Pocket Guide to Prevention of Coronary Heart Disease

This document was prepared by the
International Task Force for Prevention of Coronary Heart Disease
in cooperation with the
International Atherosclerosis Society
under the terms of the affiliation agreement between these organisations

January 2003

Pocket guide Disclaimer

This guide is primarily intended for the use of physicians and other health-care professionals. Other users of this guide should consult their physician for medical advice or treatment, and for advice regarding application of information provided by this guide to their particular case. The information contained herein should not be understood or used by any person as a substitute for obtaining medical advice or treatment from a physician.

Even a low risk assessment percentage should not be interpreted as a guarantee that the person assessed is free from risk of developing coronary heart disease, and does not need to follow a healthy lifestyle, including healthy diet and exercise appropriate to his or her circumstances.

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2003 Börm Bruckmeier Verlag GmbH
Nördliche Münchner Str. 28, 82031 Grünwald, Germany
www.media4u.com
1. Auflage 2003
ISBN 3-89862-902-3

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Introduction

The last fifteen years have seen a sharp drop in death rates from coronary heart disease in many countries in the developed world, the United States of America and several European countries in particular. Despite these welcome advances, coronary heart disease is still the number one killer and a major cause of illness and disability in populations worldwide. Moreover, the importance of coronary heart disease and the other complications of advanced atherosclerosis is likely to increase rather than decrease in the years ahead both in terms of their impact on health and their economic burden.

There are several reasons for this. The most important is that the population is getting older and atherosclerosis is, by and large, a disease of adulthood and old age. A second major reason is the alarming increase in the prevalence of type 2 diabetes mellitus and the pre-diabetic conditions of glucose intolerance, impaired fasting glycaemia and the "metabolic syndrome". Metabolic syndrome is a term used to describe the commonly seen combination of central obesity, insulin resistance, dyslipidaemia and hypertension. In many countries, the prevalence of known cases of type 2 diabetes mellitus approaches 5% of the population with the prevalence of undiagnosed cases being of the same order of magnitude. About 150 million people have diabetes mellitus worldwide, and this number may well double by the year 2025. Much of this increase will occur in developing countries. A third major reason is the steady increase in the prevalence of overweight and obesity, due in large part to an unhealthy diet and a sedentary lifestyle. Finally, while smoking prevalence rates among adults dropped sharply between the 1950s and 1980s, smoking rates among adults in many countries remained

static in the 1990s, while smoking among women and young people has been on the rise in the last 10 years.

Traditionally, strategies to reduce the risk of coronary heart disease have been divided into primary and secondary prevention. Strictly speaking, the term "primary prevention" has been used to refer to measures taken before an acute coronary event, usually a myocardial infarction, occurs, while the term "secondary prevention" has referred to steps taken to prevent recurrence of such an event. However, in recent years this distinction has become blurred. Prospective epidemiological studies such as the PROCAM study in Germany have shown that in many high-risk patients without clinically apparent coronary heart disease the risk of developing a myocardial infarction may equal or even exceed that of persons with a history of myocardial infarction. Thus the focus has shifted from a primary/secondary prevention dichotomy to the concept of actual or absolute risk expressed in terms of the event rate per year. This pocket guide places particular emphasis on this concept of absolute risk and on strategies to calculate it. The charts and algorithms in this guide may also be used to provide a rough guide to the expected benefits of modifying risky behaviour and should therefore be a useful tool in patient education.

In the direct aftermath of a myocardial infarction, acute resuscitative measures and interventions are crucial to outcome. Such measures include emergency revascularisation procedures, thrombolysis, and other pharmacological interventions. These acute measures do not fall within the scope of this guide and are not discussed further here.
This guide is based in part on recommendations published by the International Task Force for Prevention of Coronary Heart Disease,

the International Atherosclerosis Society, the American Heart Association, the American College of Cardiology, the United States National Heart Lung and Blood Institute (NHLBI), the joint European Cardiovascular Societies, the World Health Organization and on the contents of the Third Report of the Adult Treatment Panel (ATPIII) of the National Cholesterol Education Program (NCEP) of the United States of America. We hope that this will prove to be a useful *vade mecum* to all those interested in the rational prevention of atherosclerosis.

International Task Force for Prevention of Coronary Heart Disease, International Atherosclerosis Society, January 2003.

A. Risk assessment for selection of patients for clinical intervention

As noted in the introduction, recent years have seen a shift in emphasis from preventive strategies based on the primary and secondary prevention of myocardial infarction to one based on the concept of absolute risk. Absolute risk may be calculated on the basis of risk factors using one of the algorithms presented later in this guide. However, several conditions may be taken to indicate the presence of high risk of myocardial infarction independent of the levels of individual risk factors. In addition to established clinical atherosclerosis, the main conditions indicating high risk of myocardial infarction are diabetes mellitus, metabolic syndrome, and a 10-year absolute risk of coronary heart disease in excess of 20%.

Table 1: What constitutes a high-risk patient?

A patient can be classified as being at high risk of coronary heart disease if one or more of the following are present:

- Established coronary heart disease[1]
- Other clinical forms of atherosclerotic disease
  - Peripheral artery disease
  - Carotid artery disease[2]
  - Ischaemic stroke
  - Abdominal aortic aneurysm
- A calculated 10-year risk of myocardial infarction or sudden coronary death in excess of 20%

1. Signs of established coronary heart disease are the presence of:
   - stable or unstable angina pectoris
   - myocardial infarction
   - history of interventions such as coronary angioplasty or coronary artery bypass grafting

2. Carotid artery disease is signalled by the presence of:
   - transient ischaemic attacks
   - greater than 50% obstruction of a carotid artery

In recent years it has become clear that patients with diabetes mellitus and with the pre-diabetic conditions of metabolic syndrome, impaired fasting glycaemia, and impaired glucose tolerance are at particular risk of atherosclerotic disease.
In addition, the prognosis of diabetic patients following myocardial infarction is markedly worse than that of non-diabetic persons.
For this reason, many guidelines suggest classifying all patients with these conditions as being at high risk, even if their 10-year risk of coronary heart disease as calculated using conventional risk algorithms does not exceed 20%. These conditions are dealt with in more detail in Table 18 *on page 59*, Table 19 *on page 60* and Table 20 *on page 61*, and in Fig. 10 *on page 62*, Fig. 11 *on page 64*, and Fig. 12 *on page 65*. In the PROCAM study, 22% of diabetic patients had a calculated 10-year risk of coronary heart disease in excess of 20% while only 6% of the non-diabetic population fell into this risk category.

Table 2: Diabetes mellitus and metabolic syndrome: special categories of high-risk

Some authorities classify patients with the following disorders of insulin and glucose metabolism as being at high risk:

- Type 2 diabetes mellitus, particularly in association with microalbuminuria[1]
- Metabolic syndrome as defined in Table 20 *on page 61*

1. Microalbuminuria is defined as a urinary albumin excretion rate of between 20 µg/min and 200 µg/min on two of three urine samples collected over a six-month period. This is approximately equal to excretion of between 30 mg and 300 mg of albumin in 24 hours. An alternative, though less accurate means of detecting microalbuminuria is when the ratio of albumin to creatinine in a urine sample exceeds 30 mg albumin per g creatinine or 2.5 mg albumin per mmol creatinine.

Many risk scores utilise a gradation of risk factors. Others rely on the presence of one or more risk factors that are classified as being "severe". Table 3 presents a list of risk factors that comply with this definition. If one or more of these severe risk factors is present pharmacological intervention may be justified regardless of the estimated 10-year risk of a myocardial infarction. It is infrequent for high coronary risk to be conferred by the presence of a single severe risk factor. Rather, high risk is in most cases due to the concomitant occurrence of a number of risk factors of mild or moderate extent.

Table 3: What constitutes a severe risk factor?

- Persistent cigarette smoking
- LDL cholesterol >190 mg/dL (4.92 mmol/L) after therapeutic lifestyle changes
- Blood pressure >140/90 mm Hg after therapeutic lifestyle changes
- BMI $\geq$ 30 kg/m^2 in the presence of other risk factors

Quantifying risk

As noted in Table 1, a patient is said to be at high risk if his or her absolute risk of suffering a myocardial infarction or sudden coronary death within the next 10 years exceeds 20%.

Based on long-term prospective epidemiological studies, a number of algorithms and scoring systems have been developed to calculate this risk. These range from simple-to-use scores and charts to complicated algorithms that require the use of a pocket calculator or even a computer. Particularly in patients at high risk, use of scoring schemes may lead to considerable miscalculation when one or more variables lie on the cut-off between categories. Coronary risk charts provide a useful ready-reference guide to risk prevention but may suffer from lack of accuracy with particular risk factor constellations. We therefore recommend that risk should be calculated at least once in every patient using a full algorithm.

Table 4: How to determine the 10-year risk of a coronary event

- Coronary risk scores
- Computer assisted algorithms
  - Cox proportional hazards model
  - Weibull model
  - Neural network analysis
- Coronary risk charts/tables

Table 5: The PROCAM risk score

The PROCAM Risk Score[1] estimates the risk of developing a fatal or non-fatal myocardial infarction or sudden coronary death within 10 years. The tables *on page 16* show the points assigned to each level of each risk factor.

To calculate the total score, simply add up the points for each risk factor level in your patient, and then read off the absolute 10-year-risk from the table *on page 17*. You may wish to use for this purpose a form such as those shown at the end of this booklet.

The score was developed in 5,389 men aged 35-65 years at entry into PROCAM and may not be accurate in men outside this age range. Preliminary data from PROCAM indicates that the absolute risk in post-menopausal women without diabetes mellitus may be estimated by dividing the calculated risk by four. Post-menopausal women with diabetes mellitus have a risk of coronary heart disease similar to that of diabetic men of the same age and therefore do not require this correction.

Interactive assessment on the internet:
http://www.chd-taskforce.com

1. Assmann G, Cullen P, Schulte H. Circulation 2002; 105: 310-315

Number of points for each risk factor level	
Age (years)	
35–39	0
40–44	6
45–49	11
50–54	16
55–59	21
60–65	26

HDL cholesterol		
mg/dL	*mmol/L*	
< 35	< 0.91	11
35–44	0.91–1.16	8
45–54	1.17–1.41	5
≥ 55	≥ 1.42	0

Cigarette smoking during past 12 months	
Yes	8
No	0

Myocardial infarction before age 60 y in 1st degree relative	
Yes	4
No	0

Number of points for each risk factor level		
LDL cholesterol		
mg/dL	*mmol/L*	
< 100	< 2.59	0
100–129	2.59–3.36	5
130–159	3.37–4.13	10
160–189	4.14–4.91	14
≥ 190	≥ 4.92	20

Triglycerides		
mg/dL	*mmol/L*	
< 100	< 1.14	0
100–149	1.14–1.70	2
150–199	1.71–2.27	3
≥ 200	≥ 2.28	4

Diabetes mellitus [Known diabetes or fasting blood glucose levels ≥ 120 mg/dL (6.66 mmol/L)]	
Yes	6
No	0

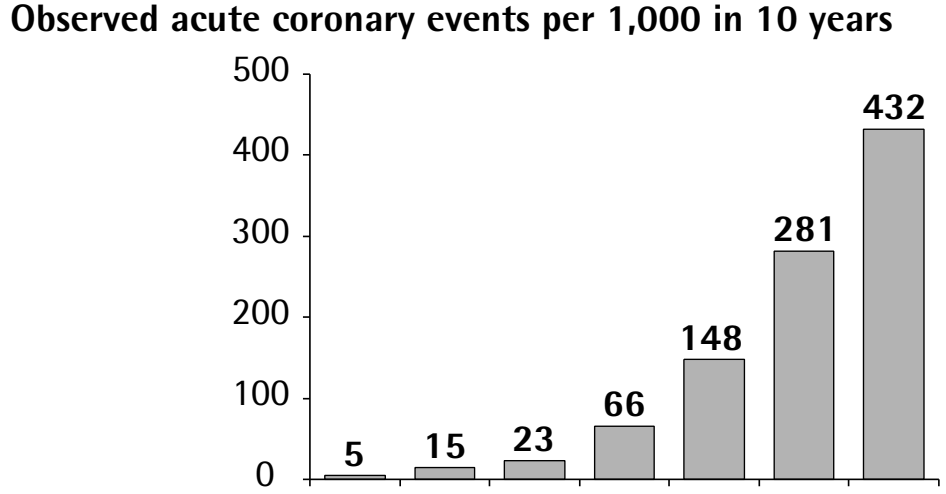
Systolic blood pressure (mmHg)	
< 120	0
120–129	2
130–139	3
140–159	5
≥ 160	8

Absolute 10-year risk of an acute coronary event for each score					
Total score	**10y risk**	**Total score**	**10y risk**	**Total score**	**10y risk**
≤ 20	< 1.0	**34**	3.5	**48**	12.8
21	1.1	**35**	4.0	**49**	13.2
22	1.2	**36**	4.2	**50**	15.5
23	1.3	**37**	4.8	**51**	16.8
24	1.4	**38**	5.1	**52**	17.5
25	1.6	**39**	5.7	**53**	19.6
26	1.7	**40**	6.1	**54**	21.7
27	1.8	**41**	7.0	**55**	22.2
28	1.9	**42**	7.4	**56**	23.8
29	2.3	**43**	8.0	**57**	25.1
30	2.4	**44**	8.8	**58**	28.0
31	2.8	**45**	10.2	**59**	29.4
32	2.9	**46**	10.5	**≥ 60**	≥ 30.0
33	3.3	**47**	10.7		

Fig. 1: Incidence of acute coronary events for each category of the PROCAM Score

The bar graph on this page shows the effect of the PROCAM score on coronary risk. In the 34% of men with a risk score below 29 points, less than 1.5 percent suffered a myocardial infarction or sudden coronary death within 10 years of follow-up. By contrast, after 10 years of follow-up, almost a third of the 7.5% of men with a score of at least 54 - the cut-off for identifying men at "high risk" - had suffered such an event. In the small group of men with a risk score above 61, the 10-year risk of a coronary event exceeded 40%.

