

Primary and secondary risk factors for coronary heart disease: Their role in prevention*

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Introduction

CORONARY HEART DISEASE (CHD) is the dominating cause of death in most industrialized countries. This group of diseases also causes considerable disability for surviving victims. The high initial mortality in combination with the above-mentioned fact as well as the limited possibilities of treatment in the acute phase have called for primary preventive efforts. The generally bad prognosis for those who survive an attack of myocardial infarction (MI), with about 30 times higher mortality during the first year of follow-up, than in a comparable age group, has also called for secondary preventive measures.

In order to enable such measures knowledge about causation is desirable, but not mandatory. If possible etiologic factors can be defined, the effect of various intervention measures is usually well worth studying. Thus, preventive trials in men might be the only possibility of answering the questions concerning etiology. An initial step in these efforts is to isolate risk factors for the various stages of the disease. The present paper summarizes studies concerning risk factors and prevention carried out at the Section of Preventive Cardiology in Göteborg.

Primary risk factors

The classical method for finding risk factors is to study a population prospectively. This method can be used if the prevalence of the risk factor and the incidence of end-points (non-fatal and fatal

myocardial infarction - MI -, sudden coronary death - SD -, etc) are sufficiently high. This is true for several of the conventional risk factors for CHD. Some factors are, however, uncommon in the population, and prospective studies might not detect such a factor, e.g. diabetes mellitus. Well designed case-control studies with carefully performed analysis of possible bias and confounding variables can be used in this case. In case-control studies it is of special importance to allow for the effects of selection due to death, as often only survivors can be analyzed. In the case of MI several factors are affected by the disease process per se, and these effects have been evaluated by us (Wilhelmsen *et al.*, to be publ).

Another problem in long-term prospective studies is that some factors might be connected with a certain end-point event only during a very limited time period before the event. Such a factor will be nearly impossible to detect by prospective studies in general populations, but might be found with the aid of case-control studies or by specially designed prospective studies using selected groups of e.g. high risk individuals. An example of such a possible risk factor is psychological stress which can precipitate an acute MI or SD.

Table I summarizes results of both prospective and case-control studies performed in the same community with standardized procedures. The results are based on data published previously (Wilhelmsen *et al.* 1973, Elmfeldt *et al.* 1975, Tibblin *et al.* 1975, Elmfeldt *et al.* 1976, Elmfeldt *et al.* 1976, Elmfeldt *et al.* 1976, Wilhelmsen *et al.* 1976, Bergstrand *et al.*, in press, Wilhelmsen *et al.*, subm for

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publ, Wilhelmsen *et al.*, in press, Wilhelmsen *et al.*, to be publ). Besides the male sex and age, early parental death (= the parents of the index case dying at low age) is associated with MI in univariate analysis, and at least in some of the studies also significant in multivariate analysis. This factor was not significantly associated with other risk factors for CHD. It is probable that this factor mirrors a genetic tendency towards CHD. Only one of the lipid factors, namely hypercholesterolemia, stands out as a significant risk factor in multivariate analysis in men. In women, it seems as if hypertriglyceridemia is more important than hypercholesterolemia. In accordance with all other studies, hypertension is a risk factor also in multivariate analysis.

Two factors directly connected with personal habits – tobacco smoking and alcoholic intemperance – are associated with MI; the first factor being the strongest risk factor in the male, middle-aged population.

In Fig. 1 is given a schematic overview of the possibilities of confounding of the risk factors for MI. The various factors may be associated directly with MI, but also in some instances via other factors. The signs in Fig. 1 can be treated in usual mathematical ways; minus times minus gives plus, and minus times plus gives minus. Both smoking and hypertension are positively associated with MI, and these associations cannot be explained by the

Table I
Risk factors for myocardial infarction and sudden coronary death according to studies in Göteborg

Factor	Type of analysis		
	Univariate	Prospective	Case-control Univariate
		Multivariate	
Male sex	†	†	†
Age	†	†	†
Parents dying early	†	(†)	0
Hypercholesterolemia	†	†	†
Hypertriglyceridemia	†	–	†
Diabetes	†	0	†
Overweight	–	–	–
Increased body fat	–	–	–
Hyperuricemia	–	–	–
Hypertension	†	†	†
Tobacco smoking	†	†	†
Alcoholic intemperance	†	†	†
High coffee consumption	–	–	–
Physical inactivity, occupation	–	–	–
Physical inactivity, leisure	†	–	†
Stress	–	–	†
Angina pectoris	†	0	†
Dyspnea	†	†	†
ST-T exercise	†	–	0
High respiratory frequency exerc.	†	–	0
Low max. exercise performance	†	†	0

† = significant association, 0 = not studied

influence of either of these factors on the other. Serum cholesterol and serum triglycerides are, however, positively associated with each other and their association with MI might well be caused by either of these factors predominantly. By using multivariate analysis it is possible to solve this problem mathematically, but the biological mechanisms can naturally not be detected by this method.

