Prevention of cardiovascular disease in asymptomatic people

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Mortality due to cardiovascular disease (CVD) has been declining rapidly in most Western European countries since the 1970s or ’80s.3 This has resulted in a significant increase in life expectancy not only at birth but also in adult and elderly people. The increase in life expectancy during the last decades in Europe is for the large majority related to the decline in CVD mortality.2 Thus, one could ask the question whether much more attention should be given to CVD prevention. What is the rationale for requesting continuous and even greater efforts in CVD prevention?

RATIONALE FOR THE PREVENTION OF CARDIOVASCULAR DISEASE

CVD is still the leading cause of premature death and disability in industrialised countries, and is taking the lead in developing countries. This results in loss of productivity and in escalating costs of healthcare. CVD due to atherothrombotic lesions is largely preventable by adopting healthy lifestyles and by controlling the major risk factors.

A comprehensive plan for prevention of CVD should include:

- a population strategy for altering, in the whole community, those lifestyle and environmental factors and their socioeconomic determinants that are the underlying causes of the mass occurrence of CVD
- a high risk strategy for the identification of high risk people and action to reduce their risk factor levels, and
- a plan for the prevention of recurrent events in patients with established CVD. In this report prevention of CVD in asymptomatic people is discussed as part of the high risk strategy; however, the population approach is of paramount importance and should always complement the other.

Given the limited resources that are available for prevention in most health care systems, priorities have to be set and the resources that are available should be used as efficiently as possible, which means that one should adapt the intensity of interventions in accordance with the total risk to the population. In the guidelines that were issued by the 4th Joint Task Force of European Societies on prevention of CVD in clinical practice3 the following priorities were set:

- Patients with established CVD should receive maximum attention; they are at high or very high risk for recurrent events, and estimation of total cardiovascular (CV) risk using specific models is not necessary and not applicable to these patients.
- The second priority relates to asymptomatic subjects at high risk for developing CVD. These are, on the one hand, subjects with type 2 diabetes or with notably elevated risk factors, particularly in the presence of target organ damage; they represent a rather small fraction of the middle aged and elderly population, and because of their condition (known diabetes, severe arterial hypertension, severe hypercholesterolaemia) the chances that they are detected by health professionals are great. On the other hand there exists a larger proportion of middle aged and elderly people at risk for developing CVD because of a clustering of multiple risk factors, resulting in an elevated total CV risk. This is the group that is addressed in this article; they make up a large fraction of middle aged subjects from which a great number of new CV events will arise.

Based on population surveys one can assume that around 10−15% of the population is at high risk because of established CVD or diabetes, only a small fraction (estimated at 5−10%) is at low risk, while between 75−80% of the asymptomatic middle aged and elderly people are at mild, moderate, high or very high total CV risk.

WHY ESTIMATE THE TOTAL CV RISK IN ASYMPTOMATIC PEOPLE, AND HOW?

Many clinicians are still looking after single CV risk factors in lipid clinics, in departments of diabetology, in hypertension clinics, etc. Within this single risk factor approach most practitioners think of risk factors in a dichotomous way; patients are divided into hypertensive versus normotensive, diabetic versus non-diabetic, hypercholesterolaemic versus normo-cholesterolaemic. This has the disadvantage that those who do not qualify for the definition of hypertension, diabetes or hypercholesterolaemia receive no attention at all because they are considered as ‘normal’.

Results from cohort studies have clearly shown the continuous character of the association between the cardinal risk factors and the risk of developing CVD. There is no ‘normal’ blood pressure or a ‘normal’ total cholesterol value. The higher the blood pressure level or the cholesterol concentration, the higher the relative and absolute risk for developing CVD; the reverse is also true; results from intervention studies show that the more the blood pressure or cholesterol can be reduced the lower the risk for developing CVD can be brought.
Table 1  Definitions of high risk in asymptomatic people based on total cardiovascular risk estimations

