Coronary risk factors: new perspectives

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The predisposing and precipitating causes of acute myocardial infarction (MI) are multiple; furthermore, different individuals may have different susceptibility, to a large extent genetically determined, to each of them. In spite of the complex aetiology of MI and of our limited knowledge of the causes responsible for the formation of persistent occlusive thrombosis in epicardial coronary arteries, the achievements obtained by controlling traditional risk factors are remarkable. Traditional risk factors, however, have a limited sensitivity among subjects with low/moderate levels of risk. Furthermore, in particular among subjects at medium risk, current preventive strategies are limited by the low incidence of preventable events which makes it necessary to also treat the vast majority of subjects who would not develop cardiac events even without any treatment. An improvement in preventive strategies for IHD can be achieved with the identification of: (1) new risk factors; (2) genotypes enhancing the susceptibility to specific risk factors; (3) phenotypes and genotypes making patients susceptible to specific preventive strategies; (4) genotypes protecting from risk factors. Although a word of caution is necessary as a number of recent studies on genetic markers, on new risk factors and on the interaction between genetic markers and environment have failed to withstand the rigour of population-based studies, the early findings available to date suggest that cost-effective preventive strategies based on individual susceptibility to specific predisposing and precipitating causes of MI may become a reality in the foreseeable future.

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More than a third of all deaths in developed countries are directly attributable to ischaemic heart disease (IHD). In the US alone, more than 1.6 million myocardial infarctions (MI) occur annually, of which 500,000 result in death before hospitalization. Moreover, recent data show an increasing burden of cardiovascular disease as suggested, for instance, (1) by the increased prevalence among teenagers of cigarette smoking, overweight and sedentary habits in the US, (2) by an increase in age-adjusted death from IHD from 1992–1993 in the US and (3) by an increase in the projected proportion of worldwide death from IHD from 28.9% in 1990 to 36.6% in 2020. There is no doubt that IHD prevention is a major public health issue for the community at large as well as for the cardiologist and the general practitioner. However, cost-effective prevention of IHD is limited by our imperfect knowledge of the multiple causes of MI.

Pathogenesis of myocardial infarction

Cardiologists are often puzzled by the extreme variability of clinical and angiographic features of patients who develop MI. A sizeable proportion of these patients, but not all of them, present one or more classical risk factors. Some patients present with unheralded MI, other patients develop MI after having suffered for years or even decades of chronic stable angina, still other patients present MI preceded by a period of unstable angina. Coronary angiography after MI can reveal lack of detectable stenoses at one end of the spectrum and severe triple vessel disease at the other extreme. These varying clinical and angiographic features indicate that MI is a multifactorial disease and that the importance of the different pathogenetic components might be different in different patients. A cost-effective prevention of IHD is made difficult not only by the multiple predisposing and precipitating causes of MI, but also by the variable individual susceptibility to each of these predisposing and precipitating causes. In order to set the stage for a cost-effective prevention of IHD it would be necessary to know in each subject: (1) his susceptibility to various atherogenic stimuli which may alter the structure and function of the arterial coronary wall and cause

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the formation of the atherosclerotic plaque; (2) his susceptibility to various destabilizing stimuli which may act on the 'locus minoris resistentiae' represented by the atherosclerotic plaque and trigger acute coronary syndromes.

Atherogenic stimuli
The atherogenic stimuli responsible for the formation and progression of the stable atherosclerotic plaque are numerous (Figure 1). The emphasis on lipid atherogenic stimuli in the last 20–30 years is related to the evidence that raised blood cholesterol levels are associated with an increased risk of IHD and to the demonstration that the reduction of blood cholesterol levels results in the reduction of the risk. A similar emphasis has been given to mechanical atherogenic stimuli, such as arterial blood pressure: indeed, raised pressure levels are associated with an increased risk of IHD and reduction of pressure levels results in a reduction of the risk. Similar considerations apply to chemical and metabolic atherogenic stimuli such as smoking and diabetes.

