportion*, despite the absolute benefit is much higher for the territory that was affected by the initial event.
   We could therefore arrive at the conclusion that prevention is achieved in the same proportion, whatever the vascular territory, and whatever the condition for which the treatment begins.
3. ***Prevention of vascular risk is linearly proportional and has no thresholds.***
   In a meta-analysis involving one million adults (5) from each decade of age (ranging from 40 to 89 years), the proportional difference in the risk of vascular death is the same for all the blood pressure rank, from levels as low as 115 mm Hg of systolic blood pressure and 75 mmHg diastolic blood pressure upwards. Each 20 mm Hg systolic increase or decrease in blood pressure (approximately equivalent to 10 mm Hg diastolic blood pressure) is associated with a twofold difference

or half the difference –respectively– in mortality rate from ischemic heart disease, stroke, and other vascular causes. Therefore, blood pressure is strongly related to vascular mortality, and there is no evidence of a threshold down to at least 115/75 mm Hg.

A meta-analysis on 900,000 adults (6) showed that 1 mmol/L lower total cholesterol was associated with about a half, a third, and a sixth lower coronary mortality at ages 40-49, 50-69, and 70-89 years respectively, throughout the main range of cholesterol, linear, proportional, and with no apparent threshold.

Since total risk increases with age, the absolute difference between the decades 40-49 and 80-89 years of age is about 30 times higher in the cohort study of blood pressure. And although the proportional difference in the risk decreases with age in the prospective study of cholesterol, absolute reduction effect on ischemic cardiac mortality is much higher for the last decade, the absolute difference is ten times larger.

4. ***As there are no thresholds, we should treat "cardiovascular risk patients" and not "risk factors" as discrete entities.***

Cohort studies and clinical trials have proved that with a *specific reduction* in LDL cholesterol level (each *reduction of 38.6 mg/dl lowers the risk by one quarter*), blood pressure (each *reduction of 5 mm Hg diastolic pressure and 10 mm Hg systolic pressure lowers it by one third*), or body mass index (10% per 1 U of BMI -approximately 3 kg) there is a *constant proportional risk reduction*, which is independent from the baseline value of the risk factor, and does not present threshold in the lowest values.

The constant proportional relation means that modifying all the risk factors in high risk individuals is of the utmost relevance, no matter what the reason for their high risk is, instead of treating risk factors –each one in particular– according to the (discreet) threshold criteria from the guidelines, which do not exist in clinical reality.

Some of the risk scores already tested in medical practice can be used to know the absolute risk of each patient, without taking into account the particular level of each risk factor.

The risk of developing cardiovascular disease can be predicted with the antecedent of age, sex, and family history of cardiovascular disease, and with other "risk markers", some lifestyle factors like smoking, body weight, diet and sedentary lifestyle, and other intermediate physiologic variables like blood pressure, total cholesterol, HDL cholesterol, and glycemia.

This way, absolute reduction of the risk due to modifying the risk factors will be greater for high risk patients, whatever the reason (for instance, elders, other risk factors, or pre-existing vascular disease).

5. ***To optimize the treatment, all the possible cardiovascular risk factors for those patients at risk should be reduced.***

Since reducing risk variables has a great therapeutic value whatever the baseline in high risk subjects, *all* the reversible factors should be reduced to the minimum values possible, and not just those included as "*abnormal*" in the guidelines, since risk reduction in patients will be additive and will have greater effect on each therapeutic maneuver. Reducing only those risk factors considered *"abnormal"* causes the loss of most of the possible benefit.

It has been proposed that the associated use of aspirin, two antihypertensives at half of the standard dosis and one statin on patients with high risk of vascular disease (15-20% at 10 years) would reduce coronary events by more than 70%, and strokes by more than 60%. (7)

THE CONTRADICTORY PARADOX IS THAT AGE IS THE MOST IMPORTANT RISK FACTOR, AND IT IS UNMODIFIABLE... OR IS IT MODIFIABLE?

Some authors (7) argue that primary prevention of cardiovascular disease should be considered for all the community –men and women– at a certain age. They back up their position by the fact that age is the most powerful predictor of coronary heart disease.