Alcoholic intemperance is of great theoretical and practical interest as a risk factor. Thus, this factor has turned out to be exclusively connected with fatal CHD events but not with non-fatal MI. This might hypothetically imply an effect on cardiac arrhythmias rather than on the atherosclerotic process per se, or on any process connected with the progress of the myocardial injury. This explanation is supported by findings at autopsy; these patients seem to die suddenly with relatively moderate coronary artery stenoses and rather uncommonly any anatomically detectable MI (Wilhelmsen *et al.*, to be publ). Further studies concerning the possible the possible mechanisms are in progress.

Confounding of risk factors for myocardial infarction.

⊕ = positive association ⊖ = negative association

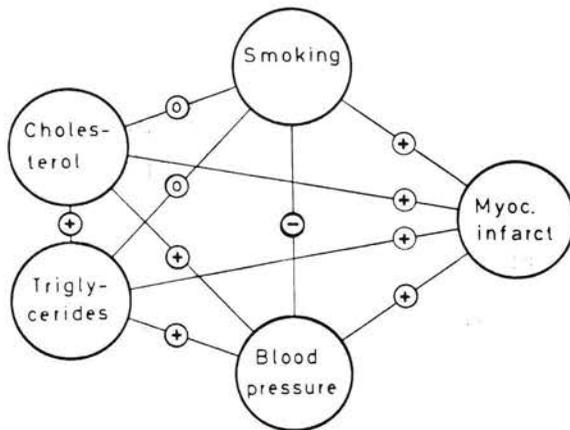


Fig. 1
Schematic overview of the confounding of risk factors for myocardial infarction.

The association between MI and the two factors physical inactivity during leisure time and stress are doubtful. None of these factors are significantly associated with MI in multivariate analysis and their significant association with CHD in case-control studies, must be regarded with great caution. The patients may have overemphasized their pre-infarct situation retrospectively. With respect to psychological stress another explanation is, however,

possible. The stressful experience might be undetected in the long-term prospective studies because the stress is only of importance during a very short time before the infarct, like what was discussed previously. Thus, psychological stress may be of importance only in certain situations when the heart is especially sensitive to various adverse influences. Continuous recording of events in subjects at high risk of suffering a MI or SD might be the only clinical – epidemiological way of looking into these problems.

Two factors associated with physical performance are risk factors in univariate as well as in multivariate analyses, namely dyspnoea during exertion and low maximum exercise performance (Wilhelmsen *et al.* 1973, Tibblin *et al.* 1975, Wilhelmsen *et al.*, 1976 and to be publ). It is of interest to note that low maximum exercise performance is of greater importance as a risk factor than ST- or T-changes in the ECG at rest or during physical exercise. Presently we cannot explain the association between low maximum performance and MI. It may be, that it is a very early sign of CHD causing reduced myocardial performance but no perceivable pain at that instance.

Possibilities of primary prevention

Out of the primary risk factors listed in Table I, the most important ones are also treatable, at least to some extent. These are tobacco smoking, hypercholesterolemia and hypertension. The statistical associations between these factors and MI do not, however, necessarily imply that a cause-effect relationship is present. Genetical or other background factors may well be responsible both for the elevations of blood cholesterol and blood pressure, or the tendency to become a smoker, and parallelly affect the coronary vessels and myocardium increasing its vulnerability. This possibility is shown in Fig. 2. If such factors are responsible for both the risk factors in question and CHD, treatment directed towards the risk factors would not be of particular value. If the mechanisms, however, are as depicted in Fig. 3, treatment against the risk factors might very well influence the incidence of MI even if the hypothetical factor X could not be influenced. As animal studies cannot mirror the circumstances in man, intervention trials aiming at reducing the risk factors have to be performed. Such a study is under way in our group (Wilhelmsen *et al.* 1972). Recently, it has been found that anti-hypertensive therapy reduces CHD morbidity (Berglund & Wilhelmsen, to be publ). Similar results concerning reduction of lipid levels and smoking habits are not available yet.