Observed incidence of acute coronary events[1] in 5,389 men aged 35–65 years according to categories of PROCAM scores



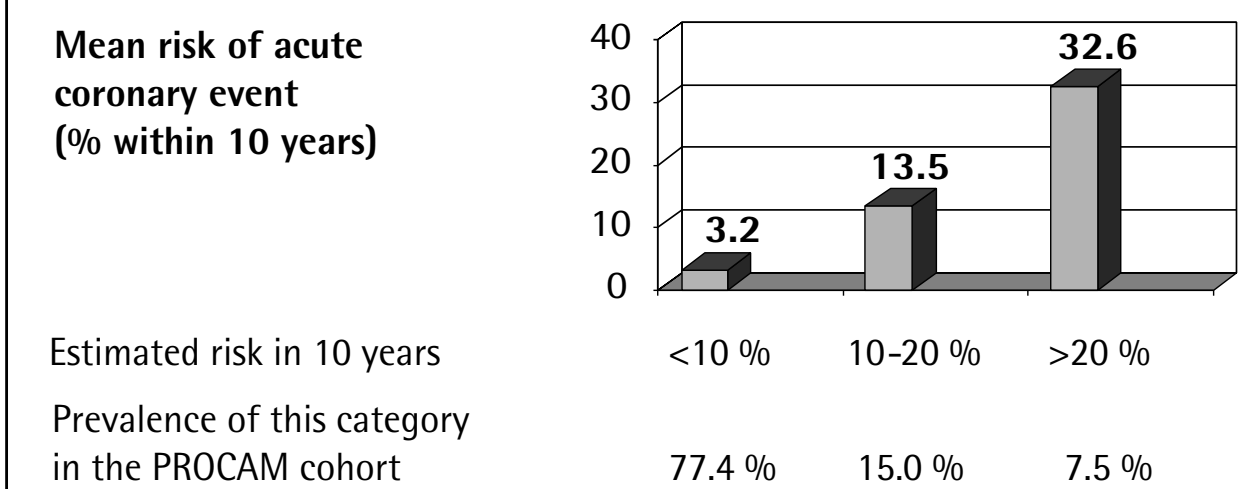
PROCAM scores	0-20	21-28	29-37	38-44	45-53	54-61	>61
Estimated risk in 10 years (%)	<1	1-2	2-5	5-10	10-20	20-40	>40
Prevalence of this category in the PROCAM cohort (%)	16.8	16.7	25.7	18.2	15.0	5.5	2.0

1. Throughout this guide, the term "acute coronary event" is taken to mean a fatal or non-fatal myocardial infarction, or sudden coronary death.

Fig. 2: Division of population into risk groups using risk algorithms

As shown in the graph on this page, use of a risk algorithm allows division of the population of middle-aged men into three groups at low or moderate risk (< 10% risk of myocardial infarction or sudden coronary death in 10 years), intermediate risk (10-20% risk in 10 years), and high risk (> 20 % risk in 10 years). More than three quarters of all middle-aged men fall into the group of low or moderate risk, with a mean incidence rate of acute coronary events of just 3% in 10 years, while 7.5% fall into the high risk group with a mean event incidence rate of nearly 33% in 10 years.

Observed risk of acute coronary events in 5,389 men aged 35–65 years according to categories of absolute risk



Note: Risk scores are a simple but accurate way to estimate coronary risk. However, inconsistencies may occur when monitoring treatment success with risk scores due to the use of discrete risk factor categories (see Table 13 *on page 44*.)
For example:

- LDL cholesterol levels between 160 and 189 mg/dL (4.14-4.91 mmol/L) are assigned a score of 14,
- LDL cholesterol levels between 130 and 159 mg/dL (3.37-4.13 mmol/L) are assigned a score of 10.

Thus,

- a reduction of LDL cholesterol of 20 mg/dL (0.52 mmol/L) from 180 mg/dL (4.66 mmol/L) to 160 mg/dL (4.14 mmol/L) *would not* appear to reduce the estimated 10-year risk for myocardial infarction,

while

- an equal reduction of 20 mg/dL (0.52 mmol/L) from 170 mg/dL (4.40 mmol/L) to 150 mg/dL (3.89 mmol/L) *would* appear to reduce the estimated 10-year risk for myocardial infarction.

By contrast, any reduction of LDL cholesterol is reflected in a lower estimated 10-year risk of myocardial infarction or sudden coronary death as calculated by the PROCAM risk algorithm, as this method is based not on categories, but on continuous variables.
For this reason, the PROCAM risk algorithm is a more accurate means to estimate risk reduction during treatment.

The Framingham Point Score

One of the largest and best-documented prospective epidemiological studies of coronary heart disease was conducted in the town of Framingham in Massachusetts in the United States of America. Based on the data from this study, a score was developed to calculate the 10-year coronary risk[1]. The following tables both for men and women show the number of points assigned to each level of each risk factor, both for men and women.

The total score is calculated by adding up the points for each risk factor. The bottom tables *on page 23* and *page 25* show the 10-year risk of heart attack or coronary death associated with each overall score.

The tables are as shown in:
http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf

1. Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. JAMA 2001; 285: 2486-2497

Table 6: The Framingham point score for men

Age (years)	**Points**
20–34	-9
35–39	-4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Systolic blood pressure (mmHg)	**points if untreated**	**points if treated**
< 120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

HDL cholesterol		
mg/dL	*mmol/L*	Points
≥ 60	≥ 1.55	-1
50–59	1.30–1.54	0
40–49	1.04–1.29	1
< 40	< 1.04	2

Total cholesterol					
mg/dL	< 160	160–199	200–239	240–279	≥ 280
mmol/L	< 4.14	4.14–5.17	5.18–6.21	6.22–7.24	≥ 7.25
Age (years)					
20–39	0	4	7	9	11
40–49	0	3	5	6	8
50–59	0	2	3	4	5
60–69	0	1	1	2	3
70–79	0	0	0	1	1

Smoking status		
Age	**non-smoker**	**smoker**
20–39	0	8
40–49	0	5
50–59	0	3
60–69	0	1
70–79	0	1

Framingham Score: risk for each level of points in men			
Total points	**10y risk in %**	**Total points**	**10y risk in %**
< 0	< 1	**9**	5
0	1	**10**	6
1	1	**11**	8
2	1	**12**	10
3	1	**13**	12
4	1	**14**	16
5	2	**15**	20
6	2	**16**	25
7	3	**≥ 17**	≥ 30
8	4		

For interpretation of scores see Table 13 *on page 44*.

Table 7: The Framingham point score for women

Age (years)	**Points**
20–34	-7
35–39	-3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Systolic blood pressure (mmHg)	**points if untreated**	**points if treated**
< 120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥ 160	4	6

HDL cholesterol		
mg/dL	*mmol/L*	Points
≥ 60	≥ 1.55	-1
50–59	1.30-1.54	0
40–49	1.04-1.29	1
< 40	< 1.04	2

Total cholesterol					
mg/dL	< 160	160-199	200-239	240-279	≥ 280
mmol/L	< 4.14	4.14-5.17	5.18-6.21	6.22-7.24	≥ 7.25
Age (years)					
20–39	0	4	8	11	13
40–49	0	3	6	8	10
50–59	0	2	4	5	7
60–69	0	1	2	3	4
70–79	0	1	1	2	2

Smoking status		
Age	**non-smoker**	**smoker**
20–39	0	9
40–49	0	7
50–59	0	4
60–69	0	2
70–79	0	1

Framingham Score: risk for each level of points in women			
Total points	10 y risk in %	Total points	10 y risk in %
< 9	< 1	19	8
9–12	1	20	11
13–14	2	21	14
15	3	22	17
16	4	23	22
17	5	24	27
18	6	≥ 25	≥ 30

For interpretation of scores see Table 13 *on page 44*.

Table 8: The PROCAM algorithm for men (Cox proportional hazards model)

The simple PROCAM scoring scheme described in this guide was derived from a more complicated Cox proportional hazards model. In the following section, we present the coefficients of the complete Cox model. This has an advantage over the simple scoring scheme in calculating the effects of treatment on coronary risk (see footnote to figure 2 *on page 19*), and also avoids the distortion that may occur when risk is calculated in persons whose risk factors lie at the border between two risk factor categories (see Table 13 *on page 44*). The Cox model may be programmed into a computer or scientific calculator, or, more simply, may be accessed online.

Estimate of 10-year risk for men

To estimate the risk for acute coronary events within 10 years based on measurements of

- Age
- Systolic blood pressure
- LDL cholesterol
- HDL cholesterol
- Triglyceride
- Smoking
- Myocardial infarction before age 60 y in 1st degree relative
- Diabetes mellitus

Estimate of 10-year risk for men

Compute an interim number a = exp(y) with

y = -8.9769

+ 0.103 x age
  (input range: 35-65 years)
+ 0.010 x systolic blood pressure
  (input range: 100-225 mmHg)
+ 0.013 x LDL cholesterol in mg/dL
  (or + 0.5026 x LDL cholesterol in mmol/L)
  (input range: 75-250 mg/dL [1.94-6.48 mmol/L])
- 0.032 x HDL cholesterol in mg/dL
  (or - 1.2372 x HDL cholesterol in mmol/L)
  (input range: 25-75 mg/dL [0.65-1.94 mmol/L])
+ 0.317 x log [triglycerides in (mg/dL)]
  (or + 0.317 x log (triglycerides in mmol/L x 88.57))
  (input range: 50-400 mg/dL (0.57-4.56 mmol/L))
+ 0.658 x cigarette smoking
  (any cigarette smoking during the past 12 months (0 = no, 1 = yes))
+ 0.399 x diabetes mellitus
  (known diabetes or fasting blood glucose levels ≥ 120 mg/dL (6.66 mmol/L) (0 = no, 1 = yes))
+ 0.382 x myocardial infarction in family history
  (myocardial infarction in 1st degree relative before the age of 60 years (0 = no, 1 = yes))

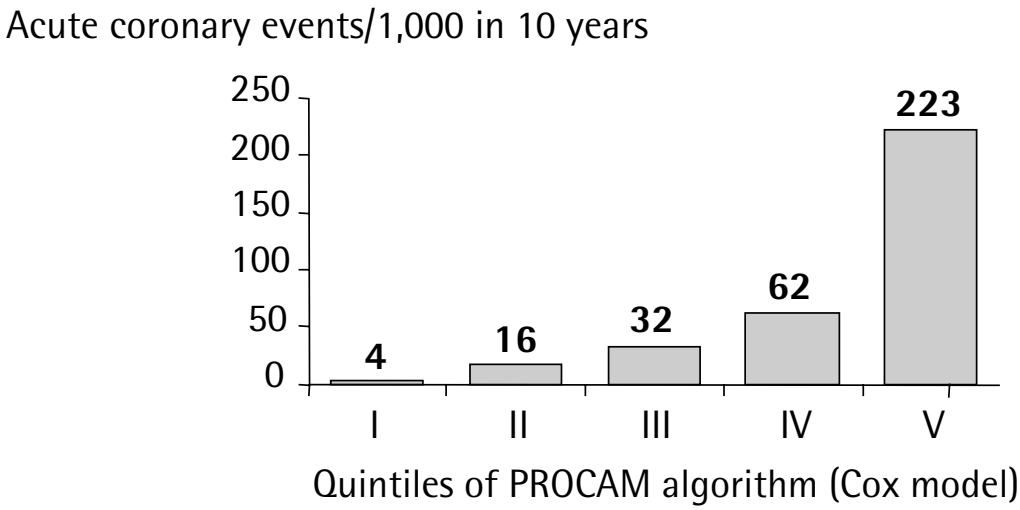
The probability for CHD in % within 10 years is: $P = 100 \times (1-0.9369^{a})$

Interactive assessment on the internet: http://www.chd-taskforce.com

Fig. 3: Incidence of myocardial infarction and sudden coronary death in men by quintiles of estimated risk

This figure divides the population of middle-aged men in PROCAM into five equally sized blocks (quintiles) arranged according to ascending risk. As can be seen, the mean 10-year risk of a coronary event among men in the upper quintile of risk was approximately 22%.

Acute coronary events in men



Independent variables were: age, systolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, diabetes mellitus, smoking, family history of myocardial infarction

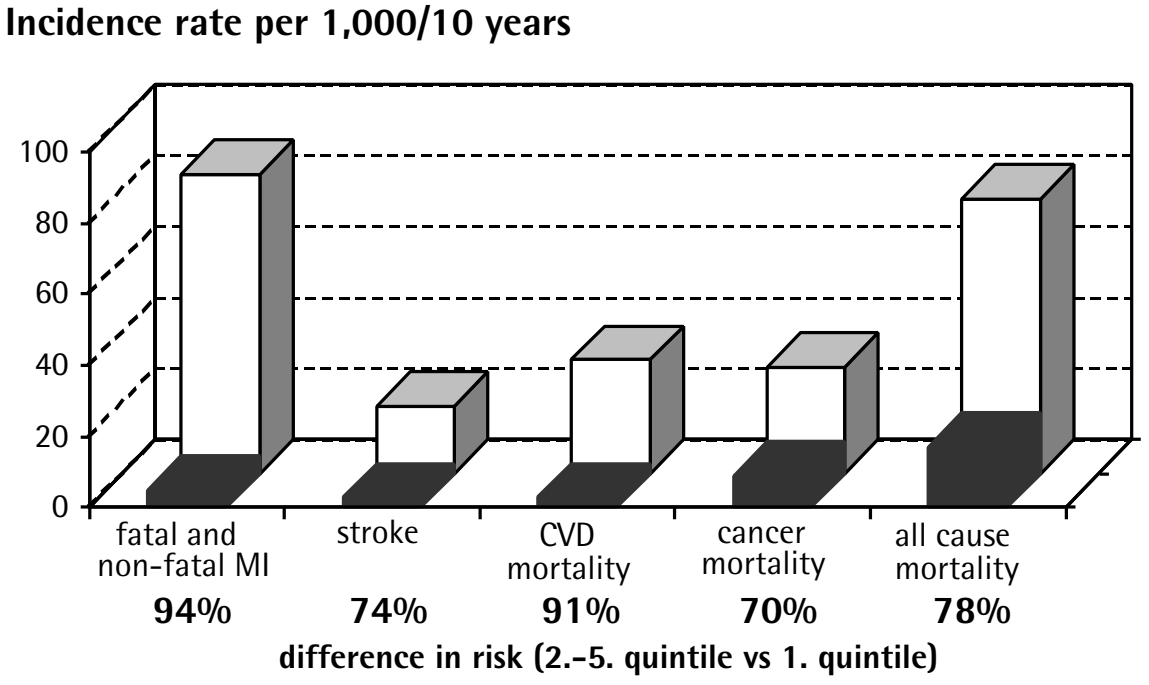
325 fatal and non-fatal myocardial infarctions in 4,818 men aged 35-65 years at entry

Data from the PROCAM Study

Fig. 4: Patients at low risk of myocardial infarction as calculated by risk algorithms also have low risk of stroke, cancer and death from all causes

In the PROCAM Study, the risk of myocardial infarction was lower by 94% in men in the lowest quintile of risk (see Figure 3 *on page 28*) compared to the men in the other four quintiles. However, this group of men also had a 84% lower risk of stroke, a 96% lower total cardiovascular mortality, a 70% lower cancer mortality, and a 68% lower all-cause mortality. This is partly explained by the strong effects of age and smoking in the PROCAM risk algorithm.

Lower morbidity and mortality in patients at low risk of myocardial infarction



Data from the PROCAM Study

Table 9: Risk of myocardial infarction in PROCAM women

In analogy to the formula used for calculating the 10-year risk of myocardial infarction or sudden coronary death in men in PROCAM, the following formula has been derived for use in women aged 45 to 65 years. This formula was derived based on the 32 myocardial infarctions that occurred during 10 years of follow-up among the 2,810 women in this age-group in PROCAM.

