

GENETIC AND ENVIRONMENTAL FACTORS FOR ISCHAEMIC HEART DISEASE

*Towards more cost-effective and personalized
preventive strategies*

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As indicated by H.E. Msgr. Marcelo Sánchez Sorondo in his introductory remarks to this conference, the major, most ambitious challenge nowadays in this field is primary prevention worldwide.

In my presentation I will discuss the potential contributions to more cost-effective preventive strategies that could derive from a more precise understanding of the varied genetic and environmental components of Ischaemic Heart Disease (IHD).

Achievements of primary prevention

Conclusive evidence indicates that the average statistical probability of developing cardiac ischaemic events in population subgroups can be identified on the basis of the presence of traditional predisposing risk factors and that such average probability can be reduced by over 50% by their correction.

These remarkable achievements indicate the opportunity for the immediate implementation of the strategies for risk reduction proven successful and cost-effective.

However the current statistical preventive approach presents limitations. These limitations could be overcome by a better understanding of the mechanism responsible for the actual development of acute ischaemic cardiac events, which could allow a more cost-effective, personalized prevention.

Limitation of statistical preventive approaches

The possibility of stratifying individuals into prognostic categories of risk, has led to focus the attention on the percentage reduction of the number of individuals who develop an event, paying insufficient attention to investigate:

1. Why the large majority, in spite of the same burden of global predisposing factors, doesn't develop events;
2. A substantial percentage develops events in spite of correction of risk, or in the absence of any known risk factor.

Indeed, if in a given group, for example, on average, 30% of individuals are estimated to be at risk of an event, this implies that the remaining 70% with the same risk level will not have an event!

At present there is no way, nor any interest, to try and identify, within the same level of risk, the 30% who are vulnerable from the 70% who are protected. Thus 100% are treated and worried (with the inherent discomfort, risk of side effects and costs) and it may be that one half of those treated will have events in spite of treatment, and in addition a substantial fraction will have events although they do not have known risk factors [1] (Figure 1, p. 196).

The overall final conclusion of the Pooling Project was that ‘coronary atherosclerosis is very common but acute cardiac events are very rare!’

Striving to implement available preventive strategies, these issues are usually neglected.

An innovative approach to these issues should start from the reconsideration of the universal validity of the traditionally established paradigm that risk factors, acting over a period of years and decades, cause the progressive accumulation of coronary atherosclerosis which, in turn, when it reaches a critical threshold, causes ischaemic cardiac events. Such paradigm is so prevalent that often the terms *coronary atherosclerosis* and *IHD* are used interchangeably.

Yet, this reductionist paradigm is true only as a crude first approximation because it does not account for many clinical observations, which are systematically disregarded, confirming Carl Popper’s statement that ‘The dogmatic way of thinking is due to a natural need of regularities and to the inherent mechanisms of discovery. Mechanisms that induce to search for regularities’.

Risk factors atherosclerosis and IHD

The universal validity of this traditionally accepted paradigm is challenged by 4 major clinical observations which demand a more precise understanding of the relationship among risk factors, atherosclerosis and ischaemic events.

1. In a recent meta-analysis of 122,450 patients with coronary disease, 15% of females and 20% of males had none of the known risk factors. About 40% had only one, about 30% had 2 and only about 10% had 3 risk factors [2]. This is in agreement with many previous findings and with the observation of the Italian registry by ANMCO, just completed (but not yet published) which reveals that, of over 10,000 consecutive patients admitted to 168 Italian coronary care units over a 6-month period, about 30% had none of the 4 major risk factors.

Thus established predisposing risk factors do not appear a necessary pathogenetic component of IHD.

2. In a metanalysis of 350,000 individuals, among those with a ≥ 2 risk factors, during an average 30-year follow up, 70% died of non cardiac causes [3].

Thus established predisposing risk factors do not appear to be a sufficient pathogenetic component of IHD.

3. Intracoronary IVUS shows a weak correlation between atherosclerotic burden and risk factors [4].

This observation is totally consistent with the findings of the Pooling Project which failed to find any correlation between coronary atherosclerotic burden, estimated at postmortem, and hypertension or smoking and only a very weak correlation with total cholesterol [5]. Indeed the same study demonstrated a very wide overlap in the extension of coronary atherosclerotic raised fibrous plaque in postmortem studies of patients who died of ischaemic heart disease and of controls who died of non cardiac causes as illustrated in Figure 2 (see p. 177).

Thus the extension of coronary atherosclerosis is on average greater in patients who died of IHD, but with a very wide overlap with controls, particularly above the age of 60, and is only weakly correlated with total cholesterol levels, but not with the other risk factors.