The 'C' statistic, or ROC (receiver operating characteristic) curve, analyzes and quantifies diagnostic reliance of the so called risk markers or factors. According to this method, the RCP (reactive C protein) and many other biomarkers scarcely improve our ability to identify subjects with risk of clinical complications of vascular disease.

But would conventional risk factors pass this test?

In the analysis of the Framingham Heart Study, the C statistic for risk due to age and sex is 0.75, and it rises to only 0.80 by adding all the conventional risk factors; secure prevention increases only 1 in 20 pairs. Cook et al. (8) present a similar analysis on women from the Framingham study; age in itself generates a C statistic of 0.731, the addition of LDL cholesterol increases it only to 0.746. Clinical variables like smoking and systolic blood pressure increase the value to 0.791, which is marginally different from the age alone but, what is even worse, the addition of LDL cholesterol does not change it prominently (C of 0.796).

Other than sex and age, it seems that blood pressure and cholesterol risk levels would not affect that much, when we have just hightlighted that the huge amount of interventional studies on controlled clinical trials show an uncontrovertible substantial benefit. In addition, in the INTERHEART Study, nine modifiable risk factors accounted for 90% of the risk attributed to populations from different countries and cultures.

A better understanding of the effect of age on the cardiovascular risk will help reveal this paradox.

However, prior to the rational analysis, we should remember that, on some occasions, all clinicians have experienced to have a patient in his/her eighties whose coronary angiography is perfectly normal, with no objective lesion. It means that sometimes, age in itself does not imply vascular disease.

While it is true we are likely to find more atherosclerotic lesions in older subjects, how many of them are due to a structural effect of tissue aging –and therefore unchangeable–, and how many are due to exposure over 30-50 years to causal risk factors of cardiovascular disease, like elevated blood lipids or blood pressure? (9)

The AMORIS (Apolipoprotein-related Mortality Risk) study (10) shows that, in more than 128,000 subjects over 40 years of age who were followed-up for a mean of 10.3 years, fatal myocardial infarction risk compared with those with the highest and the lowest deciles of apolipoprotein (apo) B/apoA-I ratio (which represents the balance between the apoB atherogenic and the apoA antiatherogenic), suggests that modifiable risk factors are responsible for 80% of the difference in the clinical result between the two groups over 16 years (Figure 1).

The authors arrive at this conclusion because they consider that the difference in risk between the highest and lowest deciles would represent the consequence of *exposure* over time to the risk factor; on the other hand, *disintegration* is the name given to the lowest decile, and it would represent the structural effect over time, which is so far nonmodifiable; this definition of *disintegration* excludes the conventional modifiable risk factors.

In this study, it appears that the effect of age on cardiovascular risk is due mainly to the outcome of an increasing exposure to conventional risk factors over a long time, which of course would be the preventable element of the risk of vascular disease imposed by the passing of time in life. This would lead us to reconsider the whole of our cardiovascular primary prevention strategy.

Most of the epidemiological studies in middle-aged populations follow participants for a relatively short time, no more than 10 years, and therefore include a small proportion of the total of cardiovascular events that will eventually arise, and which are used to develop Framingham risk scores, or others. For that reason, this calculation has a reduced true-positive fraction, which will increase over lifetime, and a high proportion of true-negatives, which will reduce in the same period. Therefore, short observation periods prevent us from fully appreciating the true importance of modifiable risk factors that cause cardiovascular disease.

Since we calculate the short–term risk, i.e. the following decade in most of the risk calculations, and because we also consider age as an independent risk

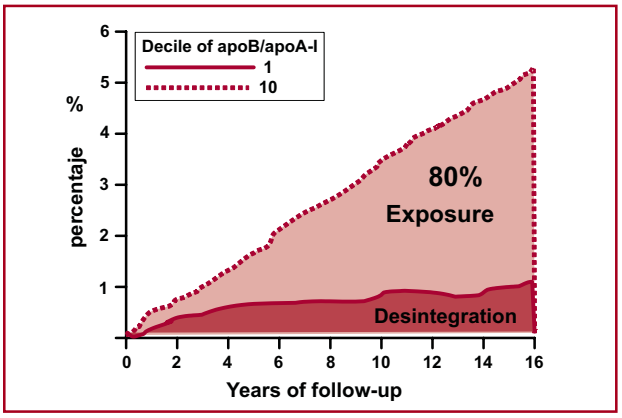

Fig. 1. AMORIS Study. Comparison of the risk of fatal acute MI among subjects with the highest and the lowest deciles of apoB/apoA-I ratio.

factor, the majority of the guidelines discourage drug therapy until the clinical events become common. We are all aware that this delay in the medical intervention can reduce side effects and drug costs.