More recently, a growing body of evidence has shown that endothelial dysfunction is an early alteration produced by the various atherogenic stimuli. Of note, endothelial dysfunction in asymptomatic subjects is associated, in turn, with an increased risk of IHD.

Finally, a number of studies have recently shown that inflammatory cell activation plays an important role in the transition from endothelial dysfunction to the formation of the atherosclerotic plaque.

Acute destabilizing stimuli
Patients with severe obstructive atherosclerosis can present stable angina for many years without developing MI thus suggesting that the latter is caused by the superimposition of acute destabilizing stimuli. Myocardial infarction may be either the result of an exceptional local event or of a very unusual coincidence of multiple, adverse local and possibly systemic events that may have a different prevalence in different ethnic, geographical, age and sex groups.

Coronary thrombosis responsible for MI can be due to three main pathogenetic mechanisms (Figure 2).

In a minority of patients smooth muscle cell hyper-reactivity causes spasm of epicardial arteries resulting in blood stasis and thrombus generation; the causes of the hyper-reactivity are still unclear.

At least half of the patients with acute coronary syndromes exhibit a marked increase of systemic markers of inflammation; of note this percentage is much lower in patients with stable angina. Indeed Liuzzo et al. found levels of C-reactive protein (CRP), a prototypic acute phase reactant, greater than 0.3 mg/dl in 65% of patients with unstable angina but only in 13% of patients with stable angina; similarly Berk et al. found levels of CRP greater than 0.6 mg/dl in 90% of patients with unstable angina but only in 13% of patients with stable angina. More recently, Heeschen et al. found levels of CRP greater than 0.5 mg/dl (prespecified as the upper limit of normal) in 62% of 447 patients with an acute coronary syndrome without persistent ST segment elevation enrolled in the CAPTURE study; in a similar population of patients enrolled in the TIMI 11 study Morrow et al. found that 25% of 437 patients had CRP levels greater than the 99th percentile of its distribution in healthy subjects. In patients in whom coronary instability is associated with markedly raised levels of systemic markers of inflammation, activation of inflammatory cells in the culprit stenosis is likely to play an important pathogenetic role. Platelet inflammation may trigger a cascade of events leading to thrombus formation. Indeed, cytokines released by activated inflammatory cells can cause: (1) endothelial activation which changes the physiological anticoagulant and vasodilator properties in procoagulant and vasoconstrictor properties; (2) smooth muscle cell hyper-responsiveness to constrictor stimuli; (3) enhanced metalloproteinase release resulting in collagen degradation of the fibrous cap, plaque fissuring and exposure of the highly thrombogenic component of the core. The causes of inflammation are still elusive.

In the remaining patients without evidence of coronary spasm or systemic signs of inflammation the precipitating causes
of coronary thrombosis responsible for acute MI are still largely unknown.

Prevention of ischaemic heart disease

Achievements

In spite of the complex aetiology of MI and of our limited knowledge of the causes responsible for the formation of persistent occlusive thrombosis in epicardial coronary arteries, the achievements obtained by controlling traditional risk factors are remarkable. Indeed, in asymptomatic subjects the risk of IHD can be reduced by 50% with smoking cessation, by 30% by 16% with a 6 mmHg lowering of arterial blood pressure.1 Furthermore, in three primary prevention trials aspirin treatment resulted in a significant reduction, ranging from 32% to 44%, of the incidence of MI during a 5-year follow-up.26–28

