Review Article

Current Concerns and Difficulties in the Prevention of Cardiovascular Diseases

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Despite the progress in the pharmaceutical management of cardiovascular diseases during the last few decades, these diseases continue to be the leading cause of death in developed countries. Large studies of statins have shown that, even if low-density lipoprotein (LDL) cholesterol targets are achieved, a significant number of individuals continue to experience cardiovascular events. Furthermore, even though the percentages of patients taking medication are "booming", interventions related to changes in lifestyle have fallen dramatically behind the levels desired, and this is reflected in the fact that obesity and diabetes mellitus have reached the dimensions of an epidemic.

Residual cardiovascular risk

The current multifactorial practice in the prevention of cardiovascular disease includes achieving low LDL cholesterol levels, controlling blood pressure, controlling blood sugar, and hygienic-dietary interventions. As regards hypercholesterolaemia in particular, the use of statins has provided a great benefit in reducing cardiac events by about 30-40% in both primary and secondary prevention of coronary artery disease (CAD). However, despite the great benefits from statin use, a meta-analysis of 14 randomised trials involving 90,056 individuals (including 18,686 diabetics) showed that 1 of every 7 patients taking statins had a cardiovascular episode within 5 years' follow up.[1] This risk still applies to studies where large doses of statins were administered and low LDL cholesterol levels were achieved (Figure 1).[2] This raises the questions: what are the causes of this "residual" cardiovascular risk? – namely, the risk of cardiovascular episodes despite satisfactory control of LDL cholesterol, blood pressure, and blood sugar – and how may it be managed? The answer to these questions is not simple and would appear to involve many factors, including the following:

1. Atherogenic dyslipidaemia, i.e. the combination of elevated triglycerides and low high-density lipoprotein (HDL) cholesterol. This is dyslipidaemia, which as a rule applies to patients with diabetes mellitus and metabolic syndrome, conditions that have today become epidemic in scope.[3] The risk from atherogenic dyslipidaemia is additional to the risk from LDL cholesterol. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[4] showed that the combination of a statin and fibrate in diabetic patients, aimed mainly at treating atherogenic dyslipidaemia, did not reduce cardiac events more than statin monotherapy. In consequence, so far there are no directed, effective pharmaceutical treatments for the reduction of the addi-

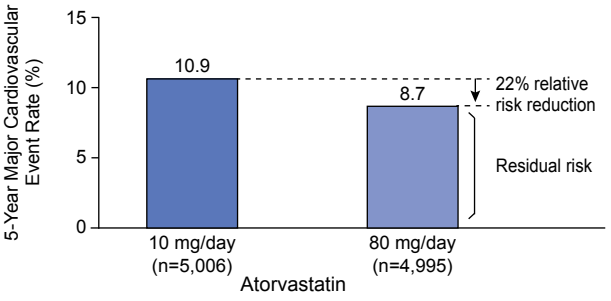

Figure 1. In the Treating to New Targets (TNT) study (comparison of 80 mg and 10 mg atorvastatin in patients with stable coronary artery disease), the group with the aggressive regimen showed a 22% reduction in relative risk for major cardiovascular events. Nevertheless, 8.7% of patients who took aggressive lipid-lowering medication (achieving a mean level of low-density lipoprotein cholesterol of 77 mg/dL) continued to manifest cardiovascular events (residual cardiovascular risk). Reprinted from The American Journal of Cardiology, Vol 102, Fruchart J-C, Sacks F, Hermans MP, et al, The Residual Risk Reduction Initiative: A Call to Action to Reduce Residual Vascular Risk in Patients with Dyslipidemia, 1K-34K, Copyright (2008), with permission from Elsevier.

tional risk arising from atherogenic dyslipidaemia, apart from statin administration.

2. Inability to make lifestyle modifications, such as a regular exercise programme, weight loss and giving up smoking, for both the primary and secondary prevention of CAD.
3. The presence of other risk factors, such as lipoprotein-alpha, for which there are no effective medications.
4. Delayed start of treatment for the management of certain risk factors, such as diabetes mellitus. It is well known that the atherogenic process in coronary vessels starts before the diagnosis of diabetes is made, in the pre-diabetic state.[5]
5. The existence of possible unknown factors that are implicated in atherogenesis.

It is clear from the above that, until we find effective and safe medications for atherogenic dyslipidaemia, any further reduction in cardiovascular risk must come mainly from appropriate hygienic-dietary interventions.

How can cardiovascular disease prediction models be improved?

The prediction of cardiovascular diseases in the general population uses various models, such as the Framingham risk score, SCORE, PROCAM, Reynolds risk score, etc. These models are based mainly on the determination of classical risk factors and do not take the latest risk factors into account. The most commonly used are the Framingham risk score and SCORE. SCORE evaluates data relating to five risk factors (sex, age, smoking, blood pressure and cholesterol), while the Framingham risk score also includes levels of HDL cholesterol. However, none of these models incorporates important risk factors such as family history of early CAD, metabolic syndrome, or obesity.