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Criteria for high risk category</th>
</tr>
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<tbody>
<tr>
<td>2nd Joint European Task Force(^7)</td>
<td>Framingham (\geq 20%) total CHD risk/10 years</td>
</tr>
<tr>
<td>NCEP-ATPIII(^7)</td>
<td>Framingham (\geq 20%) hard CHD risk/10 years</td>
</tr>
<tr>
<td>JBS2(^8)</td>
<td>Framingham (\geq 20%) CVD/10 years</td>
</tr>
<tr>
<td>3rd Joint European Task Force(^9)</td>
<td>SCORE (\geq 5%) fatal CVD risk/10 years (low and high risk countries, calibrated charts)</td>
</tr>
<tr>
<td>ESH/ESC(^11)</td>
<td>BP + aggregate of risk factors, MS, diabetes, established CV or renal disease</td>
</tr>
<tr>
<td>WHO/ISH(^10)</td>
<td>BP + aggregate of risk factors, TOD and associated clinical conditions</td>
</tr>
</tbody>
</table>

BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ISH, International Society of Hypertension; JBS, Joint British Societies; MS, metabolic syndrome; TOD, target organ damage; WHO, World Health Organization.

However, this implies that for the prevention of CVD, many people have to take precautions in order to avoid clinical events occurring in only a few. This brings us back to what Rose expressed as the prevention paradox: ‘a preventive measure that brings large benefits to the community offers little to each participating individual.’\(^4\)

When the preventive measure is completely harmless and well accepted by the community then the measure should be taken. However, when people are poorly motivated, the preventive measure is difficult to implement. Sometimes even asymptomatic people are more likely to take daily drugs to prevent CVD, although the long term compliance with such actions is also poor. Most people are generally motivated for drug treatment by the prospect of an immediate and tangible benefit. The only return for asymptomatic people who take action to prevent CVD is that nothing happens.

Furthermore, starting lifelong drug treatment in a large proportion of the population can be questioned in terms of labelling healthy people as ‘at risk’ for decades.

The search for more efficient preventive strategies leads to the high risk strategy in which efforts are focused on those people who are assessed as being most likely to develop CVD.

The understanding of the importance of clustering of risk factors is also difficult because most of these risk factors interact in a complex way to build up the total CV risk. These interactions are difficult to grasp without using appropriate models that are based on observations from prospective studies. Preventive actions should be guided in accordance with that total CV risk level.

Those at highest total risk should be identified and targeted for intensive lifestyle interventions and, when appropriate, for drug treatments; however, the rest of the population should not be left alone. The aim of introducing total CV risk in the high risk strategy by the Joint European task forces is to help the clinician in making decisions on how intense his or her action should be, ranging from a simple reinforcement of a health education message to combinations of intensive professional lifestyle change programmes in addition to drug treatments for elevated blood pressure, dyslipidaemia or dysglycaemia.

In many instances, however, clinicians use the total CV risk models in a dichotomous way: high risk, defined by whatever criteria, is a reason to do everything, particularly drug prescription; below that level, nothing is done. This may be partly due to the fact that in most guidelines an arbitrary cut point is used to define those at highest risk. However, there is no consistency in defining that arbitrary level. This is illustrated in table 1 where definitions of high total CV risk are given from different sources:

- The 2nd Joint European Societies’ Task Force\(^5\) estimated the risk for developing any coronary heart disease (CHD) event including angina, based on a model from the Framingham study by Anderson\(^6\); a total coronary risk of developing CHD of \(\geq 20\%/10\) years was labelled as high.
- In the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) guidelines\(^7\) a model is proposed to estimate CHD risk based on another Framingham model that predicts only hard coronary events; a similar cut point of \(\geq 20\%\) was used to define elevated total CHD risk.
- The second Joint British Societies guidelines\(^8\) use still another Framingham model with an estimate of CVD instead of CHD as outcome, and also define high risk as a level of \(\geq 20\%\).
- The Third Joint European Societies’ Task Force\(^9\) recommend the use of the SCORE model in Europe, either the charts for low risk countries, high risk countries or calibrated charts with \(\geq 5\%\) chances of dying in the coming 10 years from CVD as high risk criterion.
- In the guidelines of the World Health Organization/International Society of Hypertension (WHO/ISH\(^10\)) and the European Society of Hypertension/European Society of Cardiology (ESH/ESC\(^11\)) on the management of arterial hypertension, blood pressure and an aggregate of risk factors is recommended to estimate total CV risk and to define high risk.