Current limitations

Traditional risk factors have a limited sensitivity among subjects with low/moderate levels of risk. For instance, in the UK Heart Disease Prevention Project the probability of MI developing over 5 years was predicted with knowledge of age, blood pressure, cholesterol concentration and smoking habits.29 Indeed, the incidence of coronary events was much higher among subjects in the top 15% of risk distribution than among the remaining subjects (10.3% versus 3.5%). Nevertheless, the absolute number of events was lower in the former than in the latter (115 versus 235). Similarly the Multiple Risk Factor Interventional Trial (MRFIT) assessed coronary risk in 316 099 men followed up for 12 years: coronary heart disease death number was 3453 among smokers but 2874 among non-smokers, it was 2215 among subjects with cholesterol levels ≥5.7 mmol/l but 1527 among patients with cholesterol levels <5.7 mmol/l, it was 2215 among subjects with diastolic blood pressure ≥92 mmHg but 4132 among subjects with diastolic blood pressure <92 mmHg.5 Furthermore, in particular among subjects at medium risk, current preventive strategies are limited by the low incidence of preventable events which makes it necessary to also treat the vast majority of subjects who would not develop cardiac events even without any treatment. This concept is highlighted by the observation in the Framingham study that 70% of subjects at high risk because of elevated levels of total cholesterol (>6.7 mmol/l) were alive and in good health after 30 years of follow-up.30

Finally, not all subjects at risk are susceptible to untargeted prevention strategies.

The way forward

An improvement in preventive strategies of IHD can be achieved with the identification of: (1) new risk factors; (2) genotypes enhancing the susceptibility to specific risk factors; (3) phenotypes and genotypes making patients susceptible to specific preventive strategies; (4) genotypes protecting from risk factors.

New risk factors

Several potential coronary risk factors have been identified in the past few years including serum levels of lipoprotein (a) [Lp (a)],31 homocysteine32,33 and antibodies to various infectious agents.34–40 However, while the evidence of a cause-effect relation between traditional risk factors and IHD is well established, the association found between these new risk factors and IHD in cross-sectional studies can be due to the role of chance, to reverse causality or to confounders. Furthermore, the association between Lp(a),41 homocysteine42 and antibodies to various infectious agents43 and IHD is rather weak and inconsistent in prospective studies (Tables 1–2). More importantly no trial to date has shown that reduction of these potential risk factors results in a reduction of the clinical manifestations of IHD.

Recently, a surge of interest has been generated by the potential predictive role of serum markers of inflammatory cell activation. Elevated markers of inflammation might reflect the susceptibility of the arterial wall to respond with atherosclerotic plaque formation to the various atherogenic stimuli and with enhanced thrombogenicity and smooth muscle cell reactivity to acute destabilizing stimuli. Among the several systemic serum markers of inflammation found to be associated with IHD, including ICAM-1,44 heat shock proteins45 and fibrinogen,46 the most interesting for its immediate clinical applicability appears to be CRP. Indeed, this prototypic acute phase reactant, synthesized by hepatocytes following stimulation with pro-inflammatory cytokines (in particular IL-6),47 has consistently been shown to predict the risk of IHD in several prospective studies. In particular it predicts the risk of a first MI in healthy middle-aged men48 and the risk of MI and coronary death in asymptomatic individuals at high risk;49,50 moreover it predicts the risk of MI and/or coronary death in stable angina patients51,52 and the risk of complications in unstable angina or MI19–22,53,54 (Table 3). Furthermore, the assay for the measurement of CRP has been standardized by the WHO. Finally and more interestingly, serum CRP and cholesterol levels seem to have an additive or even synergistic adverse effect on the risk of IHD. Indeed, in the Physicians’ Health Study, the relative risk ratio of

Table 1 Predictive value of lipoprotein (a), and infective agents for cardiovascular events in meta-analysis of prospective studies

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori</td>
<td>1727</td>
<td>1.1</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>810</td>
<td>1.2</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>713</td>
<td>0.9</td>
</tr>
<tr>
<td>Lipoprotein (a)41</td>
<td>4044</td>
<td>1.7</td>
</tr>
<tr>
<td>Previous disease</td>
<td>1392</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Table 2 Predictive value of homocysteine for cardiovascular events in prospective studies