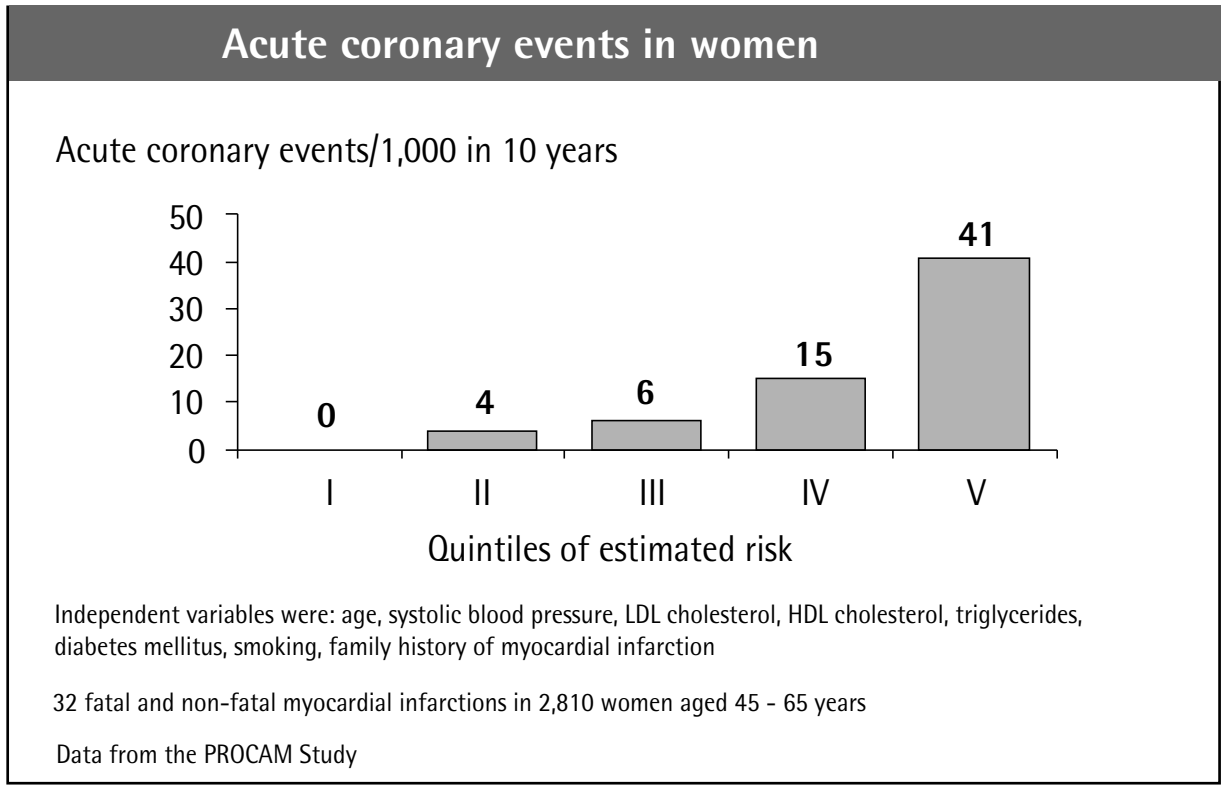
31.25/[1+exp (12.5054

- 0.1031 x age
  (input range: 45-65 years)
- 0.0117 x systolic blood pressure
  (input range: 100-225 mmHg)
- 0.0146 x LDL cholesterol in mg/dL
  (or - 0.5645 x LDL cholesterol in mmol/L)
  (input range: 75-250 mg/dL [1.94-6.48 mmol/L])
+ 0.0418 x HDL cholesterol in mg/dL
  (or + 1.6162 x HDL cholesterol in mmol/L)
  (input range: 35-85 mg/dL [0.91-2.20 mmol/L])
- 0.3362 x log (triglycerides in mg/dL)
  (or - 0.3362 x log (triglycerides in mmol/L x 88.57))
  (input range: 50-400 mg/dL [0.57-4.56 mmol/L])
- 0.9361 x smoking
- 0.3818 x diabetes mellitus
- 0.3908 x myocardial infarction in family history)]

Interactive assessment on the internet: http://www.chd-taskforce.com

Fig. 5: Incidence of myocardial infarction and sudden coronary death in women by quintiles of estimated risk

This figure divides the population of middle-aged women in PROCAM into five equally sized blocks arranged according to ascending risk. Among the 562 women in the upper quintile of risk, 23 coronary events occurred within 10 years of follow-up, indicating a mean ten-year-risk of about 4%.



Please note that in the PROCAM Study, the total number of coronary events in women after 10 years of follow-up (n=32) was only about a tenth of that seen in men (n=325) after the same period. This is because only one-third of participants were women, and because the adjusted incidence of coronary events in women was only about one-quarter that in men. Because of these limited data, the PROCAM algorithm should be applied with caution to women at the present time.

Table 10: The Framingham algorithm (Weibull model)

Numerous risk algorithms have emerged from the Framingham study over the years. One of the most commonly used is the so-called Weibull model. The coefficients of this model are provided below.

The Framingham algorithm may be programmed into your computer or scientific calculator, or, more simply, may be accessed in interactive fashion at http://www.cardiacrisk.org.uk.

As will be discussed in Table 15, problems may occur in using this algorithm to calculate risk in a population other than that in which it was derived.

Risk for coronary heart disease within 10 years, based on measurements of
• Age • Systolic blood pressure • Total cholesterol/HDL cholesterol ratio • Smoking • Diabetes mellitus • Left ventricular hypertrophy as assessed by electrocardiography

Estimate of 10-year risk of men	Estimate of 10-year risk of women
Compute an interim number X1 with	
X_1 = 11.1122 - 1.4792 x log (age) Input range: 30-74 years - 0.9119 x log (systolic blood pressure) Input range: 95-185 mmHg - 0.7181 x log (total cholesterol/HDL) Input range total cholesterol: 135-330 mg/dL (3.50-8.55 mmol/L) Input range HDL cholesterol: 25-99 mg/dL (0.65-2.56 mmol/L) - 0.2767 x smoking (nonsmoker = 0, cigarette smoker = 1) - 0.1759 x diabetes mellitus (0 = no, 1 = yes) - 0.5865 x left ventricular hypertrophy (0 = no, 1 = yes), when information not available, LVH = 0	X_1 = 5.2573 + 1.8515 x $[\log (age/74)]^2$ Input range: 30-74 years - 0.9119 x log (systolic blood pressure) Input range: 95-185 mm Hg - 0.7181 x log (total cholesterol/HDL) Input range total cholesterol: 135-330 mg/dL (3.50-8.55 mmol/L) Input range HDL cholesterol: 25-99 mg/dL (0.65-2.56 mmol/L) - 0.2767 x smoking (nonsmoker = 0, cigarette smoker = 1) - 0.3758 x diabetes mellitus (0 = no, 1 = yes) - 0.5865 x left ventricular hypertrophy (0 = no, 1 = yes), when information not available, LVH=0
Compute a second interim number $X_2 = [-2.1155149 - X_1] / \exp (-0.3155 - 0.2784 \times X_1)$ The probability for CHD (in %) within 10 years is $P = 100 \times (1-\exp [- \exp(X_2)])$	

Table 11: Neural network analysis

A fundamental problem of all risk algorithms is that they must make assumptions about the nature of the mathematical relationships that exist between the individual risk variables. In particular, complex or higher-order relationships between individual risk factors may be overlooked, leading to a loss of predictive information. Neural networks, by contrast, make no assumptions about the relationships between risk variables and therefore have the potential to improve the prediction of risk in a particular dataset compared to conventional risk algorithms. A neural network risk prediction model has been derived from the data of the PROCAM study[1]. This model, which is available on the website of the International Task Force for Prevention of Coronary Heart Disease (http://www.chd-taskforce.com), performed better than a conventional risk algorithm based on Cox proportional hazards analysis (Table 8 *on page 26*). However, apart from the PROCAM study, no experience has yet been gathered in the use of neural networks to calculate coronary risk. For this reason, the calculation of risk by means of neural networks should at the present be seen as experimental and should not be used as a sole basis for clinical decisions.

1. Voss R, Cullen P, Schulte H, Assmann G. Int J Epidemiol 2002; 31: 1253-1262

Risk factors included in the standard PROCAM algorithm and in neural network analysis.

PROCAM neural network	Standard PROCAM algorithm
• Age	• Age
• Systolic blood pressure	• Systolic blood pressure
• Diastolic blood pressure	-
• Anti-hypertensive treatment	-
• HDL cholesterol	• HDL cholesterol
• LDL cholesterol	• LDL cholesterol
• Triglycerides	• Triglycerides
• Number of cigarettes per day	• Cigarette smoking yes or no
• Presence of diabetes mellitus	• Presence of diabetes mellitus
• Fasting blood glucose	-
• Body mass index (BMI)	-
• History of myocardial infarction in a first-degree family member before age 60 years	• History of myocardial infarction in a first-degree family member before age 60 years
• Uric acid	-

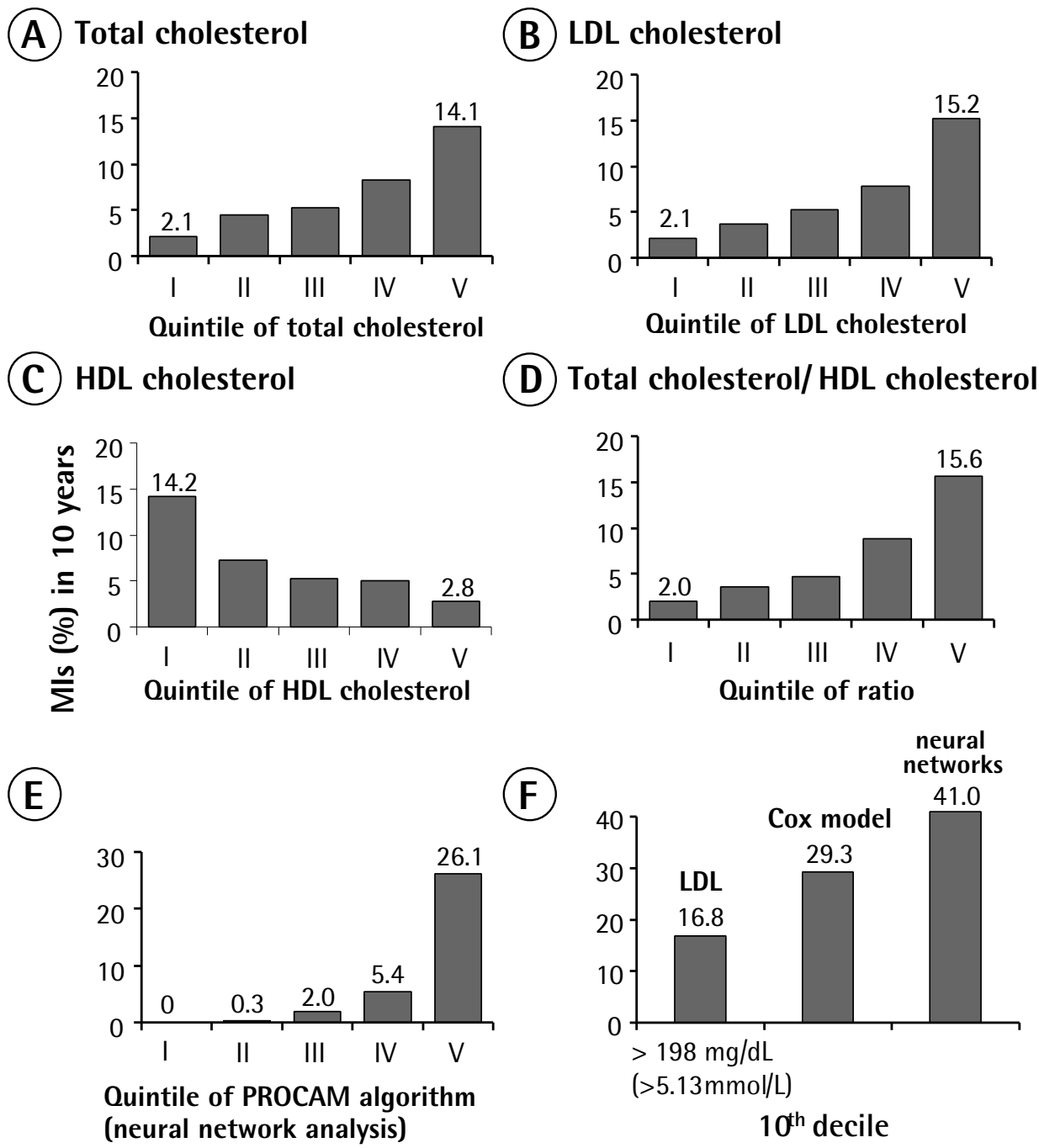
Fig. 6: Better risk discrimination by means of neural network analysis

As can be seen from the graphs *on page 37*, individual risk factors only provide a modest degree of discrimination between individuals in the top and bottom quintile of the risk factor.

For total cholesterol **(A)**, the risk ratio between the top and the bottom quintiles is 6.7, for LDL cholesterol **(B)** 7.2, for HDL cholesterol **(C)** 5, and for the ratio of total to HDL cholesterol **(D)** 7.8. By contrast, the risk ratio between the bottom and top neural network quintiles **(E)** cannot even be calculated because of the absence of events in the bottom quintile. Even comparing the second and top quintiles, the risk ratio using neural networks is no less than 87.

Part **F** shows the ability of LDL cholesterol alone, a conventional risk algorithm, and neural network analysis to segregate the population of middle-aged men into deciles of risk. The top decile of LDL cholesterol included those men with an LDL level above a cut-off of 198 mg/dL (5.13 mmol/L); 16.8% of the men in this group suffered a myocardial infarction within 10 years of follow-up (compared to 7% in the overall population of middle-aged men). By contrast, 29% of the men in the top decile of the risk algorithm and no fewer than 41% of the men in the top decile of the neural network function suffered such an event.