It should be emphasised that all these cut points are arbitrary and based on practical considerations in relation to the health care system, health insurance plans and economic determinants, but not on strong scientific bases. The choice of the cut point to define highest risk is primarily based on the need to reflect the ability of the health system and of the insurance plan to care for these high risk persons. When evidence is lacking, thresholds are often determined by balanced workload against projected costs. This has led to a simple division of the asymptomatic population into two groups: the high risk, and all the others. This again may lead to an inappropriate approach where the resources are only used in the smaller fraction of the population at highest risk, while in the large number of people at mild or moderate risk no preventive actions are taken.

The importance of this is also illustrated by recent studies where the focus has been on lifetime risk of developing CVD.\(^12\)
In the Framingham study, results from long term follow-up of the cohorts demonstrate that the absence of established risk factors at the age of 50 years is associated with a very low lifetime risk for CVD and notably longer survival. However, as soon as one risk factor is present, risk increases substantially in both men and women (table 2). Participants with an optimal risk factor profile had substantially lower lifetime risk of CVD: 5.2% vs 68.9% in men with ≥2 major risk factors; 8.2% lifetime risk in women with an optimal risk factor profile versus 50.2% in women with ≥2 major risk factors. Survival was also very different: for those men and women with an optimal risk factor profile, survival was >11 years and >8 years longer, respectively, compared with those with ≥2 major risk factors.

For both men and women the adjusted cumulative incidence curves across aggregate risk strata separated early and continue to diverge through the remaining lifespan. It should also be said that only 3.2% of all men and 4.5% of all women in that cohort had an optimal risk factor profile, defined as total cholesterol <4.65 mmol/l, blood pressure <120/80 mm Hg, non-smoker, and non-diabetic.

In a screening of a large working population of >20 000 men and 5000 women aged 55–59 years in Belgium, an optimal risk factor profile was defined as: <130/80 mm Hg for blood pressure, <190 mg/dl (<5 mmol/l) for total cholesterol, non- or ex-smoker, and a body mass index (BMI) <25 kg/m². Only 2.2% of all the men and 6.9% of the women corresponded to these criteria (unpublished results from the Belstress I study).

Another illustration of the limitation of using arbitrary cut points in defining high CV risk is given by using the concept of the metabolic syndrome.

The NCEP-ATP III group defines the metabolic syndrome when three out of five risk factors are present based on a categorical definition of elevated risk:
- abdominal obesity: men >102 cm, women >88 cm
- triglycerides ≥150 mg/dl (≥1.7 mmol/l)
- high density lipoprotein (HDL) cholesterol: men <40 mg/dl (1 mmol/l), women <50 mg/dl (1.3 mmol/l)
- blood pressure ≥130/85 mm Hg
- fasting glucose ≥110 mg/dl (≥6 mmol/l)

The prevalence of the metabolic syndrome, according to this definition, was studied in a sample of the population of a rural town in Belgium including 2524 subjects aged 35–55 years, all free of CVD. CV risk factors were measured by standardised methods, and the intima–media thickness (IMT) in both carotid and femoral arteries was assessed by a single trained observer. An increased IMT was defined as a thickness ≥0.9 mm in the common carotid arteries or in the femoral arteries.

In figure 1 the relationship is shown between the number of the different components of the metabolic syndrome and the presence of an increased IMT. The relationship is very clear, but not in the sense that all those with the metabolic syndrome have an increased IMT and all the others do not; there is a clear gradient—the more components present, the higher the prevalence of increased IMT.

Furthermore, the prevalence of the metabolic syndrome was 9% in this population, but 50% of the population had at least one component; this means that the proportion of increased IMT attributable to the metabolic syndrome was 28%, but 46% could be attributed to the presence of one or two components (figure 2).

From all this one has to conclude that prevention measures need to begin decades before the age of 50 years, because even the presence of a single major risk factor at that age is associated with substantially increased lifetime risk for CVD and notably shorter survival. Lifestyle measures focusing on diet and exercise in young adulthood and middle age could prevent the development of obesity, diabetes, hypertension and dyslipidaemia in large numbers of individuals.