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Risk ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfthan et al. 1994</td>
<td>460</td>
<td>1.3</td>
</tr>
<tr>
<td>Chasan Taber et al. 1996</td>
<td>666</td>
<td>1.7</td>
</tr>
<tr>
<td>Verhoef et al. 1997</td>
<td>298</td>
<td>1.1</td>
</tr>
<tr>
<td>Evans et al. 1997</td>
<td>712</td>
<td>0.9</td>
</tr>
<tr>
<td>Nygard et al. 1997</td>
<td>587</td>
<td>4.5</td>
</tr>
<tr>
<td>Wald et al. 1998</td>
<td>1355</td>
<td>2.9</td>
</tr>
<tr>
<td>Folsom et al. 1998</td>
<td>769</td>
<td>1.3</td>
</tr>
</tbody>
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Modified from ref. 42.
Injury. CRP is a marker of the degree of the arterial susceptibility to atherosclerosis.

CRP levels are still largely unknown; they may lie, however, in an additive or even synergistic prognostic value of cholesterol and fibrinogen levels. This is supported by the results of some recent studies carried out in Italy. Zito et al. have recently shown another interesting interaction between gene and environment by studying the relation between smoking and the PlA1/PlA2 polymorphism of the gene encoding the platelet glycoprotein IIIa. Indeed, carriers of the PlA2 allele who were smokers had a more than tenfold increase of MI compared to non-smokers. Conversely, the risk was only slightly higher in smokers than in non-smokers who were carriers of the PlA1 allele.

The effect of a specific medical treatment on atherosclerosis progression could be influenced also by genetically determined susceptibility to the treatment as shown in a substudy of the REGRESS trial. Analysing the Asp9Asn substitution in lipoprotein lipase enzyme, the authors have shown that carriers of an interaction between the 4G/5G polymorphism of the PAI-1 gene promoter and the correlation between serum PAI-1 activity and triglyceride levels in dyslipidaemic patients. Indeed, a correlation between triglycerides and PAI-1 serum levels was found in the 5G/5G carriers but not in 4G/4G carriers, thus suggesting that in the former only high levels triglycerides can be more thrombogenic.

Finally, Ardissino et al. have recently shown another interesting interaction between gene and environment by studying the relation between smoking and the PIA1/PIA2 polymorphism of the gene encoding the platelet glycoprotein IIIa. Indeed, carriers of PIA2 allele who were smokers had a more than tenfold increase of MI compared to non-smokers. Conversely, the risk was only slightly higher in smokers than in non-smokers who were carriers of the PIA1 allele.

### Susceptibility to treatment

A crucial issue in the cost-effective prevention of IHD is the identification of patients susceptible to a specific medical treatment. Some success stories indicate how rewarding this approach can be. For instance, Ridker et al. have recently shown that, in the Physicians’ Health Study, the use of aspirin was present only in the subset of patients with evidence of inflammation. It is worth noting that the intriguing association between CRP and IHD consistently found in prospective studies can be due to confounders. The final evidence of a cause-effect relationship between degree of activation of inflammatory cells and IHD can only come from randomized trials showing that inhibition of inflammatory cell activation results in a reduction of the clinical manifestations of IHD.

### Susceptibility to risk factors

The identification of subjects susceptible to risk factors is a remarkable challenge. However, the recent opportunity of genotyping on a large scale and at low cost can open the way to exciting developments that would have been unthinkable a few years ago. Common variations in genes, called polymorphisms, have been recently associated with the risk of IHD. More importantly, a growing body of evidence indicates that these genetic variations can modulate, by increasing or decreasing, the effect of environmental risk factors on the development of IHD. Very promising are the results of some recent studies carried out in Italy. Zito et al., for instance, have shown an interaction between a polymorphism of the gene encoding for the B chain of fibrinogen and seropositivity for Helicobacter pylori in determining the risk of MI. Indeed, carriers of the B2 allele who were seropositive for Helicobacter pylori had a sevenfold increase in the risk of MI as compared to seronegative carriers; conversely, seropositive and seronegative carriers of the B1 allele exhibited a similar risk of MI. These findings underscore the important role of the interaction between environment and genotype in determining clinical events. The same group has also shown...
this mutation had more progression of coronary atherosclerosis than non-carriers. More importantly, the effect of pravastatin on progression was attenuated in carriers for the Asp9Asn substitution but not in non-carriers.\textsuperscript{61} In the same study, it has been shown that the B1 variant of the cholesterol ester transfer protein gene was associated with an increased progression of coronary atherosclerosis. Pravastatin treatment was effective in slowing the progression in patients carrying the B1 variant only.\textsuperscript{62}