Improved risk prediction using neural network analysis



325 acute coronary events in 4,818 men aged 35 - 65 years
Data from the PROCAM Study

Fig. 7: Algorithms are superior to single risk factors in predicting risk of myocardial infarction

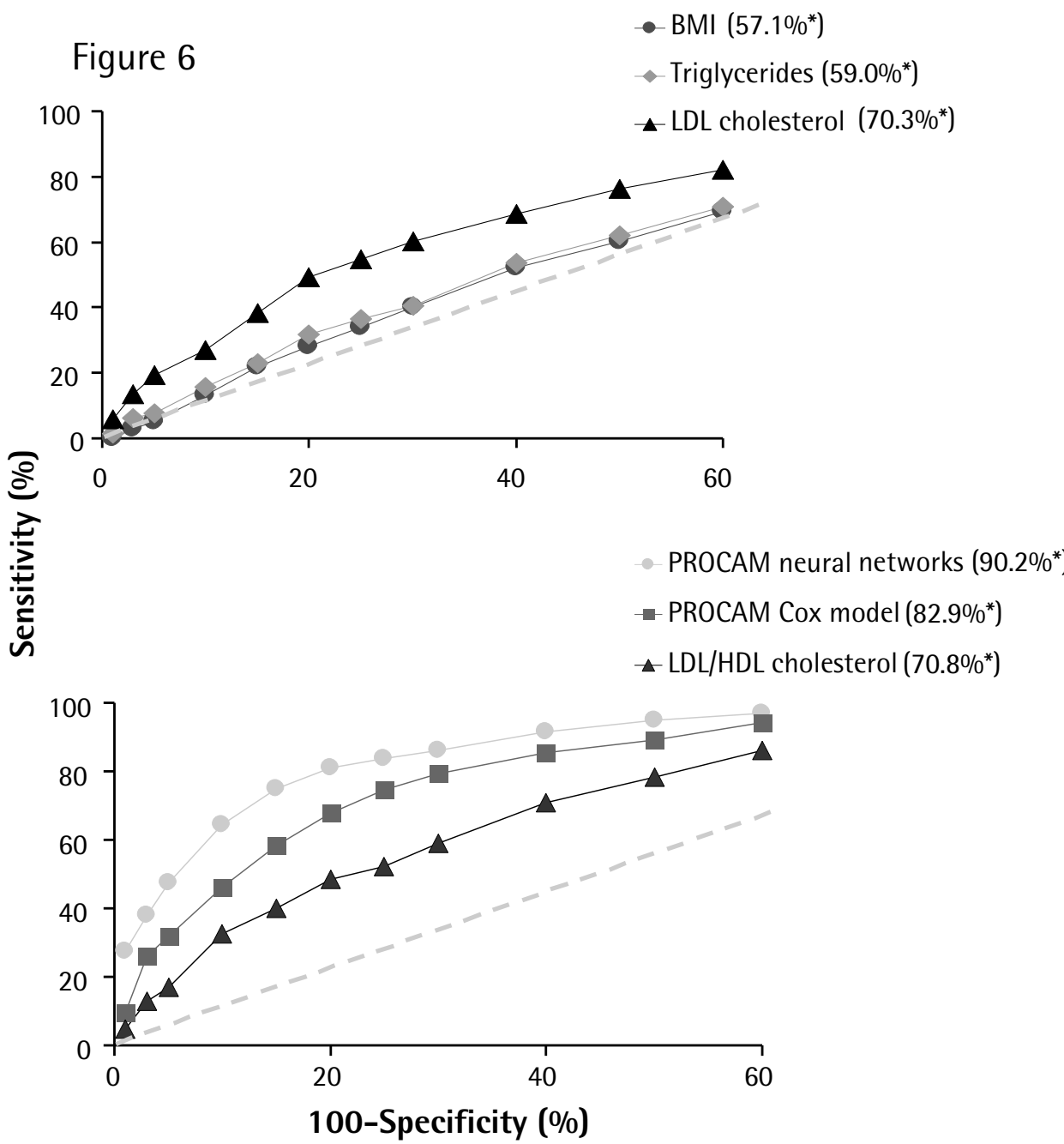
The figure *on page 39* shows a form of analysis called the receiver-operated characteristics (ROC) curve. The ROC curve is an unbiased way to assess the performance of any test in predicting a bimodal outcome such as healthy/sick, coronary event/no coronary event. The perfect test, i.e. one that is correct in every case, will produce a curve that runs vertically along the y-axis to 100% and then describes a 90° angle in order to run parallel to the x-axis. The area under such a perfect curve is 100%. By contrast, a test with no predictive power whatsoever will run along the dotted line. The more a test deviates from this line, the better it is.

Note that among isolated risk factors (upper) LDL cholesterol yields the greatest area under the ROC curve (70.3 %). By contrast, algorithms taking into consideration multiple risk factors (lower) perform much better.

In a time of constrained budgets, these findings have important implications for health economics. The better an algorithm is at identifying individuals at risk, the better we are able to target treatment and preventive measures to those who need them most.

Algorithms are superior to lipid concentration in risk prediction

Figure 6



Data from the PROCAM Study

* area under the curve

Table 12: Coronary risk charts

Several guidelines for coronary risk prevention make use of colour-coded coronary risk charts. These are sometimes referred to as the "Sheffield tables".

As noted already in this guide, these tables are a useful ready-reckoner in assessing risk in the busy clinic, but should not be used as a replacement for a formal assessment of coronary risk using a complete risk algorithm.

Women								
Total: HDL cholesterol ratio								
Hypertens. Smoking Diabetes		Yes Yes Yes		No Yes Yes		Yes No Yes		Yes Yes No	
CHD risk (%)		*15*	*30*	*15*	*30*	*15*	*30*	*15*	*30*
Age	70	2.3	4.1	2.7	4.9	3.3	6.1	3.8	7.0
	68	2.3	4.2	2.7	5.0	3.4	6.1	3.9	7.0
	66	2.3	4.2	2.8	5.1	3.4	6.2	3.9	7.1
	64	2.4	4.3	2.8	5.2	3.5	6.4	4.0	7.3
	62	2.4	4.4	2.9	5.3	3.6	6.5	4.1	7.5
	60	2.5	4.6	3.0	5.5	3.7	6.7	4.2	7.7
	58	2.6	4.8	3.1	5.7	3.8	7.0	4.4	8.0
	56	2.7	5.0	3.3	6.0	4.0	7.4	4.6	8.4
	54	2.9	5.3	3.5	6.3	4.3	7.8	4.9	8.9
	52	3.1	5.6	3.7	6.8	4.5	8.3	5.2	9.5
	50	3.3	6.1	4.0	7.3	4.9	9.0	5.6	-
	48	3.6	6.6	4.3	7.9	5.3	9.8	6.1	-
	46	4.0	7.3	4.8	8.8	5.9	-	6.8	-
	44	4.5	8.2	5.4	9.8	6.6	-	7.6	-
	42	5.1	9.4	6.1	-	7.5	-	8.6	-
	40	5.9	-	7.1	-	8.7	-	10.0	-
	38	7.0	-	8.4	-				
	36	8.5	-	10.2	-				

Instructions

Choose table for men or women

- Hypertension means systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or on antihypertensive treatment
- Identify correct column for hypertension, smoking, and diabetes
- Identify row showing age
- Read off total: HDL cholesterol ratios at intersection of column and row. If there is an entry, measure serum cholesterol: HDL cholesterol ratio. If no entry, lipids need not be measured unless familial hyperlipidaemia suspected
- If total: HDL cholesterol ratio confers coronary heart disease risk of 15%, consider treatment of mild hypertension (systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-99mmHg) and with aspirin
- If total: HDL cholesterol ratio confers coronary heart disease risk of 30%, consider statin if serum cholesterol ≥ 5.0 mmol/l (≥ 193 mg/dL)
- Decisions on statin at coronary heart disease risk between 15%-30% depend on local policy
- The table can be used to assess coronary heart disease risk at an older age

Women								
Total: HDL cholesterol ratio								
Hypertens.		No		No		**Yes**		No	
Smoking		No		**Yes**		No		No	
Diabetes		**Yes**		No		No		No	
CHD risk (%)		*15*	*30*	*15*	*30*	*15*	*30*	*15*	*30*
Age	70	4.0	7.2	4.6	8.3	5.6	10.2	6.7	-
	68	4.0	7.3	4.6	8.4	5.7	-	6.8	-
	66	4.1	7.4	4.7	8.5	5.7	-	6.9	-
	64	4.2	7.6	4.8	8.7	5.9	-	7.0	-
	62	4.3	7.8	4.9	9.0	6.0	-	7.2	-
	60	4.4	8.1	5.1	9.3	6.2	-	7.4	-
	58	4.6	8.4	5.3	9.6	6.5	-	7.8	-
	56	4.8	8.8	5.5	10.1	6.8	-	8.1	-
	54	5.1	9.3	5.8	-	7.2	-	8.6	-
	52	5.4	9.9	6.2	-	7.7	-	9.2	-
	50	5.9	-	6.7	-	8.3	-	9.9	-
	48	6.4	-	7.3	-	9.0	-		
	46	7.1	-	8.1	-	10.0	-		
	44	7.9	-	9.1	-				
	42	9.0	-	10.3	-				
	40								
	38								
	36								

Read before using table

- Do not use for secondary prevention: patients with myocardial infarction, angina, peripheral vascular disease, non-haemorrhagic stroke, transitory ischaemic attack, or diabetes with microvascular complications have high coronary heart disease risk. Treat mild hypertension:
  treat with aspirin; and treat with statin if serum cholesterol ≥ 5.0 mmol/l (≥ 193 mg/dL)
- Treat hypertension above mild range (average ≥ 160 mmHg or ≥ 100 mmHg)
- Treat mild hypertension (140-159 mmHg or 90-99 mmHg) with target organ damage (left ventricular hypertrophy, proteinuria, renal impairment) or with diabetes (type 1 or 2)
- Consider drug treatment only after 6 months of appropriate advice on smoking, diet and repeated blood pressure measurements
- Use average of repeated total:HDL cholesterol measurements. If HDL cholesterol not available, assume 1.2 mmol/l (46 mg/dL)
- Those with total:HDL cholesterol ratio ≥ 8.0 may have familial hyperlipidaemia
- The table underestimates coronary heart disease risk in
  - Left ventricular hypertrophy on ECG (risk doubled - add 20 years to age)
  - family history of premature cholesterol (add 6 years)
  - familial hyperlipidaemia
  - British Asians

Men								
Total: HDL cholesterol ratio								
Hypertens. **Smoking** **Diabetes**		**Yes** **Yes** **Yes**		No **Yes** **Yes**		**Yes** **Yes** No		**Yes** No **Yes**	
CHD risk (%)		*15*	*30*	*15*	*30*	*15*	*30*	*15*	*30*
Age	70	2.0	3.0	2.0	3.6	2.1	3.8	2.4	4.4
	68	2.0	3.2	2.1	3.8	2.2	4.1	2.6	4.7
	66	2.0	3.4	2.2	4.0	2.4	4.3	2.7	5.0
	64	2.0	3.6	2.4	4.3	2.5	4.6	2.9	5.3
	62	2.1	3.8	2.5	4.6	2.7	4.9	3.1	5.6
	60	2.2	4.1	2.7	4.9	2.9	5.2	3.3	6.0
	58	2.4	4.4	2.9	5.3	3.1	5.6	3.5	6.5
	56	2.6	4.7	3.1	5.7	3.3	6.0	3.8	7.0
	54	2.8	5.1	3.3	6.1	3.6	6.5	4.1	7.5
	52	3.0	5.5	3.6	6.6	3.9	7.0	4.4	8.1
	50	3.3	6.0	3.9	7.1	4.2	7.6	4.8	8.8
	48	3.6	6.5	4.3	7.8	4.5	8.3	5.2	9.6
	46	3.9	7.1	4.6	8.5	5.0	9.1	5.7	10.4
	44	4.3	7.8	5.1	9.3	5.4	9.9	6.3	-
	42	4.7	8.6	5.6	10.2	6.0	10.9	6.9	-
	40	2,0	9,5	6,2	-	6,6	-	7,6	-
	38	2,0	10,5	6,9	-	7,3	-	8,5	-
	36	2.0	-	7.7	-	8.2	-	9.5	-
	34	2.0	-	8.6	-	9.2	-	10.6	-
	32	2.1	-	9.8	-	10.5	-		
	30	9.4	-						
	28	10.8	-						

See footnotes *on page 40 and 41*

Note: In mathematical terms, the charts shown on this and previous pages are exactly equivalent to the Framingham risk scores contained at other positions within this document, the only difference being in the displayed format.

Men									
Total: HDL cholesterol ratio									
Hypertens. **Smoking** **Diabetes**		No **Yes** No		No No **Yes**		**Yes** No No		No No No	
CHD risk (%)		*15*	*30*	*15*	*30*	*15*	*30*	*15*	*30*
Age	70	2.5	4.6	2.9	5.3	3.1	5.6	3.7	6.7
	68	2.7	4.8	3.0	5.6	3.3	6.0	3.9	7.1
	66	2.8	5.2	3.2	5.9	3.5	6.3	4.1	7.6
	64	3.0	5.5	3.5	6.3	3.7	6.8	4.4	8.1
	62	3.2	5.9	3.7	6.7	3.9	7.2	4.7	8.6
	60	3.4	6.3	3.9	7.2	4.2	7.7	5.0	9.2
	58	3.7	6.7	4.2	7.7	4.5	8.3	5.4	9.9
	56	4.0	7.2	4.6	8.3	4.9	8.9	5.8	10.6
	54	4.3	7.8	4.9	9.0	5.2	9.6	6.3	-
	52	4.6	8.4	5.3	9.7	5.7	10.4	6.8	-
	50	5.0	9.1	5.7	10.5	6.1	-	7.3	-
	48	5.4	9.9	6.3	-	6.7	-	8.0	-
	46	5.9	10.8	6.8	-	7.3	-	8.7	-
	44	6.5	-	7.5	-	8.0	-	9.6	-
	42	7.2	-	8.2	-	8.8	-	10.5	-
	40	7,9	-	9,1	-	9,7	-		
	38	8,8	-	10,1	-	10,8	-		
	36	9,8	-						
	34								
	32								
	30								
	28								

Table 13: Pitfalls of using charts and scores for calculating coronary risk

Today, a wide variety of instruments is available to assist the physician in calculating coronary risk, as has been described in this guide. None of these instruments is perfect, however, and clinical judgement still plays an important role in deciding the optimal treatment for the individual patient.

For the busy doctor, charts and scores have the advantage of being easier to use. Both are substantially easier to use than complete risk algorithms, which require access to the internet or at least to a pocket computer.

However, this ease of use should not obscure the difficulties that may arise when coronary risk is calculated solely on the basis of a risk chart or a risk score. In particular, note the following 3 examples:

- **Miscalculation of risk in high-risk patients with risk factor levels that lie on the boundaries between two risk factor categories**
  Because of non-additive interactions that exist between coronary risk factors, the coronary risk curve rises much more steeply at high levels of risk than at low levels of risk.
  This means that even small rounding errors that occur with the use of risk scores or charts may lead in high-risk patients to significant errors in the calculation of absolute risk.
  Such rounding errors may also occur in interconverting the units for triglyceride or cholesterol between mg/dL and mmol/L. Consider the following two examples:

Example 1	Person 1		Person 2	
	mg/dL	mmol/L	mg/dL	mmol/L
LDL cholesterol	190	4.92	189	4.90
HDL cholesterol	34	0.88	35	0.91
triglycerides	220	2.51	220	2.51
systolic blood pressure	160 mmHg		159 mmHg	
age	50		49	
smoker	no		no	
diabetes mellitus	no		no	
family history of premature myocardial infarction	no		no	
10 y risk (PROCAM score)	**29.4%**		**7.4%**	
10 y risk (PROCAM algorithm)	**14.3%**		**12.4%**	

Using the PROCAM risk score, person 1 is calculated to have a 10-year risk of myocardial infarction or sudden coronary death of 29.4%. Using the full PROCAM algorithm, his risk is calculated to be less than half as high at 14.3%. The PROCAM score thus places him clearly within the category of "high risk" requiring intensive intervention, while the full algorithm calculates his risk as moderate, requiring lifestyle intervention in the first instance. This error is clearly shown by person 2, who is only one year younger than person 1 while his LDL cholesterol and HDL cholesterol are only slightly different. This is reflected by the 10-year risk calculated using the risk algorithm, which is only slightly less than that calculated for person 1 - thus indicating that the risk algorithm correctly predicts the patient's risk. However because age, HDL cholesterol and LDL cholesterol are now in lower categories, the apparent risk of person 2 calculated using the PROCAM score has fallen by 75% and is now less than that calculated by the full algorithm.