However, all physicians go through the unpleasant experience –either their own, or heard from other physicians, or in seminars– that vascular events, and even cardiovascular death, may occur at very early stages of life, and despite the fact that these circumstances are unusual and their frequency is of little importance, the loss for the family and the society as a result of these early events and deaths is tremendous.

As an example, a 40 year old man with a total cholesterol limit of 200-239 mg/dl has a risk of coronary heart disease of only 5% in the next 10 years, but this risk increases to 43% during its course, until the subject reaches the age of 80. And even an abnormal total cholesterol ^{3} 240 mg/dl in a 40 year old man only implies a risk of 12% at 10 years, but it increases to 57% in 40 years. (11)

We thus arrive at the following question: is age a modifiable risk factor? If, as is argued, age is as important as it appears to be in conventional prediction analyses, and its effects cannot be modified, then the potential for cardiovascular health promotion and prevention would have its limitations. But as far as we have been trying to prove, this conclusion is fortunately incorrect. Age can be deconstructed in a structural effect of *disintegration* related to the passing of time, which affects us all, versus an exposure effect to modifiable causal factors, also related to the passing of time, which affects some subjects more than others.

Now, we will analyze if this first act of the vascular disease in young or middle-aged subjects –whose main actors are dyslipoproteinemia, high blood pressure, and smoking–, can be evaluated.

PREDICTION OF LIFETIME RISK OF CARDIOVASCULAR DISEASE BY RISK FACTORS BURDEN AT 50 YEARS OF AGE

In the participants of the prospective cohort Framingham study who were free of cardiovascular disease at the age of 50 (followed for 111,777 persons-years), the lifetime risk of having cardiovascular disease (until 95 years of age) was 51.7% (95% CI, 49.3% to 54.2%) for men, and 39.2% (95% CI, 37.0% to 41.4%) for women, with median survivals of 30 and 36 years, respectively. (12)

In addition to recognizing the importance of the vascular disease burden, what is even more important is that, at that age and with more adverse levels of risk factors, the likelihood of lifetime risk of cardiovascular disease increased, and the median survival decreased. Compared to participants with ^{3} 2 risk factors, those with optimal levels (Table 1) had substantially lower risks, around 10 times lower lifetime risks (5.2% versus 68.9% in men, and 8.2% versus 50.2% in women), and markedly longer median survivals (by > 39 versus 28 years in men, and > 39 versus 31 years in women); men survived for 11 years, and women, for 8 years.

Therefore, we could not rely solely on estimates of the short-term absolute risk, ten years as indicated by the guideline scores, because it may be problematic.

As we have seen, any single risk factor can produce cumulative damage and high risk if it is left untreated for many years.

Long term risk assessment is particularly relevant for younger patients, in whom exclusive attention to low short-term risk may discourage initiation of or adherence to lifestyle modification and even treatment; it would be different if we adopted a wider view of what lifetime risk is, which would be added to short-term risk data, as recommended in the guidelines.

Let's see how it works in clinical practice if we have the case of a 50-year-old nonsmoking, nondiabetic man with total cholesterol of 6.47 mmol/L (250 mg/dL), HDL cholesterol of 1.55 mmol/L (60 mg/dL), and systolic blood pressure of 160 mm Hg; using the ATP-III online risk estimator, he has an estimated 10-year risk for hard coronary heart disease of 7%. In contrast, his average lifetime risk for cardiovascular disease is nearly 70%, and his median survival is >11 years shorter than that for a man at the same age with optimal risk factors (Table 2).