The models are not comparable, since they have been studied in different populations and they also define cardiovascular risk in different ways. Thus, the Framingham risk score calculates the absolute ten-year risk of CAD occurrence, whereas SCORE gives the ten-year risk of cardiovascular death. Furthermore, the data on which these models are based are relatively old. The problem is greater for the Framingham risk score, which reflects the trends in cardiovascular morbidity that existed in a specific region of the USA (Framingham town) two decades ago, whereas we know that in recent years there has been a significant reduction in the risk of CAD in the USA. This is the main reason for the lower predictive value of the Framingham risk score today, since it tends to overestimate the risk when it is small and to underestimate it when it is large.[6] It thus becomes clear that for these models to be accurate they must be updated at least every decade.

Despite their weaknesses, these models provide the capability of identifying in the general population those individuals with intermediate cardiovascular risk who require the implementation of preventive interventions. The physician's clinical "antennae" often under- or overestimate the cardiovascular risk in these cases, with the result that correct decisions may not be always taken.[7]

New biomarkers whose predictive capacity and incremental predictive value are being studied in comparison to existing models include the following.

C-reactive protein

C-reactive protein (CRP) is an index of systemic inflammation. A meta-analysis[8] showed that the addition of CRP to the Framingham risk score improved its predictive capacity in individuals with intermediate risk. The role of CRP was bolstered by the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER),[9] in which administration of rosuvastatin to healthy individuals who did not have hypercholesterolaemia

(LDL cholesterol <130 mg/dL) but did have elevated CRP (≥2 mg/L) led to a large reduction in cardiovascular events and overall mortality. Indeed, following that study the US Food and Drug Administration (FDA) approved the administration of rosuvastatin to men aged ≥50 years and women aged ≥60 who had no cardiovascular disease or hypercholesterolaemia but had CRP ≥2 mg/L and one or more cardiovascular risk factors. Similar approval was granted in the European Union for individuals without hypercholesterolaemia who had a high risk of cardiovascular events – ten-year risk of a coronary episode >20% (Framingham risk score) or ten-year risk of cardiac death ≥5% (SCORE).

However, not even the JUPITER study addressed the question of how CRP is a causative risk factor for CAD, while the benefit found in that study from statin administration cannot be attributed solely to a reduction in CRP, as there was also a further drop in cholesterol levels.

Lipoprotein-associated phospholipase A_2

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a specific index of inflammation in the arterial wall. A meta-analysis[10] that included 32 prospective studies with a total of 79,036 individuals with or without cardiovascular disease showed that both the mass and the activity of Lp-PLA_2 were associated with the risk of occurrence of cardiovascular events. The identification of Lp-PLA_2 as a risk factor for cardiovascular disease led to the discovery of specialised inhibitors of the enzyme's activity, such as darapladib, whose usefulness is under investigation in clinical studies.

Coronary artery calcium score

The coronary artery calcium score is calculated from computed tomography. It is an indirect index of the presence of calcified atheromatous plaques in the coronary arteries. Polonsky et al[11] showed that the addition of this score to prediction models that included the classical risk factors improved their predictive capacity. Furthermore, coronary artery calcium score is an independent predictor and also offers additional predictive value to the Framingham risk score, especially in individuals with low or intermediate ten-year risk.[12,13] The absence of calcium in the coronary arteries (score 0) almost rules out the presence of severe coronary atheromatosis and in asymptomatic individuals is associated with an extremely low ten-year risk for cardiovascular events. The disadvantage of this technique is the exposure of the patient to radiation, while there are no randomised, prospective studies to show how much it improves the clinical outcome when used as a tool for the prediction of cardiovascular events.

Carotid intima-media thickness

The calculation of carotid intima-media thickness is an index of subclinical atheromatosis. Several prospective studies[12,14,15] have shown that an increase in carotid intima-media thickness to above the 75th percentile is associated with an increased future risk of cardiovascular events and in many cases this risk is independent of the traditional risk factors.

There is a trend today towards using multiple biomarkers and evaluating their combined predictive value in statistical models (C-statistics). However, none of the proposed multifactorial models has yet replaced the existing models (Framingham risk score, SCORE) in daily clinical practice.

Implementation of guidelines – the Achilles' heel of cardiovascular disease prevention

The European Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE) III survey (2006-7) and its comparison with the previous EUROASPIRE I (1995-6) and II (1999-2000) showed the large and continuing gap between guidelines and clinical practice.[16-18] This gap mainly concerns the inability to change lifestyle, namely to adopt a more healthy diet model, to take up regular exercise, and to stop smoking.