Example 2	Person 2		Person 3	
	mg/dL	mmol/L	mg/dL	mmol/L
LDL cholesterol	189	4.90	175	4.53
HDL cholesterol	35	0.91	40	1.04
triglycerides	220	2.51	220	2.51
systolic blood pressure	159 mmHg		150 mm Hg	
age	49		47	
smoker	no		no	
diabetes mellitus	no		no	
family history of premature MI	no		no	
10 y risk (PROCAM score)	**7.4%**		**7.4%**	
10 y risk (PROCAM algorithm)	**12.4%**		**6.7%**	

Person 2 is as in the previous example. In this man, the score somewhat underestimated the true risk of myocardial infarction or sudden coronary death.
In person 3 the age, LDL cholesterol and HDL cholesterol have been chosen to be approximately in the centre of their respective risk factor categories (see Table 5). For example, the LDL cholesterol value was chosen to lie mid-way between 160 and 190 mg/dL. As a result, the risk estimated using the score is now very similar to that estimated using the complete algorithm.
Thus, in selected cases, sole use of the risk score (or of risk charts) may lead to a substantial over- or underestimation of the true level of risk. We therefore recommend assessing each patient's risk at least once using the full algorithm. This is especially important when considering use of pharmacological therapy.

- **Inconsistencies due to non-continuous nature of risk categories**
  Because of the non-continuous nature of risk factor categories, inconsistencies may arise in the calculation of risk using scores instead of the complete algorithms underlying them.
  Consider the following example in which the Framingham score is used to calculate the 10-year-risk of coronary heart disease in smoking and non-smoking women of different ages (Example 3). Note the absence of the expected consistent increase in risk with age in smoking women.

Example 3

	10- year risk (%) for	
Age (years)	Non-smoker	Smoker
< 35	1	14
35-39	4	≥ 30
40-44	4	22
45-49	8	≥ 30
50-54	8	22
55-59	14	≥ 30
60-64	11	17
65-69	17	27
70-74	17	22
75-79	27	≥ 30

10y risk in % of a woman with:
- total cholesterol > 280 mg/dL (7.3 mmol/L)
- HDL cholesterol < 40 mg/dL (1.0 mmol/L)
- untreated systolic blood pressure ≥ 160 mmHg

The inconsistent risk values for women shown in this table are the result of two factors: the extreme nature of the lipid values in the case shown, and the small number of coronary events occurring in women in the Framingham study. Moreover, based on the above table, despite the high total cholesterol level and high blood pressure, among non-smoking women only those above the age of 75 would be in the category of high risk and require pharmacological treatment, which is an improbable result.

- **Miscalculation of expected effects of treatment on coronary risk**
  As explained in the footnote to Figure 2 *on page 19*, use of risk charts or risk scores may miscalculate the effect of treatment on a patient's coronary heart disease risk if the patient's risk factor level lies at the extreme of a risk factor category.

Table 14: Framingham and PROCAM risk scoring may yield different outcomes

The two major risk scores and algorithms that exist today were derived from the German PROCAM study and the US Framingham study. Several important differences exist between the PROCAM and the Framingham scores, and each has its particular usefulness.

- The most obvious difference is the difference in the study population. The PROCAM study was performed in the working population of north-western Germany and included participants with both blue-collar and white-collar occupations. In the study in Framingham, a largely blue-collar suburb of Boston with a population of mostly Irish extraction, the entire population of the town was surveyed.
- PROCAM is a newer study, and contains data on fasting triglycerides, LDL cholesterol levels and family history of myocardial infarction in all participants.
- The algorithms derived from the Framingham study are mainly constructed on the basis of data that were collected in the 1970s, when coronary event incidence rates were much higher than they are now.
- PROCAM registered only the hard end points of fatal and non-fatal myocardial infarction and sudden coronary death, while many of the earlier Framingham algorithms included also the soft end-point of angina pectoris.

The absolute risk calculated by a scoring scheme is dependent on two factors, the level of risk factors, and the underlying risk of coronary heart disease in a population. Thus an algorithm or score derived in one population may not deliver an accurate estimate of risk when used in another. As can be seen from the following example, in smokers, the estimation of risk provided by the Framingham and PROCAM scores differed by a factor of 2.5.
In clinical practice, it is therefore advisable to use the risk score that was derived in the population most similar to that from which the patient originates.

		points	
Male person:		**Framingham**	**PROCAM**
age	35-39 y	- 4	0
total cholesterol	262 mg/dL (6.79 mmol/L)	9	-
HDL cholesterol	38 mg/dL (0.98 mmol/L)	2	8
LDL cholesterol	200 mg/dL (5.18 mmol/L)	-	20
triglycerides	120 mg/dL (1.37 mmol/L)	-	2
systolic blood pressure	135 mmHg	1	3
diabetes mellitus	no	-	0
family history of premature myocardial infarction	yes	-	4
smoker	yes	8	8
score		16	45
10-year risk		**25%**	**10%**

Table 15: Regional adjustment factors for use of risk scores

Calculation of risk factor algorithms requires good quality long-term prospective epidemiological data. In many regions of the world such data is in short supply. In addition, even within a circumscribed geographical region such as continental Europe, significant variations of absolute risk may be seen among persons with similar risk profiles. For this reason, an algorithm derived in one population may give an incorrect estimate of absolute risk when used in another.

Ideally, the solution to this problem lies in the gathering of more prospective data. However, failing this, a pragmatic approach is to recalibrate existing algorithms based on cross-sectional observational data, which is much easier to collect.

The table on the next page presents such an approach based on recalibration of the PROCAM algorithm using the observed coronary heart disease morbidity, mortality and case fatality data from the World Health Organization Monitoring of Trends in Cardiovascular Disease (MONICA) project.

Augsburg is a town in southern Germany. In the MONICA study[1], the citizens of Augsburg were found to have a coronary event rate and a risk factor profile similar to those of the participants in the PROCAM study. The ratio of coronary heart disease mortality in a specific region relative to the coronary heart disease mortality observed in the Augsburg MONICA cohort may therefore be used as a rough conversion factor when calculating absolute coronary event rates using the PROCAM algorithm in other populations. This approach assumes comparable case fatality rates in Augsburg and any comparison region. Current evidence suggests that the case

1. Tunstall-Pedoe H et al. for the WHO MONICA Project. Lancet 1999; 353: 1547-1557

fatality of coronary heart disease in many countries is about 40%. In other words, the incidence of coronary events (defined as non-fatal or fatal myocardial infarction and sudden coronary death) is about 2.5 times the coronary heart disease mortality.

To obtain a rough estimate of the absolute coronary risk in your country or region, multiply the risk calculated by the PROCAM algorithm by the factor given below for the country or region most similar to your own.

Country	Region	Conversion factor	
		men	women
Australia	*Newcastle*	1.22	1.54
	Perth	0.90	0.95
Belgium	*Charleroi*	1.51	1.71
	Ghent	1.03	1.10
Canada	*Halifax Country*	1.24	1.15
China	*Beijing*	0.31	0.61
Czech Republic	*Czech Republic*	1.69	1.37
Denmark	*Glostrup*	1.73	2.00
Finland	*Kuopio Province*	2.06	1.17
	North Karelia	2.54	1.44
	Turku/Loimaa	1.69	1.12
France	*Lille*	1.10	1.07
	Strasbourg	0.90	0.88
	Toulouse	0.58	0.54

Country	Region	Conversion factor	
		men	women
Germany	**Augsburg**	**1.00**	**1.00**
	Bremen	1.13	1.02
	East Germany	1.18	1.22
Iceland	*Iceland*	1.13	0.83
Italy	*Area Brianza*	0.71	0.54
	Friuli	0.71	0.59
Lithuania	*Kaunas*	1.73	1.07
New Zealand	*Auckland*	1.36	1.44
Poland	*Tarnobrzeg Voivodship*	2.41	2.39
	Warsaw	2.21	2.22
Russia	*Mosow-Control*	1.82	1.34
	Mosow-Intervention	1.78	1.49
	Novosibirsk-Control	1.76	1.80
	Novosibirsk-Intervention	1.78	2.22
Spain	*Catalonia*	0.48	0.39
Sweden	*Gotheburg*	1.01	0.95
	Northern Sweden	1.18	1.00
Switzerland	*Ticino*	0.61	--
	Vaud/Fribourg	0.55	--
UK	*Belfast*	1.78	1.93
	Glasgow	2.32	3.00
USA	*Stanford*	1.28	1.76
Yugoslavia	*Novi Sad*	1.37	1.24

Table 16: How to interpret the 10-year risk of coronary heart disease

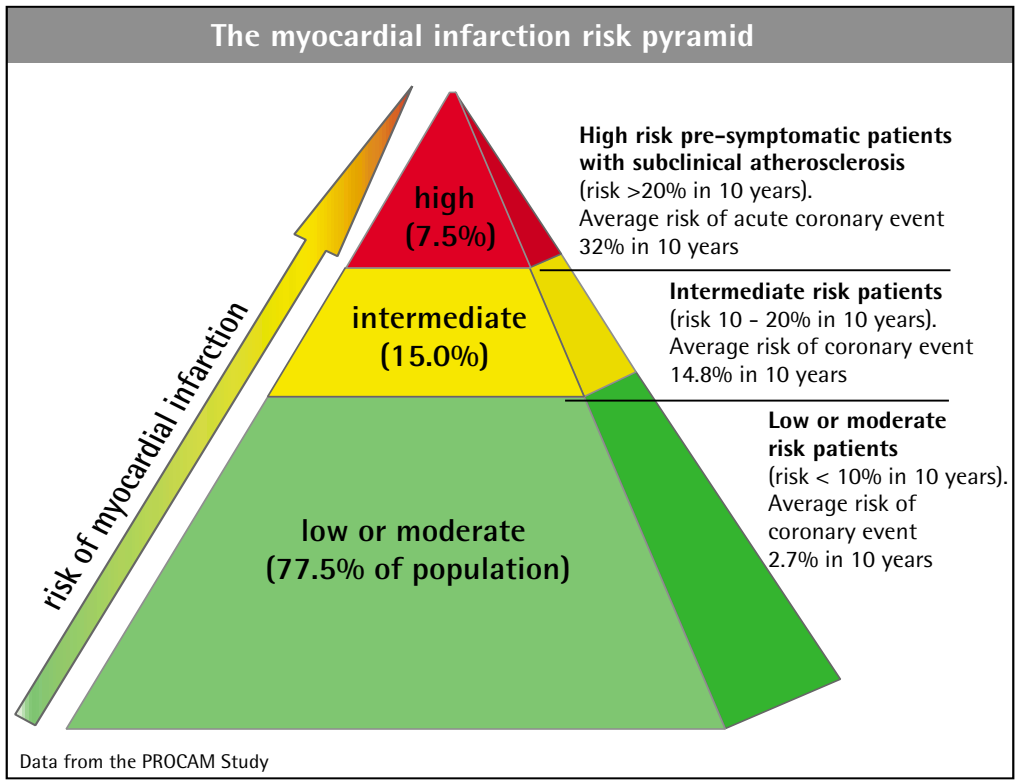
This table shows a view on the steps that need to be taken for various levels of coronary risk. The population intervention strategy refers to general health-promoting measures such as a balanced diet, regular exercise and avoidance of smoking and overweight that are of benefit to every member of the population. Therapeutic life-style changes represent a more stringent variety of the population strategy and are described in detail *on page 72* ff. For patients at persistently high risk of coronary heart disease, pharmacological intervention is usually required.

10-year risk	
< 10%	**Low or moderate risk of coronary heart disease** • Population intervention strategy
10–20%	**Moderately high risk of coronary heart disease** • Initiate therapeutic life-style changes (see page 72 ff) • Consider drug therapy depending on risk factor constellation • Review risk at regular intervals
> 20%	**High risk of coronary heart disease** • Initiate therapeutic life-style changes (see page 72 ff) • Lipid-lowering ± anti-hypertensive ± anti-diabetic drug treatment ± acetyl salicylic acid/clopidogrel usually required

The above stratification has important implications for the rational use of health resources. Patients at low risk using conventional risk markers do not require further evaluation. Equally, in patients at high risk using conventional risk markers, emerging risk factors do not influence therapeutic decisions and need therefore not be measured (Table 17 *on page 58*). In patients at intermediate risk the prognostic value of most emerging risk factors, e.g. CRP, is unclear at the present time. Such factors therefore cannot form the basis of therapeutic decisions.

Fig. 8: The myocardial infarction risk pyramid

This figure shows the prevalence of low or moderate, intermediate, and high risk of coronary heart disease in the PROCAM cohort of middle-aged men.

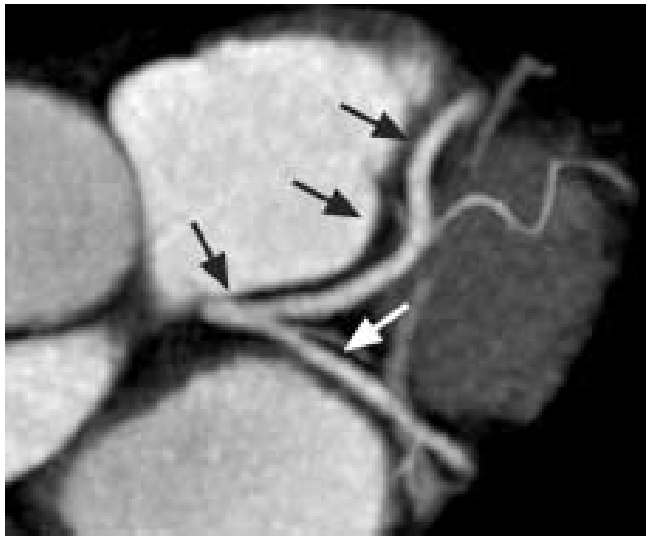


Non-invasive measurement of the atherosclerotic burden may be particularly useful in improving stratification of individuals at intermediate risk. Such tests include carotid artery duplex scanning, magnetic resonance imaging and multi-slice spiral computed tomography. In the figures on the following pages, the use of computed tomography in patients with multiple risk factors for coronary artery disease is described in more detail.

The finding of advanced atherosclerotic lesions in the vascular tree may justify more aggressive treatment of patients in the intermediate risk category.

Fig. 9: Multi-slice computed tomography images of the coronary vasculature in pre-symptomatic patients at high risk of coronary artery disease[1]

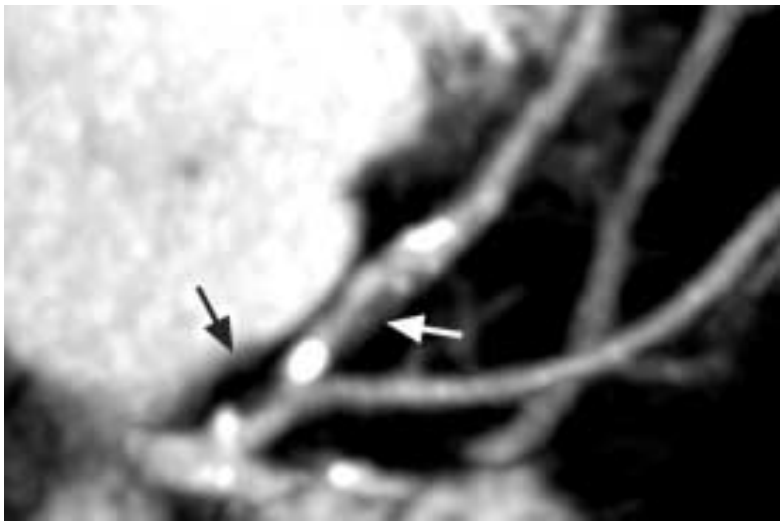
Use of the risk algorithms described in this guide identifies a population of asymptomatic patients at high risk of coronary heart disease. These high-risk individuals should be classified as pre-symptomatic patients with subclinical atherosclerosis. In most of these individuals, myocardial infarction results from a thrombosis at the site of so-called culprit lesions. Such lesions, which are characterised by a lipid-rich core with or without areas of calcification, usually cause only 30-60% diameter stenosis[2].
As shown in these images on non-invasive angiography by means of a computed tomograph fitted with a multi-row detector, such pre-symptomatic patients often demonstrate non-calcified lesions and various degrees of coronary calcification.