If it were the case of a woman at 50 years of age with identical risk factor levels, she would have an estimated 10-year risk of only 2% compared with a lifetime risk for cardiovascular disease of 50% and >8-years-shorter median survival compared with a woman at the same age with optimal risk factors (Table 2).

These data, placed in the clinical context when dealing with a patient having these characteristics, may be much more useful to motivate therapeutic lifestyle changes and promote adherence to therapy.

The most striking findings in the present analysis are the enormous differences in lifetime risk and survival between participants with optimal risk factor levels and those with 2 or more risk factors (see Table 2).

The next question is obvious: patients who manage to live 11 years, or even more, will reach that age being disabled and with a poor quality of life, so will they be older but less self-sufficient?

However, this is not the reality. A recent study (14) shows us that individuals with a favorable risk factor profile at middle age are associated with better quality of life related to health after around 26 years of follow-up, compared with those who had intermediate or high risk factors. For example, after 26 years, both men and women with low risk factors in middle age saw themselves in excellent or very good health, and were more than twice those who had three risk factors. Moreover, they also had twice the possibility of walking without limitations, and feeling energetic, sociable and with mental health. These findings emphazise the fact that early primary prevention of major cardiovascular risk factors is a key strategy, not only to lessen the epidemic of vascular diseases and improve survival, but also to improve quality of life with better health in older age.

This new information suggests that drastic changes in lifestyle and risk factors should be considered for middle-aged individuals with one or more intermediate or high risk factors, due to the strong association with lifetime cardiovascular risk, with special emphasis on individuals with diabetes who have the highest risk and the shortest life expectancy, as well as on smokers.

	Total cholesterol (mg/dl)	Blood pressure (mm Hg)	Current smoker	Diabetes	Population (%)
All optimal RF	< 180	< 120/< 80	No	No	4
≥ 1 not-optimal RF	180-199	120-139/80-89	No	No	12
1 elevated RF	200-239	140-159/90-99	No	No	24
1 major RF (*)	≥ 240	≥ 160/≥ 100	Yes	Yes	41
≥ 2 major RFs (*)					19

(*) If the subject is a current smoker or has diabetes, these are considered major risk factors.

Table 1. Risk factors and distribution in the population at 50 years of age

Table 2. Estimation of long-term risk for cardiovascular disease and median survival

	Men			Women		
	Risk for cardiovascular disease		Median survival	Risk for cardiovascular disease		Median survival
Risk strata (*)	To 75 yers	To 95 years		To 75 years	To 95 years	
All optimal RFs	5.2	5.2	> 39	8.2	8.2	> 39
≥ 1 not-optimal RF	17.6	36.4	36	6.9	26.9	39
1 elevated RF	26.0	45.5	35	14.6	39.1	39
1 major RF (%)	37.6	54.4	30	18.0	38.8	35
≥ 2 FR major RFs	53.2	68.9	28	37.7	50.2	31

(*) The levels of risk factors are defined as in Table 1.

AN INTRODUCTORY OUTLINE TO HEALTH PROMOTION BY CHANGING LIFESTYLE

The true primary prevention measure would be to promote a healthy lifestyle which should start at birth, or otherwise during adolescence or adulthood. During these stages of life, the established social structure or the strong voices of society encourage and promote the absence of major risk factors, such as non smoking or having an active (non sedentary) life, and the inclusion of a healthy diet, which also serves to prevent overweight and obesity, two determinant factors of the exponential increase of diabetes.

Research on neurobiological, behavioral, and social sciences conclusively show that early adverse experiences can affect brain development and increase vulnerability to a wide range of physical and mental disorders. In addition, health depends on the competences built on the foundation of a stable and safe upbringing, which contents early in life, and copes with early adversities. (15)

Hardship and social negligence, exposure to violence between parents or other adults, addictive substance abuse, and mental or affective disorders destroy the protective upbringing environment that children need to become healthy adolescents and adults. Early exposure to such early adversities during adolescence lead to emotional problems and behavior disorders that include agressions, antisocial behavior, toxic substance abuse, crime, dating violence, adolescent pregnancy, anxiety, depression, and even suicide. In addition, these adverse exposures are associated with risks in adult health, like smoking, alcoholism, obesity, sexually transmitted diseases, diabetes, hypertension, and cardiovascular diseases.

