Clinical practice guideline for cardiovascular risk management in the Netherlands

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INTRODUCTION

Preamble
In most developed countries, including the Netherlands, cardiovascular disease (CVD) is a leading cause of morbidity, mortality, and health care costs. Guidelines for CVD prevention should contain a comprehensive, evidence-based strategy towards both primary and secondary prevention. In addition, guidelines should be aimed at a broad spectrum of health care providers, both in primary care as well as in more specialised hospital settings.

Until recently, different national guidelines existed for the management of hypercholesterolaemia and hypertension in the Netherlands, whereas the emphasis has nowadays shifted to management of global CVD risk. In addition, separate guidelines existed for primary care and hospital care settings.

In 2001, the Medical Council of the Dutch Institute for Healthcare Improvement CBO took the initiative to develop a national multidisciplinary guideline for global cardiovascular risk management. This paper provides a summary and short commentary on this guideline.

Aims and scope
The aim was to establish a guideline for optimal and cost-effective primary and secondary CVD prevention. The guideline is based on assessment of absolute CVD risk and replaces previous separate guidelines for hypertension and hypercholesterolaemia. In addition, the guideline integrates separate guidelines for general and hospital-based practice, and is intended for use by general practitioners, medical specialists and allied health professionals, such as dieticians, physiotherapists, nurse practitioners, and physician assistants.

The guideline addresses the most common forms of CVD: coronary artery disease, cerebrovascular disease, and peripheral arterial disease. It does not address screening for CVD in the general population, genetic disorders of lipid metabolism or excessive forms of dyslipidaemia, and management of hyperglycaemia in diabetes mellitus.

Finally, the Working Group emphasises that the recommendations reflect ‘best practice’ for the average patient, not statutory regulations for all individual patients. In general, the guideline advocates individualised care and shared decision making. Non-adherence to the recommendations is not a basis for formal complaints or financial sanctions (such as non-reimbursement by health insurance companies). Health care workers are advised, however, to document their motivation for not adhering to the guideline recommendations.

Methods
A guideline development group was formed, involving all the relevant professional disciplines. All group members as well as the associations they represented are listed at the end of this paper. The guideline development group comprised general practitioners (5), internists (3), cardiologists (3), a vascular surgeon, a neurologist, epidemiologists (3), a health economist, and two methodologists from the CBO.

The group started by discussing the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Third Joint Task Force), as well as the existing national
guidelines for hypertension and for hypercholesterolaemia. Additional literature searches were conducted for updating the literature. The recommendations in the European guideline were used for adaptation to the Dutch context. Data on absolute CVD risk were derived from original Dutch epidemiological studies. The guideline working group formulated recommendations based on informal consensus within the group. The first draft of the guideline was finished in June 2005. This draft was sent for external review to all relevant stakeholders. The final guideline was endorsed by all scientific associations represented in the guideline development group in June 2006.

**GUIDELINE SUMMARY**

The guideline is summarised in figure 1. This figure as well as the full text version of the guideline can be downloaded at www.cbo.nl/product/richtlijnen/folder200021023121843/rl_overzicht.htm. The full text version includes an extensive

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**Figure 1. Flowchart Dutch guideline cardiovascular risk management 2006**

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*Additional risk factors: father, mother, brother or sister with CVD <60 years; obesity (BMI >30 kg/m², waist circumference >88 cm in women or >102 cm in men); end organ damage, such as (micro)albuminuria, impaired renal function or left ventricular hypertrophy.
technical background document containing the supporting evidence as well as a budget impact analysis.

The subsequent steps of the guideline are outlined below.

**Identification of high-risk patients**

All patients with a previous CVD diagnosis are considered as high-risk patients. The risk of most patients with type 2 diabetes mellitus (DM2) is also elevated. In both patient categories, a full risk profile should be obtained. In individuals without previous CVD or DM2, signs or symptoms, a family history of premature CVD, visible overweight or a specific request from the patient may prompt inquiry into smoking behaviour or measurement of blood pressure or serum cholesterol levels. It is recommended to obtain a complete CVD risk profile if one of the following is present:
- systolic blood pressure ≥140 mmHg
- total cholesterol ≥6.5 mmol/l
- smoking in men ≥50 years or women ≥55 years of age.