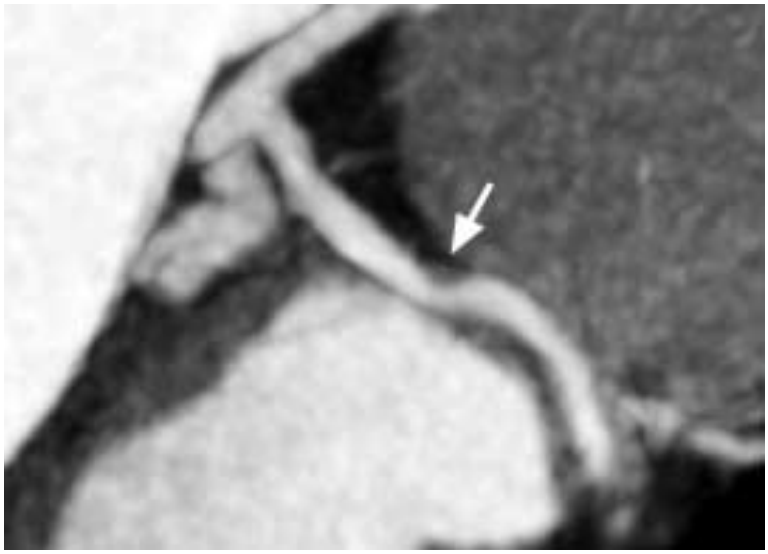
Normal non-invasive angiography of the left coronary artery by means of multi-slice computed tomography. The left main and the left anterior descending coronary arteries show normal calibre and a normal arterial wall (black arrows). The left circumflex coronary artery, which is also depicted, shows no wall changes (white arrow).

1. Courtesy: Dept. of Radiology, University of Münster (Prof. D. W. Heindel, PD Dr. R. Fischbach); Working group of preventive medicine, Medical Faculty

2. Mancini JGB, Pitt B, on behalf of the PREVENT Investigation. Am J Cardiol 2002; 90: 776 - 778



Left main and left anterior descending coronary arteries showing non-calcified and calcified atherosclerotic plaque. A flat, hypo-dense lesion affecting the left main coronary artery can be seen proximal to a small calcified nodule (black arrow). The left anterior descending coronary artery (white arrow) shows irregular wall changes containing calcified and non-calcified atheromatous material.



Left circumflex artery showing a flat non-calcified lesion (white arrow). Note absence of calcifications.

Table 17: Underlying and emerging risk factors for coronary heart disease

Underlying risk factors

- Atherogenic diet
- Overweight (BMI 25.0-29.9 kg/m^2), obesity (BMI $\geq$ 30 kg/m^2)
- Physical inactivity
- Genetic factors

Emerging risk factors

In recent years, a number of non-classical risk factors have been identified that are associated with an increased risk of coronary events and stroke. The relative importance and independent predictive power of these risk factors has yet to be rigorously assessed in prospective studies.

- Lipoprotein (a) $\geq$ 30 mg/dL
- Presence of small dense LDL
- Apolipoprotein B level > 140 mg/dL
- Prothrombotic state
  - Plasma fibrinogen > 350 mg/dL
  - Plasminogen activator inhibitor 1 > 7 IU/mL
- Pro-inflammatory state
  - C-reactive protein elevated in the absence of an acute inflammatory condition > 3mg/L[1]
- Soluble adhesion molecules, cytokines, WBC count
- Plasma homocysteine $\geq$ 12 µmol/L
- Calcification of the coronary arteries on computerised tomography

1. Some authors consider a level > 1.2 mg/L to be elevated. However, at very low levels, CRP may vary in an individual over time. This limits the clinical utility of high-sensitivity CRP assays in predicting coronary risk. Campell B et al. Ann Clin Biochem 2002; 39: 85-88

Table 18: Why is type 2 diabetes mellitus a high-risk condition for coronary heart disease?

- Persons with type 2 diabetes mellitus are two to four times more likely to develop cardiovascular disease than people without diabetes mellitus. Risk is particularly high in patients with diabetes mellitus who exhibit microalbuminuria[1], frank proteinuria or renal impairment
- Persons with type 2 diabetes mellitus often have the same risk of myocardial infarction as people without diabetes mellitus who have already had a myocardial infarction (> 20%), since multiple risk factors such as hypertension, dyslipidaemia and obesity frequently co-exist in patients with diabetes mellitus
- Persons with type 2 diabetes mellitus who experience a myocardial infarction display increased death rates both immediately and in the long term compared to myocardial infarction patients without diabetes mellitus
- Persons with diabetes mellitus may suffer a myocardial infarction without even realising it

1. Microalbuminuria is defined as a urinary albumin excretion rate of between 20 µg/min and 200 µg/min on two of three urine samples collected over a six-month period. This is approximately equal to excretion of between 30 mg and 300 mg of albumin in 24 hours. An alternative, though less accurate means of detecting microalbuminuria is when the ratio of albumin to creatinine in a urine sample exceeds 30 mg albumin per g creatinine or 2.5 mg albumin per mmol creatinine.

Table 19: Assessing risk of coronary heart disease in patients with diabetes mellitus

Most adult patients with diabetes mellitus are at high risk of coronary heart disease. Nevertheless, formal risk assessment should be carried out in such patients in order to determine which risk factors confer the largest increase in risk for coronary heart disease and therefore require the most aggressive treatment.

- Patients with type 2 diabetes mellitus commonly display a number of other risk factors for coronary heart disease. For this reason, a scoring system or risk algorithm that includes diabetes mellitus and also takes account of these risk factors should be used to calculate risk
- Coronary heart disease risk in patients with diabetes mellitus may be calculated using the PROCAM risk score (Table 5 *on page 15*) or the PROCAM algorithm (Table 8 *on page 26*)
- The risk of coronary heart disease in women with diabetes mellitus is equivalent to that of men of the same age with diabetes mellitus
- Alternatively, a specific risk score for calculating risk in diabetes mellitus may be used[1]. This takes account of the variables:
  - Age
  - Sex
  - Ethnicity (increased risk in persons of Afro-Caribbean origin)
  - Smoking history
  - Level of glycaeted haemoglobin (HbA_{1C})
  - Systolic blood pressure
  - Total cholesterol
  - HDL cholesterol

1. The diabetes mellitus risk engine may be downloaded from the internet at http://www.dtu.ox.ac.uk/. In contrast to the PROCAM point score, the diabetes risk engine requires use of a computer and values from measurements extending over two years.

Table 20: Aggregation of risk factors: the metabolic syndrome

The so-called "metabolic syndrome" also confers particular risk of atherosclerosis. It represents a special combination of risk factors, for which the following definition has been proposed:

- HDL cholesterol < 40 mg/dL (1.04 mmol/L) in men or < 50 mg/dL (1.30 mmol/L) in women
- Fasting triglycerides ≥ 150 mg/dL (1.71 mmol/L)
- Waist circumference > 102 cm in men or > 88 cm in women or body mass index > 29.0 kg/m^2 in men or > 27.5 kg/m^2 in women (see Figure 10 *on page 62*)
- Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg
- Fasting glucose 110 - 125 mg/dL (6.1 - 6.9 mmol/L)

Fig. 10: Use of body mass index and waist circumference in the diagnosis of the metabolic syndrome: which measure better?

Authorities vary in recommending either BMI (weight in kg ÷ (height in m)^2) or the waist circumference in diagnosing metabolic syndrome. A practical difficulty in using waist circumference is in deciding in obese exactly where the patient's waist is. In such cases it is recommended to measure the largest circumference. However, both measures show a very high degree of overlap, as illustrated in the following investigation from the PROCAM study. As can be seen *on page 63*, 16.1% of middle-aged men in PROCAM were found to have the metabolic syndrome based on a waist circumference in excess of 102 cm, while 15.5% had metabolic syndrome based on a BMI above 29 kg/m^2. 14.4% of the men fell into both categories. Similar relationships were found in women (note the different cut-offs of 88 cm for waist circumference and 27.5 kg/m^2 for BMI). Thus, in practice, the clinician may confidently use the measure with which he or she is most familiar.

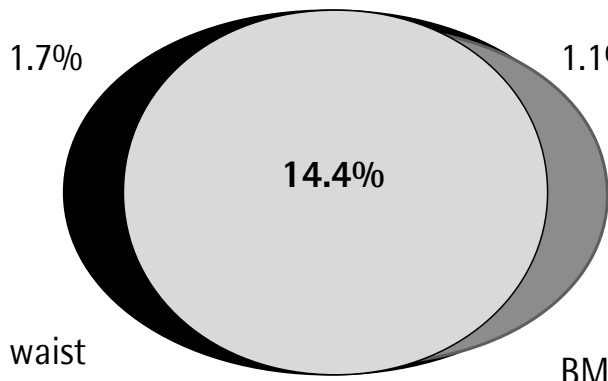
Table 21: Body mass index for selected heights and weights

Body weight in kg							
Height in cm	BMI 25	BMI 27	BMI 30	Height in cm	BMI 25	BMI 27	BMI 30
147	54	59	65	175	77	83	92
150	56	60	67	178	79	85	94
152	58	63	69	180	81	87	98
155	60	65	72	183	83	90	100
158	62	67	74	185	86	93	103
160	64	69	77	188	88	95	106
163	66	71	79	191	91	98	109
165	68	73	82	193	93	100	112
168	70	76	84				
170	72	78	87				
173	74	80	89				

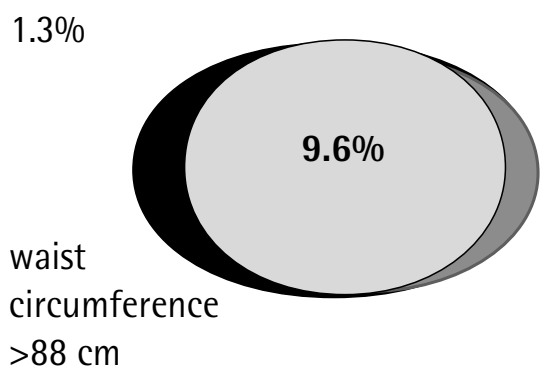
National Institutes of Health. Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults. Bethesda, MD; National Institutes of Health, 1998

Prevalence of metabolic syndrome according to definition based upon waist circumference or body mass index

Men



Women



Subgoups of 4,883 men and 2,316 women, aged 18 to 65 years

Data from the PROCAM Study

Fig. 11: Prevalence of metabolic syndrome according to age
The metabolic syndrome increases in prevalence with increasing age. In the PROCAM study, only 3% of women and 6% of men aged 16-25 showed this syndrome. This sex difference persisted until age 45. Thereafter, the prevalence of metabolic syndrome in both sexes exceeded 20%.

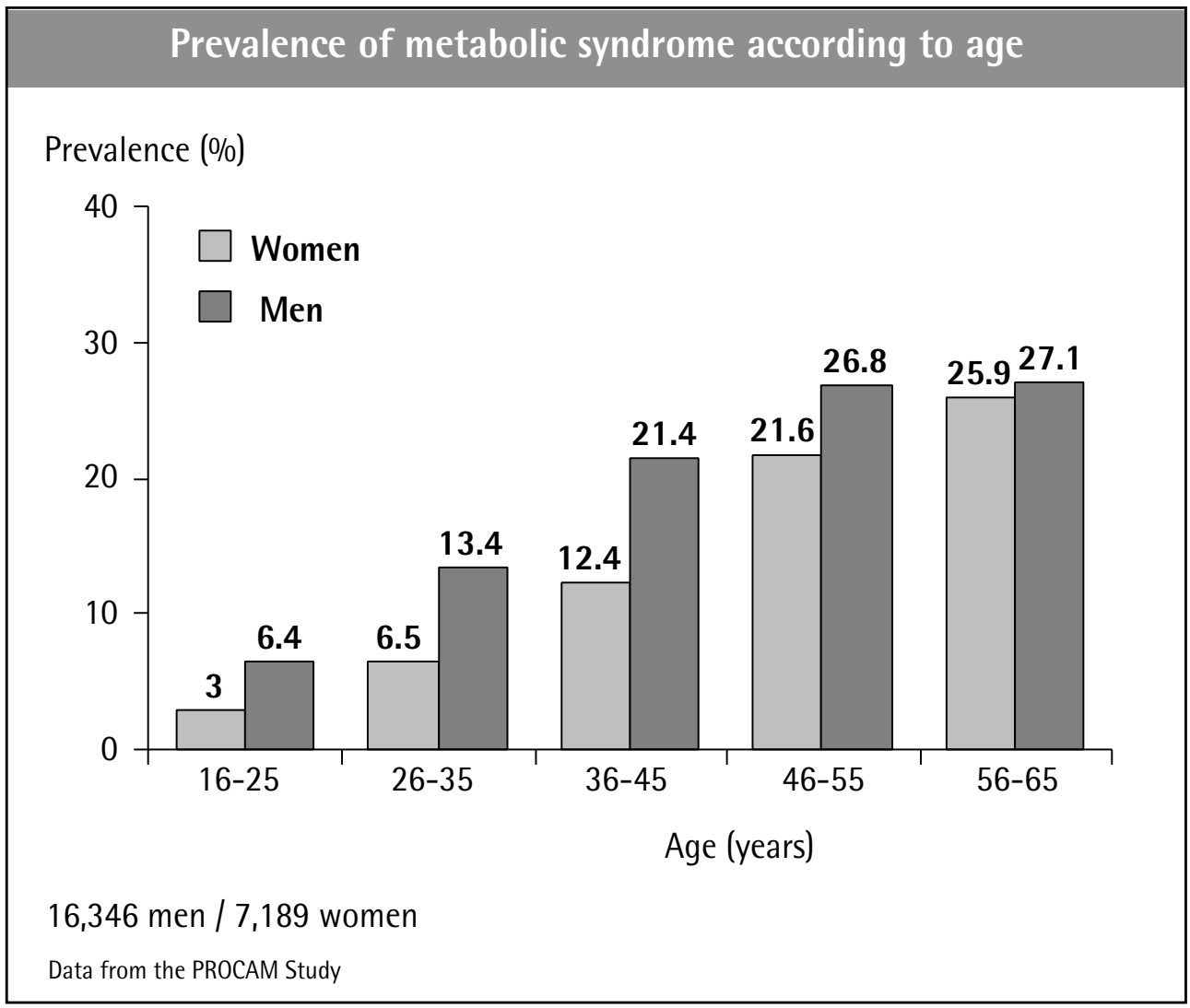
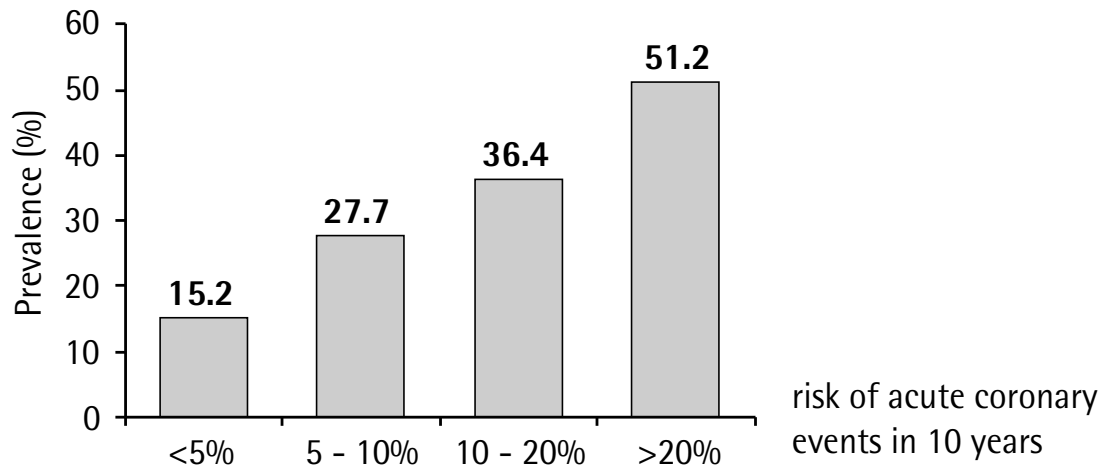


Fig. 12: Influence of metabolic syndrome on risk of myocardial infarction

As noted elsewhere in this guide, the metabolic syndrome is a major risk factor for development of coronary heart disease. In the PROCAM study, the incidence of myocardial infarction occurring within 10 years of follow-up was more than twice as high in patients with the metabolic syndrome than in patients without this condition.