It is less known than programs such as Nurse-Family Partnership, which provides visits to low-income primiparous women or single mothers during pregnancy and their infants until their first two years of age; compared to the controls, when these children reach the age of 15, they have a lower incidence of running away from their homes, they suffer fewer arrests, tend to have steady relationships, tend not to smoke, and do not consume alcohol so often. (16)

It is also known that, over the last decades, the increase of fast food habits in a cohort of young adults of the CARDIA study (17) showed a significant association between the body weight and the number of fast foods when participants were enrolled, and showed that changes over the 15 years of follow up were directly related to changes in the body weight. Participants who went to fast food restaurants twice a week or more gained an extra weight of 4.5 kg ($p = 0.005$), and their insulin resistance increased more than double ($p = 0.008$), compared with those who went less than once a week.

The same cohort registry CARDIA (18) recently showed that active commuting to work (walking or biking from home to work), which only less than 17% took, was positively associated with physical capacity (almost one more minute walk on a treadmill), and inversely associated with 50% obesity reduction, 1.7 mm Hg reduction in diastolic blood pressure, lower triglyceride and insulin levels.

Therefore, when certain situations in the social lifestyle cause deaths –as in the case of a new epidemic of influenza A H_1N_1–, the State regulation on the market seems to be reasonable, and should not be objected. For that reason, banning fast food in schools and replacing it by fruit, subsidizing or tax-relieving the produce market, increasing taxes on fast food, and reducing salt in bakery or processed foods are sensible and feasible policies which have already been implemented in some countries.

The artificial trans-fat (also called trans-fatty acids or partially hydrogenated vegetable oils, terms that fell into disuse), an invention of the 20th century civilization, are unnecesary ingredients, and also harmful for health. A simple 2% increase in energy consumption due to trans-fat increases 23% the risk for a coronary event, and it is believed to contribute up to 23% to coronary artery disease in the United States. Over the past years, the New York City Health Department (19), in the absence of changes through voluntary initiative, banned the use of artificial trans-fats for foods prepared in restaurants and fast food sites. This resulted in a fall of 51% to 1.6% in their use in less than two years.

In the Second Nurses' Health Study, the attributable risk (AR) of developing hypertension for a population of young women (27-44 years of age) who had six risk factors, (20) with 14 years of follow up, was 78%. The AR with only a BMI > 25 is of 40%.

In the prospective cohort of the Physicians' Health Study I, (21) the lifetime risk of heart failure in men at around 50 years of age (mean follow-up of 22.4 years) was 21% versus 10% in those adhering to four or more desirable risk factors.

It is clear that creating an urban architecture that includes routes, pedestrian and bike lanes, as well as improving urban bus transportation are also the State's responsibility to improve overall and cardiovascular health.

When a public scope focusing on healthy life is created, the steps needed to maintain an appropriate weight and to give up smoking are intensified and accumulated when they spread through the informal networks of our friends.

Citizens' awareness of their short-term (10 years) and long-term (the whole life) cardiovascular risk should also be a priority of the public policy. This should be easy to achieve by themselves, since any individual is capable of recognizing his/her overweight or smoking habit, two major criteria, just through the senses, and almost everybody can measure by themselves easily or have their blood pressure checked. These data, in addition to age and sex, should be enough to be aware of the risk and, at the same time, what it is that he/she should do to change it, or which community center to ask for help. This should be feasible if the role of public education on our health were, by all the possible means, a State priority.

Finally, all the health staff, and not only doctors but also nurses, ancilliary staff, and secretaries, should become educators and learners of the health promotion and the cardivascular prevention when people resort to a health care –as is said to be called– system.

Lastly, doctors, acting only on the visible part of the epidemic iceberg during an interview with enough time to dedicate to our patients, could make use of all our professional capacities and skills, from empathy to drugs, to change the natural evolution of those who might still have risk criteria, or that could have had a cardiovascular event. But we should not forget the responsibility we also have, as professionals, to promote a health system and a society to keep them healthy.

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