**Diagnostic procedures**

A complete risk profile should be obtained by collecting information on the risk factors listed in figure 1. Blood pressure should be measured twice on at least two separate days, adhering to specific instructions outlined in the guideline. In addition to the recommended blood tests in figure 1, patients with hypertension require measurement of serum creatinine and potassium level. Testing for microalbuminuria and obtaining a 12-lead electrocardiogram can be considered in individual cases. Additional investigation for secondary hypertension is warranted in case of:
- specific clinical signs (e.g. Cushing habitus);
- strongly elevated systolic blood pressure (>180 mmHg);
- hypokalaemia (serum potassium <3.5 mmol/l);
- renal insufficiency;
- unresponsiveness to treatment.

In addition, further testing is recommended for excessive hyperlipidaemia (e.g. total cholesterol >8 mmol/l or total cholesterol/HDL cholesterol ratio >8).

**Assessment of absolute CVD risk**

For individuals without previous CVD and DM2, the ten-year risk of developing fatal CVD is assessed using the SCORE risk table, calibrated for Dutch CVD mortality data (table 1). The values for blood pressure and lipid levels in the table are applicable regardless of whether patients are treated with antihypertensive or lipid-lowering drugs.

<table>
<thead>
<tr>
<th>Table 1. Risk of fatal cardiovascular disease (CVD) for patients without CVD and without diabetes mellitus type 2</th>
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<td><strong>Women</strong></td>
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<td><strong>Total cholesterol/HDL cholesterol ratio</strong></td>
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Estimate of the level of the ten-year risk (%) of death from CVD in the Netherlands for non-smoking and smoking women and men aged 65, 60, 55, 50 and 40 years with the aid of the SCORE risk function.

The presence of additional risk factors, including family history of premature CVD, (central) obesity, and physical inactivity, may lead to a higher risk than suggested in the SCORE risk table.

Nonpharmacological treatment
Recommendations for lifestyle modifications are given to all individuals with previous CVD, DM2 or an estimated ten-year risk of fatal CVD of ≥5%. Specific recommendations are outlined in Figure 1, and are discussed in detail in the technical background document. Patients should be offered contact details of patient organisations that provide information and support for lifestyle interventions.

Pharmacological treatment
As illustrated in Figure 1, three categories of individuals are distinguished for the purpose of tailoring pharmacological treatment. All recommendations are accompanied by footnotes in the technical background document.

Patients with CVD
- Aspirin is recommended, unless there is a concomitant condition requiring oral anticoagulation. In case of intolerance to aspirin, clopidogrel is a suitable alternative.
- Antihypertensive therapy is recommended if systolic blood pressure is ≥140 mmHg or if a history of cerebrovascular disease (TIA or stroke) is present. The choice of drugs depends on comorbidity
- Beta-receptor blockers are recommended for patients with a history of coronary artery disease or heart failure due to coronary artery disease.
- Angiotensin-converting-enzyme (ACE) inhibitors are recommended for patients with a history of coronary revascularisation, myocardial infarction or heart failure due to coronary artery disease, even if systolic blood pressure is <140 mmHg.
- Statin therapy is recommended if the plasma LDL-cholesterol level is ≥2.5 mmol/l or, if LDL cholesterol is ≤2.5 mmol/l in very-high-risk patients characterised by the presence of multiple other risk factors (e.g. recurrent myocardial infarction, clustering of uncontrolled risk factors).

Patients with DM2
- Antihypertensive therapy is recommended if systolic blood pressure is ≥140 mmHg.
- Statin therapy is recommended if the plasma LDL-cholesterol level is >2.5 mmol/l, except in young patients with a low risk profile and good glycaemic control (i.e. HbA1c <7%). Conversely, a highly unfavourable risk profile (e.g. poor metabolic control, renal complications, clustering of risk factors) justifies statin treatment even if LDL cholesterol is ≤2.5 mmol/l.