The interaction between metabolic syndrome and coronary risk is also evident from the following graph, showing that while the prevalence of metabolic syndrome is only 15% among middle-aged men at low risk of myocardial infarction, it is present in more than half of men at high risk of myocardial infarction.

Prevalence of metabolic syndrome according to risk of acute coronary events



325 acute coronary events in 10 years in 4,818 men aged 35 to 65 years

Data from the PROCAM Study

Fig. 13: Acute coronary events and metabolic syndrome
Data from the PROCAM study indicate that the risk of coronary heart disease in men with the metabolic syndrome is about twice that of men without the metabolic syndrome. Overall, however, the risk of coronary heart disease in men with metabolic syndrome did not exceed the high-risk cut-off of 20% in 10 years. Nevertheless, because of the multiplicity of genetic and acquired components of this syndrome, some affected individuals may have a greater actual coronary heart disease risk than the risk algorithm might suggest (see also the figure *on page 67*).

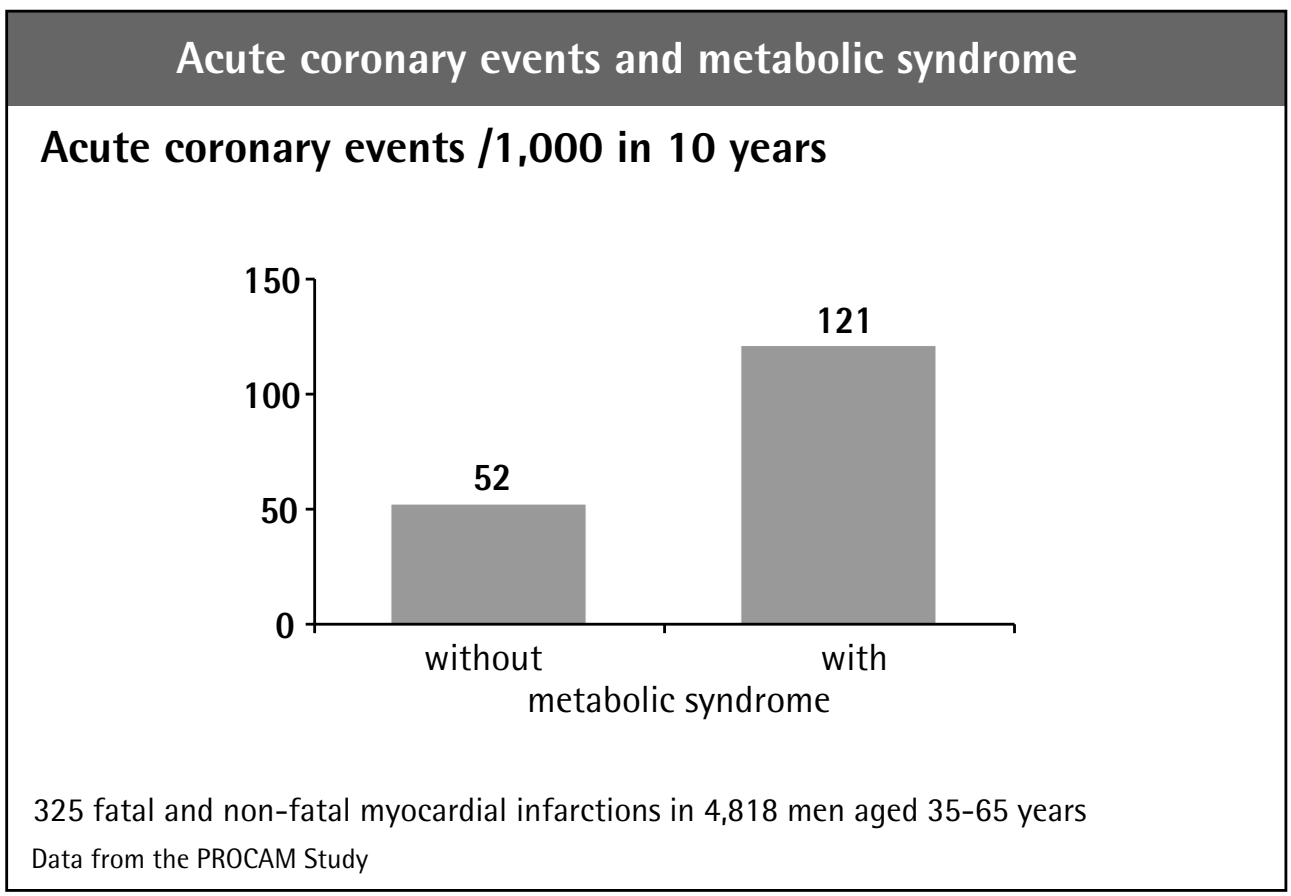


Fig. 14: Pathophysiology of the metabolic syndrome

The pathophysiology of the metabolic syndrome is complex and includes a wide range of both inherited and acquired risk factors. These in turn impact with the underlying person-specific genetic risk in order to produce the disorder. Because not all of these factors are completely accounted for by existing risk algorithms, the actual risk of coronary heart disease in a patient with metabolic syndrome may be higher than an algorithm suggests.

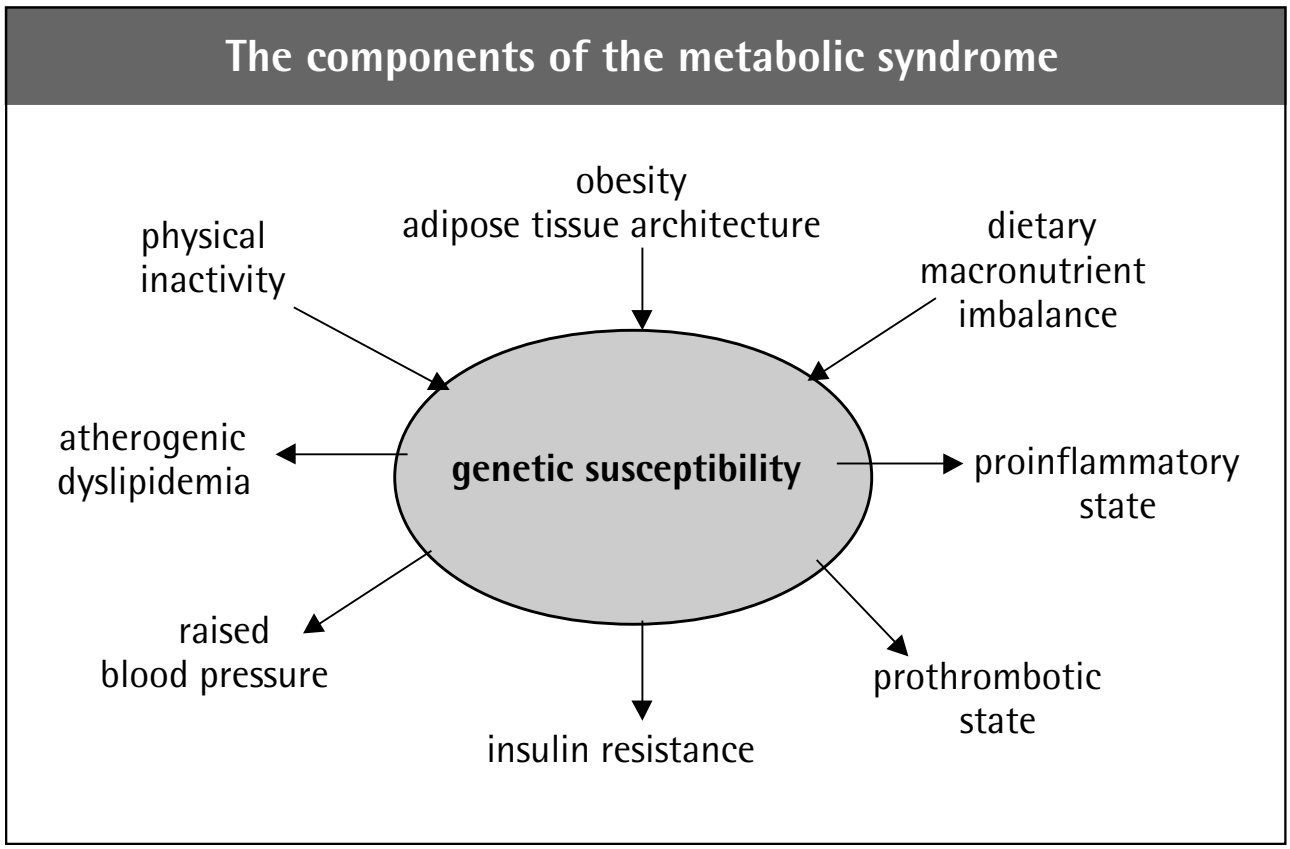


Table 22: Clinical monitoring

Risk factor screening should begin at age 20 years. All adults aged 40 years or older should be aware of their absolute risk of developing coronary heart disease. Consider the following:

History

- Angina pectoris, myocardial infarction, stroke, intermittent claudication, transient ischaemic attacks, aortic aneurysm or other objective evidence of atherosclerosis
- Myocardial infarction or stroke in a first-degree relative before the age of 60 y
- Use of anti-hypertensive, lipid-lowering, anti-thrombotic or anti-diabetic medication
- Smoking history: type of smoking, duration of smoking, number of cigarettes/d
- Intensity and frequency of physical activity
- Nutritional habits

Physical examination

- Height, weight, waist circumference
- Blood pressure
- Active search for clinical signs of atherosclerosis: aortic, femoral, carotid, popliteal bruits, absent or reduced pulses, dystrophic changes in lower extremities

Laboratory investigation

After an overnight fast, draw blood for

- Total cholesterol
- LDL cholesterol (see Table 24 *on page 69*)
- HDL cholesterol
- Triglyceride
- Blood glucose

Other investigations as required

- Resting ± exercise electrocardiogram
- Lipoprotein (a)[1] in high-risk individuals
- CRP
- 24-hour blood pressure monitoring
- Doppler ultrasound
- Non-invasive computerised tomographic angiography
- Coronary angiography

1. von Eckardstein A et al. J Am Coll Cardiol. 2001, 37: 434-439

Table 23: Exclude causes of secondary hyperlipidaemia[1]

Related to plasma cholesterol	Related to plasma triglycerides
•Diet rich in saturated fatty acids •Hypothyroidism •Nephrotic syndrome •Chronic liver disease (mainly primary biliary cirrhosis) •Cholestasis •Monoclonal gammopathy •Cushing´s syndrome •Oral contraceptive use •Anorexia nervosa •Acute intermittent porphyria •Protease inhibitor use	•Diet rich in carbohydrates •Excessive alcohol consumption •Obesity •Pregnancy •Diabetes mellitus •Hypothyroidism •Chronic renal failure •Pancreatitis •Bulimia •Cushing´s syndrome •Hypopituitarism •Monoclonal gammopathy •Glycogen storage disease, Lipodystrophy, Acute intermittent porphyria, Systemic lupus erythematosus, Beta-blocker, Diuretic use, Estrogen use (contraceptive or replacement), Gluco-corticoid use, Isotretinoin use, Protease inhibitor use, Tamoxifen use

Table 24: Estimating LDL cholesterol with the Friedewald formula[1]

Units	Formula
Conventional *(mg/dL)*	LDL cholesterol - Total cholesterol - HDL cholesterol - (Triglycerides/5)
Système International (SI) *(mmol/L)*	LDL cholesterol - Total cholesterol - HDL cholesterol - (Triglycerides/2.2)

Note: The formula does not apply if the patient has:

- Triglycerides > 400 mg/dL (> 4,5 mmol/L)