However, too much emphasis has been given to an arbitrary cut point of high risk, defined as a total risk of dying from CVD of ≥5% within the coming 10 years by the SCORE model, or a total risk of developing CHD of ≥20% by the Framingham model. Some practitioners have reduced these recommendations to the simple approach that drug treatment for elevated blood pressure or total cholesterol should be prescribed if total CV risk exceeds that arbitrary cut point. Consequently, very little is done in that large proportion of the asymptomatic population who are at lower risk but certainly not at optimal levels.

Focusing solely on short term risk results in treatment only for older individuals with substantial risk factor burden. Younger and middle aged individuals at a modest risk factor level may have low short term risk but substantial lifetime risk. Therefore, not only should those individuals at highest risk be identified and managed, but also those at high risk should receive professional advice regarding lifestyle changes and, in certain cases, drug treatment to control their risk factors. Moreover, those at modest risk should not be ignored; in these subjects, measures should be taken to prevent the further development of their total risk, increase awareness of the danger of CV risk, improve risk communication, and promote efforts of primary prevention. In those at low risk, all actions necessary to keep their risk as low as possible should be taken.

Table 2  Lifetime risk for cardiovascular disease (CVD) by risk factor burden at 50 years of age

<table>
<thead>
<tr>
<th>Risk factor burden*</th>
<th>Adjusted cumulative CVD incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>All optimal</td>
<td>6</td>
</tr>
<tr>
<td>≥1 not optimal</td>
<td>36</td>
</tr>
<tr>
<td>≥1 elevated</td>
<td>46</td>
</tr>
<tr>
<td>One major risk factor</td>
<td>50</td>
</tr>
<tr>
<td>≥2 major risk factors</td>
<td>69</td>
</tr>
</tbody>
</table>

Adapted from Lloyd-Jones et al.12

*For definitions see the original article.
MANAGEMENT OF RISK FACTORS IN ASYMPOTOMATIC PEOPLE AT HIGH CV RISK

After assessing the total CV risk level, the next important step in management is setting appropriate goals. These goals are given in different guidelines such as the WHO/ISH guidelines on hypertension with emphasis on developing countries, in those from the NCEP-ATPIII developed in the USA, or the most recently developed guidelines in Europe from the ESH/ESC on hypertension and from the 4th Joint European Societies’ Task Force on prevention of CVD in clinical practice.

Thresholds and goals can be used for different purposes. In the guidelines they are mainly used as management tools to help the clinician and the patient to reach the most optimal situation regarding the prevention of a first or recurrent event.

Goals can also be used as tools for auditing the care of high risk subjects and of patients in general practice or in hospitals.

In the guidelines of the 4th Joint European Societies’ Task Force, there are two sets of goals:

- a number of objectives that one should try to reach in the community at large
- a number of more stringent goals set for patients with established CVD or at high absolute risk.

At the level of the community one should try to keep the small minority that is at low risk in that optimal state, while the larger group at mild or moderate risk should be helped to reduce their risk as low as possible with lifestyle changes in the first place. The goals are:

- being physically active, which means at least 30 min of moderate activities per day
- maintaining BMI <25 kg/m² and avoiding central obesity
- maintaining blood pressure <140/90 mm Hg, total cholesterol <5 mmol/l, and low density lipoprotein (LDL) cholesterol <3 mmol/l
- having a fasting glycaemia <6 mmol/l.

In asymptomatic subjects at high CV risk, estimated with the most appropriate model, a more rigorous risk factor control should be achieved and therefore the goals set in these subjects are more stringent:

- when it comes to lifestyle changes the goals may be similar, but dieticians, exercise physiologists and smoking cessation advisors should be taken on board whenever needed
- regarding the classical risk factors, the goals are now at lower values:
  - blood pressure <150/80 mm Hg if feasible
  - total cholesterol <4.5 mmol/l with an option of <4 mmol/l if feasible
  - LDL cholesterol <2.5 mmol/l with an option of <2 mmol/l if feasible
  - fasting blood glucose <6 mmol/l and HbA1c at <6.5% if feasible.