Individuals free of CVD or DM2
- Treatment recommendations for this group are based on the estimated ten-year risk of fatal CVD. In general, smoking cessation is recommended prior to initiation of drug treatment.
- Antihypertensive therapy is recommended if systolic blood pressure is ≥140 mmHg and estimated ten-year risk of fatal CVD is ≥10%. Patients with a systolic blood pressure of ≥180 mmHg should receive antihypertensive treatment, regardless of their risk profile.
- Statin therapy is recommended if the plasma LDL-cholesterol level is >2.5 mmol/l and estimated ten-year risk of fatal CVD is ≥10%.
- Individuals at intermediate CVD risk (5-10%) and systolic blood pressure ≥140 mmHg or LDL cholesterol >2.5 mmol/l are amendable to antihypertensive or lipid lowering treatment, respectively, if at least one of the following is present:
  - family history of premature CVD, i.e. <60 years in a parent or sibling;
  - obesity, i.e. body mass index >30 kg/m², or waist circumference >88 cm (in women) or 102 cm (in men);
  - target organ damage, such as (micro)albuminuria, renal insufficiency, or left ventricular hypertrophy.
- Young individuals (<50 years) almost universally have a ten-year risk of fatal CVD of <5%. Such individuals are nonetheless candidates for pharmacological treatment if there is clustering of multiple risk factors or a strongly positive family history of premature CVD.
- Elderly individuals (>70-75 years) often have a high (>10%) ten-year risk of fatal CVD based on their age alone. In principle, these individuals are candidates for preventive pharmacological treatment, but mass-scale polypharmacy and medicalisation should be avoided. Thus, treatment decisions must be individualised. As a rule, pharmacological primary CVD prevention requires that life expectancy is not limited due to comorbidity.

Drug classes
- Antiplatelet drugs are prescribed to all patients with documented CVD. The standard recommended dose is 80 mg of acetylsalicylic acid. Combination therapy with oral anticoagulants is not recommended. Aspirin is not recommended for primary prevention.
- Antihypertensive drugs of different classes have, on average, equally strong antihypertensive effects. Compelling indications for specific classes of antihypertensive drugs are listed in the full-text version of the guideline. If none are present, low-dose hydrochlorothiazide is recommended as initial drug. In the elderly, β-receptor blocker monotherapy is discouraged. Combination therapy is preferred over high-dose single-drug therapy. Blood pressure should be
checked at two to four weekly intervals until the treatment goal is reached. The target level for systolic blood pressure is <140 mmHg. In patients with DM2, further lowering of systolic blood pressure is recommended.

- Cholesterol-lowering drugs include statins as the only standard recommended drugs. Simvastatin (40 mg) or pravastatin (40 mg) are drugs of first choice. The effect on LDL cholesterol should be assessed within three months of treatment. Target values are different for the following categories:
  - patients with CVD or DM2 should reach a target LDL-cholesterol level of <2.5 mmol/l. If not, switching to atorvastatin or rosuvastatin could be considered. Addition of other lipid-lowering drugs lacks evidence base;
  - individuals without CVD or DM2 who are prescribed a cholesterol-lowering drug for primary prevention should reach a target LDL-cholesterol level of <2.5 mmol/l, or a decrease in LDL cholesterol after statin treatment of at least 1 mmol/l.

Follow-up
An individualised follow-up schedule is recommended for all patients. The aims of regular visits are to discuss compliance to lifestyle measures and drug treatment, and to evaluate treatment effects. A follow-up interval exceeding 12 months is not recommended. Laboratory investigations depend on comorbidity and drug use. As most high-risk patients are at increased risk of developing DM2, fasting glucose measurement is recommended every three to five years. Interruption of pharmacological treatment is not recommended.

DISCUSSION
In the full-text version of the guideline, many aspects of the guideline are discussed in more detail. However, a few areas of discussion deserve specific attention in this article.

Morbidity versus mortality risk
The guideline development group adopted the SCORE risk chart for estimating absolute cardiovascular risk, in contrast to previous Dutch guidelines, in which the Framingham risk score was used. The choice for SCORE was based on the higher number of included subjects in the source population and the fact that the risk model is based on a European population. The major drawback of SCORE is that only the risk of fatal CVD is estimated. Including nonfatal CVD risk, however, is paramount to quality-of-life aspects and to cost-effectiveness analyses of guidelines. Moreover, patients themselves are commonly interested in risk of morbidity rather than in risk of death alone. In annex 2 of the guideline, a method for converting fatal to fatal plus nonfatal CVD risk is presented.