\textbf{Protective factors}

Another important challenge is the identification of protective risk factors. It would be important to establish why many subjects with multiple risk factors do not develop MI or even obstructive atherosclerosis during their lifetime. The identification of genetically determined protective factors would be important not only because carriers of such protective factors would not need aggressive preventive measures, but also because the identification of these protective factors might allow the development of new preventive strategies.

A successful example of genetically determined protective mechanisms is provided by the results of a study carried out by Iacoviello et al. These authors, studying two polymorphic regions of the gene encoding for factor VII (R353Q and HVR4), have shown that subjects with the QQ or H7H7 genotype have a much lower risk of MI (odds ratios 0.08 and 0.22 respectively). Of note, patients with the QQ or H7H7 genotype had lower levels of both factor VII antigen and factor VII clotting activity than those with the RR or H6H6 genotype.\textsuperscript{63,64}

Like air-bags in a car, ‘protective’ factors may not be necessary if the driving style is safe and no accident occurs. Air-bags show their life-saving effect, however, in the case of hazardous driving leading to a crash. The protective effect of the Q allele of factor VII genotype, indeed, was evident in smokers as compared to never smoker subjects, although genetic protection should not prevent people from avoiding dangerous lifestyles.

\textbf{Conclusions}

The achievements obtained by controlling traditional coronary risk factors are remarkable. Community-based interventions aimed at influencing lifestyle, diet and smoking and pharmacological treatment of risk factors both in high risk patients without clinical evidence of IHD and in secondary prevention have probably played a key role in determining the substantial reduction in mortality from IHD observed in Western countries in the last 30 years\textsuperscript{65} and should further be encouraged. A growing body of evidence, however, indicates that both predisposing and precipitating causes of MI are multiple. Therefore, the current approach of utilizing the same preventive strategy in all subjects has been remarkably rewarding, but it can only be considered as a first approximation.

The demonstration that inflammatory cells play a pivotal role both in atherogenesis and in the transition from stable to unstable phases of IHD is already opening the way to more specific forms of prevention. Indeed, patients with raised CRP levels, a marker of inflammatory cell activation, appear to be more susceptible to the detrimental effects of atherogenic stimuli (lipids in particular) and to the beneficial effects of various preventive strategies than patients with low CRP levels.

Furthermore, a more creative utilization of genotyping focused on the interaction between genes and environment is opening the way to the understanding of genetically determined enhanced susceptibility to old and new risk factors and to specific treatments.

Although a word of caution is necessary as a number of studies on genetic markers, on new risk factors and on the interaction between genetic markers and environment have failed to withstand the rigour of population-based studies, the early findings available to date suggest that cost-effective preventive strategies based on the individual susceptibility to specific predisposing and precipitating causes of MI may become a reality in the foreseeable future.

\textbf{KEY MESSAGES}

\begin{itemize}
\item The predisposing and precipitating causes of acute myocardial infarction are multiple.
\item Different individuals may have different susceptibility, to a large extent genetically determined, to each of them.
\item Traditional risk factors have a limited sensitivity and specificity, in particular, among subjects with low/moderate levels of risk.
\item An improvement in preventive strategies of IHD can be achieved with the identification of: (1) new risk factors; (2) genotypes enhancing the susceptibility to specific risk factors; (3) phenotypes and genotypes making patients susceptible to specific preventive strategies; (4) genotypes protecting from risk factors.
\end{itemize}

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\begin{enumerate}
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\end{enumerate}