The EUROASPIRE studies, which recorded risk factors in European countries in individuals with established CAD, registered a dramatic increase in obesity rate (body mass index ≥30 kg/m^2), which within a single decade rose from 25% to 38%. Also disturbing are the data for smoking, since the percentage of smokers among CAD patients has remained unchanged in recent years at around 20%. Indeed, in women aged ≤50 years there has been a significant increase in smoking, from 30% to 50% (Figure 2). As regards the treatment of hypertension, the percentage of patients who continue to have high blood pressure (≥140/90 mmHg) has remained stable at around 60%, as it was a decade ago. Where there has been significant progress is in the treatment of hypercholesterolaemia. The percentage of coronary patients

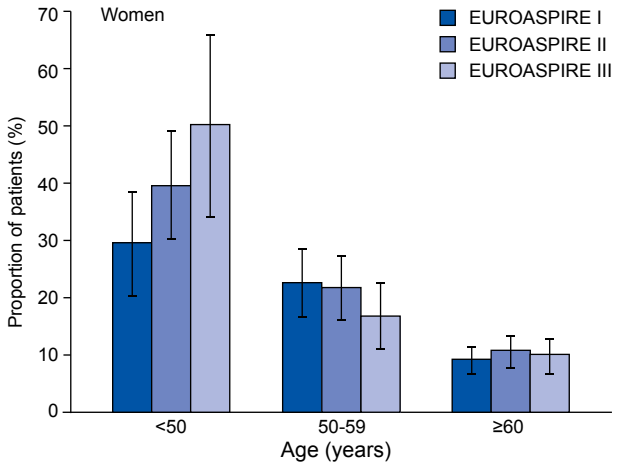

Figure 2. Percentage of women smokers in three age groups: <50 years, 50-59 years and ≥60 years. There is a progressive increase in the percentage of smokers aged <50 years from EUROASPIRE I to III. Reprinted from The Lancet, Vol. 373, Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U, Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries, Pages 929-940, Copyright (2009), with permission from Elsevier.

with hypercholesterolaemia (cholesterol ≥175 mg/dL) has fallen within a decade from 94.5% to 46.2%, a fact that is attributable to the more frequent prescribing of statins.[18] Thus, while in EUROASPIRE I only 32.2% of patients were taking lipid-lowering medication, in EUROASPIRE III this had risen to 88.8%. However, even in the realm of lipid management there is a therapeutic deficit, since only about half those taking lipid-lowering medication achieved the therapeutic cholesterol target (Table 1). Furthermore, the therapeutic deficit is even greater in those coronary patients at very high risk, where the optional LDL-cholesterol target is stricter, ranging from 50-70 mg/dL.[19,20]

Coronary patients at very high risk are defined as those with additional risk factors, such as diabetes mellitus, smoking or metabolic syndrome, or those who manifest CAD as an acute coronary syndrome. According to existing data, the majority (70-75%) of coronary patients are at very high risk and of those only 15-21% achieve LDL cholesterol levels <70 mg/dL.[21-23] In consequence, the therapeutic deficit in lipid-lowering treatment today arises chiefly from the inadequate upward titration of statin doses to achieve the desired LDL cholesterol targets.

Conclusions

In order for interventions for the prevention of cardiovascular disease to be effective, they must combine the targeted management of all risk factors. Everyone involved in prevention realises that lifestyle changes are the big stumbling block in preventive medicine. At the population level, the role of the state[24] is fundamental in implementing special educational programmes or laws related to correct dietary habits, the need for exercise, and the avoidance of smoking from school age. At the level of individual intervention, for the individual at very high risk, and especially those who have suffered a myocardial infarction and have many modifiable risk factors, help should be sought from a group of specialists who include a cardiologist specialised in rehabilitation programmes, a dietician, a psychologist and a physiotherapist.[25] This counselling should ideally be carried out at rehabilitation centres and should be sustained until it becomes effective. Unfortunately, such centres are rare, even in counties with well developed health care systems.

Finally, since family doctors or general practitioners play a basic and primary role in CAD prevention, it is essential that they should undergo continuing medical education and that the guidelines drawn up by scientific societies should be short, simple, and should carry clear and not conflicting messages.

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Table 1. Percentages of coronary patients who were evaluated six months after discharge from hospital and were taking lipid-lowering medication, statins, and who achieved their cholesterol target.

	EUROASPIRE I (1995-6)	EUROASPIRE II (1999-2000)	EUROASPIRE III (2006-7)
Lipid-lowering medication	32.2%	62.7%	88.8%
Statins	18.1%	57.3%	87%
Achieved cholesterol <175 mg/dL	5.5%	23.3%	53.8%

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