Risk threshold for treatment
In the previous Dutch guideline for treatment of hypercholesterolaemia, a 20% ten-year risk of fatal plus nonfatal CVD was recommended as a treatment threshold. This risk corresponds to the currently recommended risk threshold of 10% for fatal CVD. When the previous guidelines were being designed, arguments for determining the risk threshold included a cost-effectiveness analysis based on a cost estimate of € 20,000 per quality-adjusted life year (QALY) for statin treatment. In the past decade, however, the cost of simvastatin, which is now available generically, has dropped from € 700 to approximately € 180 per year. Likewise, the cost of several antihypertensive drugs with established effectiveness and safety has decreased. The guideline development group decided that this decrease in costs should not lead to a lower risk threshold for preventive treatment. Lowering the risk threshold for fatal CVD from 10 to 8%, for example, would have a major impact. Firstly, it would increase the ten-year number-needed-to-treat for simvastatin from 33 to 42 per fatal CVD event prevented. On a population scale, the impact would be substantial, as the number of currently untreated individuals in the Netherlands amenable to treatment with either a statin and/or an antihypertensive drug would increase by almost one million (from 3,270,500 to 4,125,800). As a consequence, the impact this would have on the national health care budget would be substantial (1.1 billion euro after five years, assuming 100% prescription of the cheaper, generic drugs). Moreover, the guideline development group concluded that such large-scale medicalisation of the population would be undesirable.

Risk assessment in DM
The SCORE risk chart does not calculate risk in patients with DM2. Although some studies have suggested that CVD risk in these patients equals risk in patients with a previous CVD diagnosis, the results of later studies were not conclusive. Obviously, there is substantial heterogeneity between patients with DM2 in terms of their CVD risk. The guideline development group decided to recommend low risk factor threshold levels for initiation of antihypertensive therapy (systolic blood pressure >140 mmHg) and lipid-lowering therapy (LDL cholesterol >2.5 mmol/l). Entering these thresholds in the United Kingdom Prospective Diabetes Study (UKPDS) risk engine (www.dtu.ox.ac.uk/index.php?maindoc=/outcomesmodel) revealed that these values were usually related to absolute CVD risk levels above the 10% threshold used for preventive drug therapy in nondiabetics. Only if the remaining variables of the risk profile (e.g. age, glycaemic control, family history, ethnicity) are favourable do these blood pressure and LDL-cholesterol levels translate into risks lower than the treatment threshold. Therefore, the guideline included a statement on considering no statin treatment in young DM2 patients with a favourable risk profile.
Risk estimation in young and elderly individuals
A major area of controversy is the use of absolute CVD risk estimates to guide preventive treatment in young and in elderly people. As is evident from figure 2, absolute ten-year CVD mortality risks rarely reach the 10% threshold in individuals below the age of 50 years. The guideline development group discussed the option of recommending extrapolation of absolute risk to the age of 60 years, as is suggested in the 2003 ESH/ESC hypertension guidelines. However, such extrapolation would result in an enormous increase in relatively young people who would be considered for drug therapy. Moreover, no strong evidence is available on the efficacy and safety of pharmacological CVD prevention beyond a period of more than ten years. Based on these arguments, the guideline development group decided to recommend drug treatment for primary CVD prevention in young individuals only if a risk factor is markedly increased or if clustering of multiple risk factors is present. It was also felt that no strict criteria should be defined for this purpose, and treatment decisions should always be individualised.

The reverse problem is encountered in elderly individuals, who almost universally reach the treatment threshold for preventive drug treatment as age progresses. This can be appreciated from table 1, although it requires extrapolation of the calculated risks, as the SCORE model does not calculate risks for individuals older than 65 years. The guideline development group acknowledged that antihypertensive and cholesterol-lowering drugs are also effective in the elderly. However, a standard recommendation to initiate these drugs in all elderly patients with a >10% ten-year risk of fatal CVD was considered undesirable, as it would lead to massive prescription, and thus medicalisation, in elderly people. Hence, as in younger people, a more liberal recommendation was made to consider preventive treatment in elderly, and to decide on drug treatment based on risk profile, general health and life-expectancy and patient preferences.

Implementation of the guideline
The guideline was made publicly accessible via the internet (www.cbo.nl/product/richtlijnen/folder20021023121843/rl_overzicht). The printed version of the guideline was freely distributed to all general practitioners, as well as to all physicians registered in Internal Medicine, Cardiology, and Neurology. In addition, a patient brochure and risk calculator were produced and distributed. Based on the guidelines, an internet-based ‘decision aid’ was made publicly available to help patients to make informed treatment decisions. Following endorsement of the guideline, a nationwide platform was established consisting of representatives from patient organisations and health professional associations. The mission of this platform is to facilitate and optimise implementation of the guideline.

Updating of the guideline
The Dutch Institute for Health Care Improvement CBO aims to update the literature and modify the recommendations, if needed, at least every two years.

NOTE

REFERENCES


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