4. Following an acute myocardial infarction, many patients remain totally symptom-free for years and decades (also in the pre-statin era). Moreover patients who present with chronic stable effort angina, on average, have a much greater extension and severity of coronary atherosclerosis than those presenting with their first myocardial infarction [6], who often have single vessel coronary disease and only a mild or moderate stenosis in the infarction-related artery in about 70% of the cases.

Thus the paradigm of a critical threshold of coronary atherosclerosis which, once reached, causes an acute ischaemic event, appears too simplistic and not easily compatible with these observations. In many cases severe coronary atherosclerosis may remain stable, or may return quiescent for years or decades (did the atherosclerotic burden decrease?), conversely some patients may develop infarction also with a mild atherosclerotic burden.

Environmental and genetic risk factors for acute myocardial infarction

We just completed a multiethnic study in which we obtained a blood sample within a maximum of 6 hours from the onset of symptoms in patients with their first ST segment elevation myocardial infarction (FAMI project) admitted for emergency coronary recanalization belonging to

three ethnic groups from metropolitan areas: Italian, Scottish and Chinese and in matched controls (Tables 1, 2 and 3). They had no previous evidence of IHD and, given their very early assessment, their risk factors should closely reflect those immediately before the development of symptoms.

The initial analysis of the data demonstrated a very large dispersion of all individual risk factor values about the medians, similar in the three ethnic groups, and overlapping very widely with those of controls.

Thus the similarity of risk factor levels in very carefully selected patients, with an unequivocal diagnosis of acute infarction, from metropolitan areas of three distinct ethnic groups, suggests a large prevalence of 'western' lifestyle predisposing risk factors compared to genetic mechanisms, which may play a modulatory role in some individuals.

This observation is consistent with the discouraging results obtained by the candidate gene approach and by the limited quantitative success obtained so far by genomic wide screen in the search for single common genetic correlates in a broad clinical syndrome such as myocardial infarction [7]. These findings are not a surprise for haematologists who followed a pathogenetic rather than a statistical preventive approach for anemia!

Future development of cardiovascular prevention

The immediate goal is undoubtedly the promotion of the preventive strategies which are already proven to be, on average, cost-effective. In countries which had great excess of cardiovascular mortality such as Norway and Finland, control of risk factors, produced by extensive lifestyle changes, reduced risk to the level of Mediterranean countries.

Similar results can also be achieved in countries which did not have such a high baseline risk to start but certainly will require massive coordinate campaigns by physicians, mass-media and departments of health and education.

However, preventive strategies should not rely only on what we already learned. The promotion of healthier lifestyles and the timely correction of elevated risk factors should be associated to novel research strategies which should complement the information collected by focusing the attention on 'average' prognosis and 'average' response to intervention, during the last century.

The time has come to focus research on the two extreme group of patients who deviate most from the average prediction: those who do not develop events in spite of a large risk factor burden (in order to discover their protective factors) and in those who develop events in the absence of risk factors (in order to discover their novel risk factors).

Finally known predisposing factors only indicate the statistical probability of an event, but cannot tell in whom and cannot tell whether the event will develop in one month, in one year or in ten years. Thus it would be essential

to concentrate research also on the actual triggers of acute myocardial ischaemic events, responsible for the transition from stability to instability of coronary atherosclerosis (which appears to be largely independent from total coronary atherosclerotic burden!).

FAMI STUDY	
•	First STEMI
•	No previous history of CAD
•	Within 6 hours of onset of symptoms
•	Matched Controls

Table 1.

Patients Enrolment	
	FAMI
Italy	370
Scotland	234
China	443
<i>Total</i>	1047

Table 2.

FAMI BioBank	
•	WHOLE BLOOD: 10 ml
•	SERUM: 10 ml divided in 0.5 ml cryovials
•	PLASMA (NA-Citrate): 6-8 ml stored in 0.5 ml Cryovials
•	PLASMA (Li-Heparin): 6-8 ml in 0.5 ml cryovials
Stored at -80°C	

Table 3.