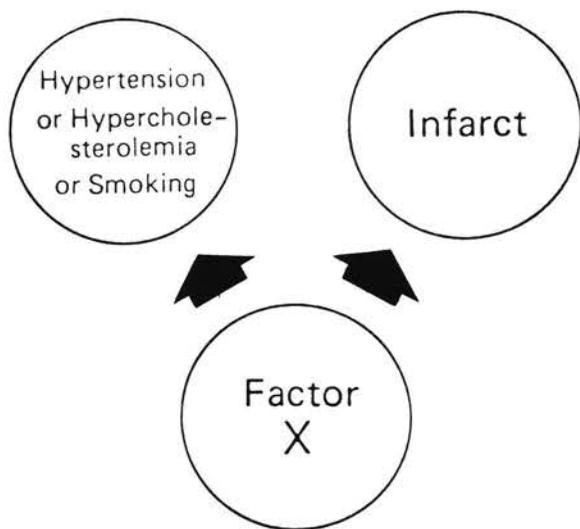


Fig. 2

Schematic relationship indicating that (perhaps) genetical or other background factors may affect the coronary vessels and myocardium increasing its vulnerability.

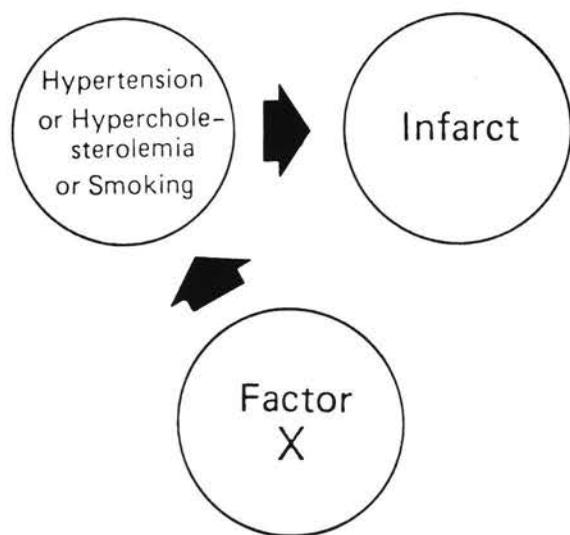


Fig. 3

Schematic relationship to show that (perhaps) the risk factors are intermediate between factor X and myocardial infarction.

Secondary risk factors

Cardiovascular diseases are the immediate causes of death in 90% of the cases during at least 5 years' follow-up. It can be expected that certain factors will stand out as more closely associated with new events of CHD among individuals already

having demonstrated their susceptibility to CHD. Furthermore, it is probable that risk factors might be different in different stages of the disease.

In Table II are listed the risk factors for a following event after a MI found in the studies in Göteborg. From several studies it is evident that other factors than the conventional primary risk factors are more important during the hospital phase (Henning *et al.* 1975) and during the first 2 years of follow-up (Vedin *et al.*, in press) and even up to 4 years' follow-up (Wilhelmsen *et al.* 1975). The most important of these factors all mirror the size of the myocardial damage as this is evaluated by clinical methods. Hitherto, there is no proof available that those who suffer an extensive myocardial damage are more heavily burdened by known primary risk factors. Some indications in this direction were, however, found in one study comparing patients with non-fatal MI and fatal CHD (Tibblin *et al.* 1975). It seems as if the infarct size is more dependent on other factors such as local catecholamine release or some other (undefined) factor (Wilhelmsen 1976). The infarct size may also be a reflection of a more extensive coronary

Table II

Risk factors for a following event after a myocardial infarction according to studies in Göteborg

	Type of analysis	
	Univariate	Multivariate
A. Fatal		
Age	†	†
Previous infarction	†	†
Major myocardial injury	†	†
Arrhythmias	†	-
Angina pectoris	†	(†)
Hypercholesterolemia	-	-
Hypertriglyceridemia	-	-
Diabetes	†	0
Hypertension	-	-
Smoking	†	†
Physical inactivity	-	-
B. Non-fatal		
Hypertension	†	†
Smoking	†	†

artery disease, which is indicated by a study of coronary angiography and autopsy in non-fatal and fatal cases of CHD (Wilhelmsen *et al.*, to be publ). This might also be the reason for the increased mortality after a first MI in patients with angina pectoris (Wilhelmsson *et al.*, to be publ). The hemodynamic load during the acute, vulnerable phase of the MI is certainly of great importance.