With the wording ‘if feasible’ the guidelines refer both to clinical and economic conditions. For example, establishing a cholesterol goal for treatment is mostly an extrapolation from the apparent benefits indicated by major trials of lipid lowering; these trials have a limited external validity; in particular cases of complex dyslipidaemia goals need to be adapted; and health economic conditions may also prevent the use of certain very expensive drug regimens.
Applied to the lipid management of high risk individuals, this means that the first step is to assess total CV risk and to identify those components of risk that are to be modified. If the 10 year risk of CV death according to the SCORE model—including also the qualifying risk factors that can be considered outside those in the charts—is <5%, professional advice on diet, regular activity and smoking cessation should be given to keep the CV risk low. Risk assessment should be repeated at 5 year intervals.

Note that the estimation of total CV risk does not pertain to patients with familial hypercholesterolaemia, since this condition by itself places these patients at high total CV risk.

If the 10 year risk of CV death is $5\%$ a full analysis of plasma lipoproteins should be performed and intensive lifestyle advice should be given. If values of total and LDL cholesterol fall below 5 and 3 mmol/l, respectively, and the total CV risk estimate has become $<5\%$, then these individuals should be followed at yearly intervals. In contrast, if total CV risk remains $\geq 5\%$, lipid lowering drugs should be considered to lower total and LDL cholesterol even further to the goals that have been set. These guidelines on lipid management are in accordance with those that have been given by the US NCEP-ATP III panel.\textsuperscript{7}

Regarding the management of elevated blood pressure, a stepwise approach is recommended. First, it should be emphasised that ‘management’ means a variety of lifestyle advice for all those with raised blood pressure, including dietary changes and appropriate recommendations regarding physical activity, in addition to the judicious use of medication in some individuals.

The decision to start antihypertensive drug treatment depends on the presence or absence of established CVD, diabetes, renal disease, target organ damage and, of critical importance in all other persons, on the estimate of total CV risk.

Those individuals in whom repeated blood pressure measurements show grade 2 or 3 hypertension are generally regarded as candidates for antihypertensive treatment; this is because a large number of placebo controlled trials have conclusively demonstrated that in patients with these blood pressure measurements, reduction lowers CV morbidity and mortality.

The likely benefits of drug treatment should be weighed against side effects, costs, the use of medical resources, and turning healthy people into ‘patients’.

In all grade 1–3 hypertensives, comprehensive risk factor assessment and appropriate lifestyle counselling should be provided after hypertension is diagnosed, while promptness in the initiation of drug treatment depends on the level of the total CV risk. Drug treatment should be initiated promptly in grade 3 hypertension as well as in grade 1 and 2 hypertensives with increased or notably increased total CV risk—for example, in hypertensives with established CVD or renal disease, target organ damage, diabetes or a SCORE risk $\geq 5\%$.

In grade 1 or 2 hypertensives with moderate total CV risk, drug treatment may be delayed for some time to allow evaluation of the effects of lifestyle interventions on total CV risk. However, even in these individuals, lack of blood pressure control after a suitable period of non-pharmacological intervention should lead to the initiation of drug treatment in addition to lifestyle measures.
When initial blood pressure is within high-normal range (130–139 mm Hg systolic) the decision on drug intervention depends heavily on total CV risk. In case of diabetes or a history of CVD, evidence justifies the recommendation to start antihypertensive drug treatment.

Lifestyle changes are very important in all patients:
- to reduce the blood pressure
- to reduce CV risk in general
- to help in limiting the number and doses of drugs.

Lifestyle changes are also important in subjects with high-normal blood pressure levels in order to prevent or delay the development of overt hypertension. Recommendations should not be given as a one-size fits all strategy, but instituted with adequate behaviourial and expert support and periodic reinforcement.

The primary goal of good management of arterial hypertension is to achieve maximal reduction in the long term risk of CVD. This requires treatment of the raised blood pressure as well as all other reversible risk factors.

In conclusion, applying guidelines is a balancing act of patient individualised care, improved patient adherence to lifestyle changes and medication regimens, and working within healthcare systems intent on controlling costs. The objectives are to help health professionals to reduce the occurrence of CVD and their complications, and to encourage the development of recommendations through the formation of multidisciplinary national guidance and implementation partnerships that are compatible with local political, social, economic and medical circumstances.

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11. Original approach of CVD risk prediction moving from 10 year risk estimation into lifetime risk.