References

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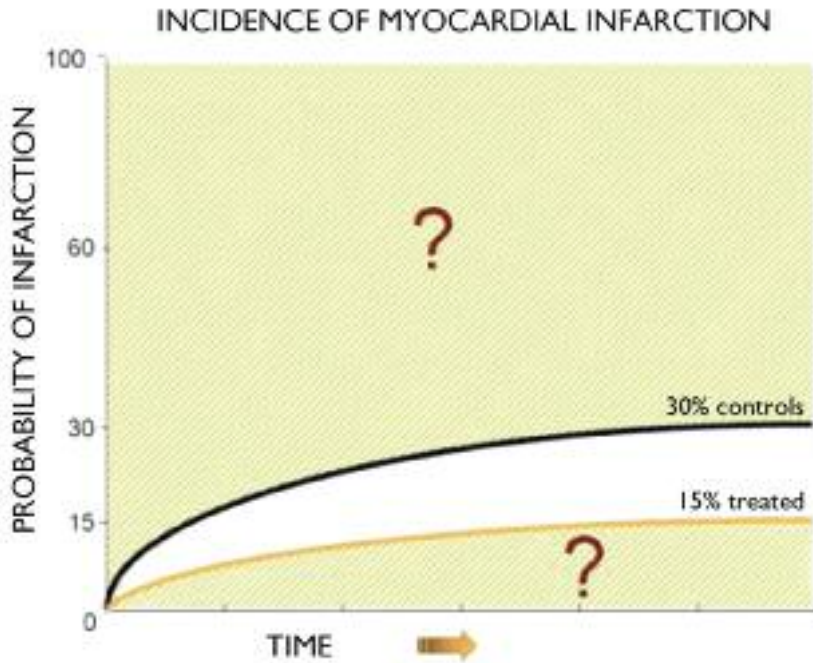


Figure 1. The diagram illustrates a preventive intervention that reduced the rate of MACE by 50% in patients with an average risk of 30%. This is remarkable, yet 15% of the treated patients had events despite treatment, and the remaining 70% had no events with no treatment. Socio-economic, clinical, and psychological factors demand a shift of research from the white area to the hashed areas.

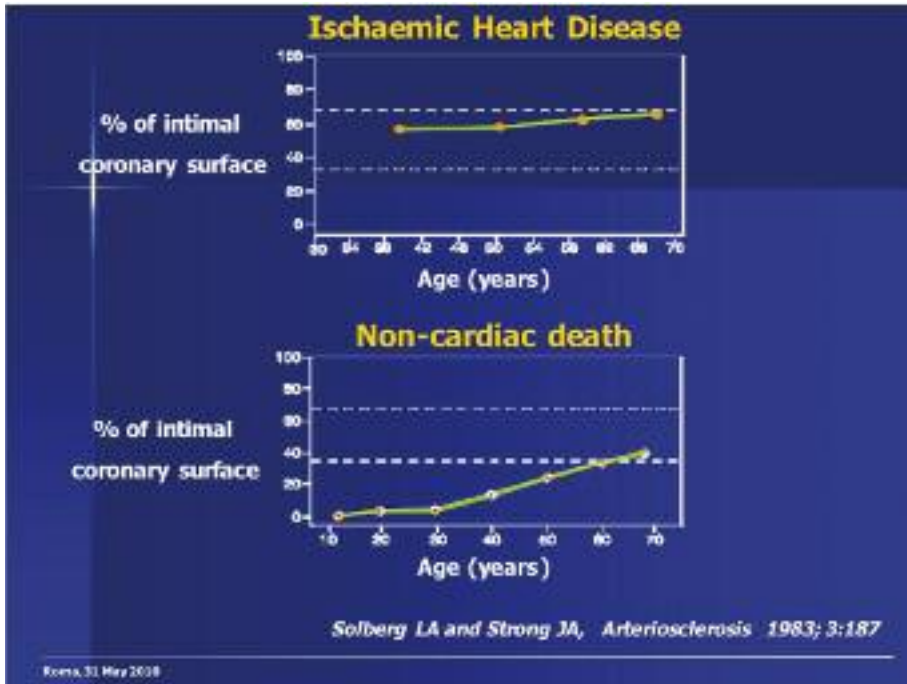


Figure 2. Percentage of the intimal surface of the major coronary arteries covered by raised fibrous plaque in patients dying of IHD and in controls. Data from the Oslo study, one of the centers involved in the International Atherosclerosis Project; the results from the other centers were similar. The percentage of the intimal surface of the coronary arteries covered by raised fibrous plaques in patients dying of IHD (A) was, on average, higher than that found individuals dying of noncardiac causes (B), but there is considerable overlap between the two groups (mean values are indicated by open circles connected by dashed lines). Many patients in the IHD group had less than one-third of the intimal surface of the coronary artery covered by plaque; conversely, many individuals in the control group had more than two-thirds of the intimal surface covered by plaque. Some individuals have no plaques, even in old age, indicating that the process is not an inevitable consequence of aging (modified from ref. 5).