The importance of cardiac arrhythmias for prognosis has been extensively studied, but interestingly enough our studies have not shown that arrhythmias are of predictive importance when other variables indicating an extensive myocardial damage have been taken into consideration. That might have to do primarily with the fact that the tendency towards cardiac arrhythmias during the acute stage is very closely related to the infarct size. A very careful analysis of the importance of arrhythmias in addition to infarct size variables during the hospital phase is going on.

Of the most important primary risk factors hypercholesterolemia, hypertension and smoking only the last mentioned factor is a significant risk factor for a fatal event after a MI (Wilhelmsson *et al.* 1975, Wilhelmsson *et al.*, subm for publ, Aberg *et al.*, subm for publ, Johansson *et al.*, to be publ). The effect of these (primary) factors has only been studied for a 5-year follow-up period, and it is possible that they are of importance only for those patients who have survived that time. The present findings, however, indicate that other means of secondary prevention than dietary advices and hypotensive therapy might be more useful for preventing death. Hypotensive therapy is evidently indicated from other reasons (e.g. preventing stroke) in these patients.

An interesting result is that we only found hypertension and smoking to be risk factors for a non-fatal MI after a first event (Table II). As these two factors are also primary risk factors, it might had been expected that also hypercholesterolemia had been connected with the rate of non-fatal recurrences after the initial phase, but there was no tendency whatsoever in this direction (Johansson *et al.*, to be publ).

It should be remembered that patients having suffered a MI are selected in several respects. They have demonstrated themselves to be sensitive to myocardial damage. The finding that the post-MI cholesterol value does not have any importance for prognosis does not imply that cholesterol-lowering regimen is of no value. The same reasoning applies to other "primary" risk factors. A patient with

MI and low cholesterol (or low blood pressure, or low/no tobacco consumption) has probably other factors (known or unknown) which are of importance for the risk.

During the first year after an initial MI the excess mortality and morbidity is approximately 30 times, and during the second year 10 times among MI patients in comparison to healthy men of the age group 40–49 years (Vedin *et al.*, in press). In this period, and even up to 5 years after a MI, the risk is predominantly determined by the size of the previous MI. So far, we have had very little knowledge concerning possibilities of reversing the serious effects of the big MI. Recent studies have shown that beta-blockade can reduce the infarct size in animals.

Secondary prevention

Knowing the adverse effects of a big MI another interesting intervention measure would be to try to reduce the initial infarct size. One of the most interesting group of drugs which has turned out to be of some value in animal studies is beta-blockers. A double-blind clinical trial using beta-blockers in the acute stage of MI is going on. One aim is to study the effect on long-term mortality.

As already discussed above stopping smoking after a MI was of value (Wilhelmsson *et al.* 1975). This has already been discussed. Any trial concerning the effect of hypotensive treatment after MI is not ethically acceptable and of minor interest as there are reasons for treating hypertension whatever the effect might be on CHD mortality. We did not find any association between cholesterol values and prognosis after a first MI during 5 years' follow-up, and cholesterol-lowering drugs was not either of value according to the Coronary Drug Project (Coronary Drug Project Research Group 1975).

Physical inactivity has been discussed as a risk factor both for a primary event and for following events, but our results are largely negative. In a controlled trial it was also shown that physical training did not improve prognosis with the respect to non-fatal or fatal recurrences (Wilhelmsen *et al.* 1975). Some effects on the psychological and physiological well-being were, however, found (Sanne *et al.* 1973).

Concluding remarks

It has been found that the risk factors for a primary CHD event differ from a secondary event to some degree, and this fact logically implies different preventive measures in primary and

secondary prevention. Antismoking advice is logical from many aspects, but it is not yet proven whether or not it has any preventive effect for a first MI. Treatment of hypertension seems to be beneficial, but it is uncertain whether decrease of cholesterol values will lower incidence of CHD. A practical problem in this context is also the possibilities of inducing these changes in the population. Ongoing primary preventive trials will give answers to these questions.

In secondary prevention there are good evidence for the beneficial effect of beta-blocking agents at least in the earlier stages of the disease, and furthermore cessation of smoking is evidently beneficial during up to 5 years after MI. The possible effects of other intervention measures are not settled yet.

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