- APO E2/2 phenotype or genotype, or

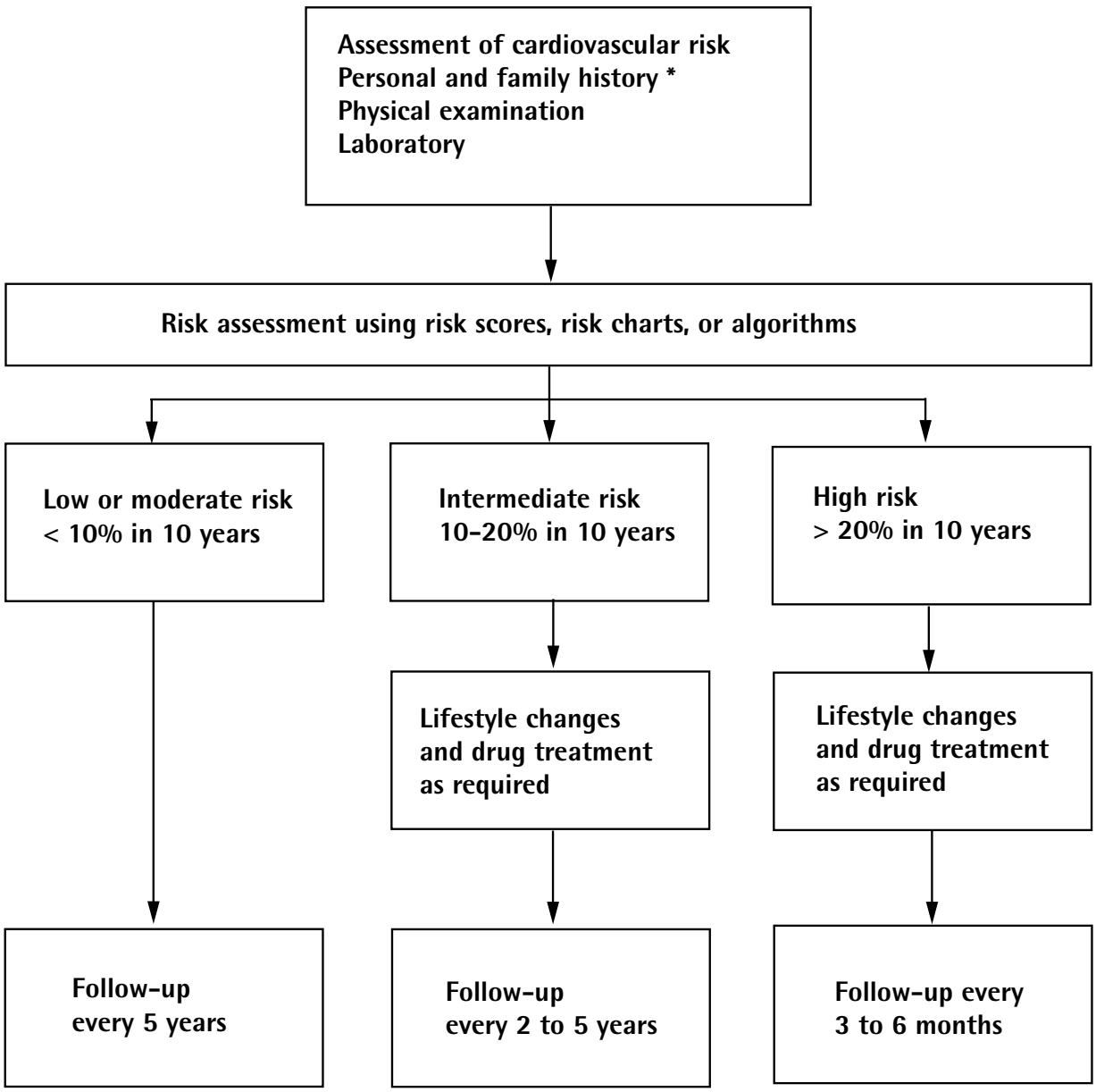
- Fredrickson type III hyperlipidaemia

In each of these circumstances, direct determination of LDL cholesterol in a specialised laboratory is required for accuracy. Also, high Lp(a) diminishes the accuracy of the Friedewald formula. Ideally, the calculated LDL cholesterol value should be adjusted to reflect the contribution of Lp (a) cholesterol:
LDL cholesterol ~ LDL cholesterol $_{\text{calculated}}$ - (Lp[a]/3) (in mg/dL).

Conversion values: 0.02586 for cholesterol (total cholesterol, HDL cholesterol, LDL cholesterol) and 0.01129 for triglycerides (as multiplier from mg/dL to mmol/L; as divisor from mmol/L to mg/dL).

1. Gotto AM Jr., Assmann G, Carmena R, Davignon J, Fernández-Cruz A, Fruchart J-C, Kastelein JJP, Paoletti R. The ILIB Lipid Handbook for Clinical Practice. Blood lipids and coronary heart disease. International Lipid Information Bureau, 2000, New York

Fig. 15: Flow-chart for assessment of cardiovascular risk



*for details see page 71

Table 25: Step-by-step family history [1]

1. Draw a pedigree	Index patient, parents, siblings, children, grandparents, aunts, uncles. In general, women give a better family history than do men.
2. Check	Are all blood relatives?
3. Ask	Is relative alive or dead?
If relative is alive	How old? Any cardiovascular disease (CVD)? If so, at what age? Smoke? Other CVD risk factors?
If relative has died	Age at death? Cause of death? Other major illness? If CVD present, at what age? CVD risk factors?
4. Discard	All uncertain information
5. Assume	Family history is uninformative but not negative for CVD if patient knows little about relatives' cardiovascular health
6. Consider in general	Number and sex of relatives at risk Current age and age when CVD developed Additional risk factors in those positive for disease Number of expected cases of CVD given family risk factors Number of observed vs. number of expected cases
7. Favourable family history when	Longevity in most members

1. Gotto AM Jr., Assmann G, Carmena R, Davignon J, Fernández-Cruz A, Fruchart J-C, Kastelein JJP, Paoletti R. The ILIB Lipid Handbook for Clinical Practice. Blood lipids and coronary heart disease. International Lipid Information Bureau, 2000, New York

B. Clinical management of coronary heart disease risk factors

The cornerstone of clinical management of risk factors for coronary heart diseases lies in the initiation of therapeutic life-style changes.

These are described in greater detail in the sections of the guide that follow.

- Pay particular attention to stopping smoking (Table 26 *on page 73*)
- Ensure a healthy diet (Table 27 *on page 74*)
- Pay particular attention to weight reduction in the overweight (Table 29 *on page 78*)
- Ensure adequate physical activity (Table 30 *on page 80*)

Table 26: Stopping smoking

- Tobacco dependence is a chronic condition. Many tobacco users require recurrent intervention before stopping completely
- Give your patient practical advice on how to deal with the problems that may arise on giving up smoking
- Provide active social support to your patient in his or her attempt to stop smoking
- Encourage family, friends and colleagues of your patient to support his or her efforts at stopping
- Effectiveness increases with treatment intensity.
  Direct contact between patient and counsellor is preferable. Results improve with increased consultation time
- Treatments are available that double the chance of success. These include:
  - First-line drugs that increase long-term abstinence: Bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, nicotine patch
  - Second-line drugs that may be considered if first line agents are not effective: Clonidine, nortriptyline

Offer these treatments to patients willing to stop. Persons with coronary heart disease, pregnant or breastfeeding women and teenage smokers should contact their physicians before taking any medication.

- Give patients not willing to stop clear advice to do so. Tailor this advice to the patient's individual social and economic circumstances and repeat it often
- Urge avoidance of exposure to second-hand smoke at work and at home

Table 27: Tips for a diet that is good for the heart
(see detailed information at http://www.chd-taskforce.com/heart-healthy)

- Encourage patient to eat at least five servings of vegetables and/or fruit every day
  - Vegetables and fruits contain few calories and supply plenty of soluble fibre, vitamins, antioxidants, minerals and other beneficial minor components
  - Fresh fruit have a low glycaemic index
- Encourage patient to eat plenty of grain products (bread, cereals, pasta, rice), potatoes and legumes (peas, beans, lentils). Give preference to whole-grain products
  - These foods are rich in starch, fibre, vitamins and minerals and enhance satiety
  - Many of these foods (e.g. legumes, oats, pasta and parboiled rice) have a low glycaemic index
- Encourage patient to eat fish at least twice a week. Give preference to oily sea fish (herring, mackerel, salmon and tuna)
  - Oily sea fish has a high content of n-3-fatty acids
  - Lean fish is low in saturated fat
- Encourage patient to use olive oil or rapeseed (canola) oil. Avoid hardened (hydrogenated) fat, which is present in some baked products, some types of deep-fry fat and some margarines
  - Olive and rapeseed oil have a high content of monounsaturated fats; canola oil is also rich in n-3 fatty acids

- Encourage patient to add some nuts to his or her diet
  - Nuts are rich in unsaturated fatty acids (except for coconut, which is rich in saturated fatty acids), some are rich in monounsaturated fats (e.g. hazelnuts, peanuts and macadamia nuts), some are good plant sources of n-3 fatty acids (e.g. walnuts, almonds and cashews)
- Encourage patient to give preference to low-fat or non-fat dairy products
  - This food choice will decrease intake of saturated fats while ensuring a sufficient intake of calcium
- Advise patient to eat meat no more than three times a week, with a preference for lean meat such as poultry or lamb.
  - This limits the intake of saturated fatty acids, cholesterol and total fat
- Advise patient to avoid salty food such as salty crackers, smoked meat or instant food

The **traditional Mediterranean diet** is a good example for a healthy food choice. This diet contains lots of fruit, vegetables, bread, cereals, potatoes, beans, nuts, and seeds. This food is minimally processed and fresh. Olive oil is the main source of fat. Dairy products are consumed daily in low to moderate amounts, usually in the form of cheese or yoghurt. Fish and poultry are eaten in small to moderate amounts. Red meat is rare and modest amounts of wine are taken, usually with meals.
A further example of an enjoyable balanced diet is the traditional **East Asian diet.**

Table 28: Principles underlying nutritional recommendations
(see detailed information at http://www.chd-taskforce.com/heart-healthy)

Energy

- Adjust energy intake to maintain or achieve normal body weight (Table 29 *on page 78*)

Fat

- Reduce saturated and trans fatty acids to
  - < 10% of energy intake
  - < 7% of energy intake in those with elevated LDL cholesterol
- Increase monounsaturated fats to 15-20% of energy intake
- Polyunsaturated fats should comprise 7 - 8% of energy intake
  - Aim at a ratio of n-6 to n-3 fatty acids of 5:1 or less
- Total fat intake may range from 25 to 35% of energy intake
  - At the lower end of the range for treatment of overweight or obesity
  - Up to 35% for persons with sustained physical activity and normal body weight

Carbohydrates

- Use carbohydrates that are rich in fibre and have a low glycaemic index. Limit intake of refined sugar to < 10% of energy

Alcohol

- Limit alcohol consumption to 20 g (2 glasses of beer or wine) per day in men and 10 g (1 glass of beer or wine) per day in women

Cholesterol

- Limit cholesterol intake to
  - < 300 mg/day
  - < 200 mg/day in those with elevated LDL cholesterol

Salt

- Limit salt intake to 6 g per day

Table 29: Management of overweight and obesity

Assessment of overweight and obesity[1]

- **Body mass index** (BMI) is the most useful measure of overweight and obesity and the risk associated with it. It is calculated by dividing body weight in kilograms by the square of the height in meters.

• Underweight	< 18.5 kg/m^2
• Normal weight	18.5-24.9 kg/m^2
• Overweight	25-29.9 kg/m^2
• Obese	≥ 30 kg/m^2

- **Waist circumference** is a convenient alternative to BMI. Increased waist circumference is frequently associated with risk factors for cardiovascular disease.

Risk of coronary heart disease	men	women
Normal	< 94 cm	< 80 cm
Increased risk	94-101 cm	80-87 cm
Substantially increased risk	≥ 102 cm	≥ 88 cm

Cut-off points for BMI and waist circumference may vary between populations, depending on other risk factors for cardiovascular disease and type 2 diabetes.

1.World Health Organization. WHO Technical Report Series 1999; 894

Treatment goals in weight reduction

- Initial goal is to reduce body weight by 10% over a period of 6 months
- Aim for weight loss of between 0.5 kg and 1.0 kg per week
- Thereafter, priority is long-term maintenance of the lowered body weight
- In overweight persons who cannot lose weight, focus on preventing further weight gain

Strategies for reducing body weight

Successful long-term weight loss requires **sustained life-style changes**

- **Diet.** Reduce energy intake by 500 kcal/day to 800 kcal/day. Note that energy intake should not fall below
  - 1.200-1.600 kcal/day in men
  - 1.000-1.200 kcal/day in women
- **Behavioural therapy**
  - Train patient to monitor his or her eating habits and physical activity
  - Enrol patient in stress management course if required
  - Provide social support
- **Physical activity.** Physical activity is crucial to weight loss and long-term maintenance of lowered body weight (Table 30 *on page 80*)

For some severely obese patients or persons suffering medical complications of obesity pharmacotherapy or weight loss surgery may be an option if lifestyle modifications fail.

Table 30: Recommendations for physical activity

- Encourage your patients to take at least 30 minutes of moderate-intensity physical activity (see box below) every day
  - This activity level will expend approximately 200 kcal/day
  - This activity may be accumulated in short bouts of about 10 min duration
  - Patients completely unused to exercise should build up to this goal over a period of 4 weeks as follows
    - Week 1 10 minutes vigorous walk or cycling every day
    - Week 2 15 minutes vigorous walk or cycling every day
    - Week 3 20 minutes vigorous walk or cycling every day
    - Week 4 30 minutes vigorous walk or cycling every day
- Encourage your patients to attempt a longer bout of enjoyable exercise such as jogging or swimming 3 or 4 days a week. This bout should be structured as follows
  - 5 minutes warm-up
  - 30-60 minutes exercise within 50-75% of maximum heart rate, which is calculated as 220- age in years beats per minute
  - 5 minutes cool down
- Encourage your patients to increase their everyday physical activity: taking stairs instead of lift, gardening, housework
- Make sure your patients are aware of the following warning symptoms and report them to the instructor or physician
  - recovery time > 5 minutes
  - chest pain
  - syncope (black out)
  - persistent coughing
- Overweight or obese and high-risk patients should have a medical evaluation prior to initiating a programme

Examples of moderate physical activity[1]	
Everyday activities	**Sporting activities**
Brisk walking (about 3 km) for 30 minutes	Cycling 8 km in 30 minutes
Walking stairs for 15 minutes	Running 2.5 km in 15 minutes
Gardening for 30-45 minutes	Dancing fast for 30 minutes
Raking leaves for 30 minutes	Swimming laps for 20 minutes
Washing and waxing a car for 45-60 minutes	Playing basketball for 15-20 minutes
Shovelling snow for 15 minutes	Skipping rope for 15 minutes
Washing windows or floors for 45-60 minutes	Playing volleyball for 45-60 minutes

1. NHLBI Obesity Education Initiative 1998

Table 31: Target LDL cholesterol, triglyceride and HDL cholesterol levels

LDL Cholesterol levels:

- In high risk patients (Table 1 *on page 11*) LDL cholesterol target is ≤ 100 mg/dL. The results of the recently published Heart Protection Study[1] indicate that high-risk patients may benefit from treatment with statins irrespective of their initial LDL cholesterol level

- In patients free of overt coronary heart disease, the decision to start individualised treatment including drug therapy should be taken on the basis of the LDL cholesterol level and the absolute level of coronary risk. The LDL cholesterol goals are shown in the following table.

Global risk of coronary heart disease	Treatment goal for LDL cholesterol	
	mg/dL	*mmol/L*
> 20% in 10 years	≤ 100	≤ 2.59
10-20% in 10 years	< 130	< 3.37
< 10% in 10 years	< 160	< 4.14

1. Heart Protection Study Collaborative Group. Lancet 2002; 360: 7-22

Elevated triglycerides

- 150-199 mg/dL (1.71-2.29 mmol/L): reduce weight (Table 29 *on page 78*), increase physical activity (Table 30 *on page 80*), triglyceride-lowering diet (Table 32 *on page 84*)
- 200-499 mg/dL (2.28-5.69 mmol/L): reduce non-HDL cholesterol to 30 mg/dL (0.78 mmol/L) above LDL cholesterol goal. If drugs required consider statins, fibrates or nicotinic acid (Table 33 *on page 86*, Table 34 *on page 88*)
- $\geq$ 500 mg/dL (5.70 mmol/L): Very high triglyceride levels, for example exceeding 1,000 mg/dL (11.40 mmol/L) are associated with a substantial risk of acute haemorrhagic pancreatitis. Such high levels mostly occur in two conditions. The first is type I hyperlipoproteinaemia, a rare condition characterised by an increase in chylomicrons alone. It is caused by a deficiency of lipoprotein lipase and is manifest in childhood. The second condition is severe type V hyperlipoproteinaemia, characterised by an increase in chylomicrons and very low density lipoproteins. This is relatively uncommon and occurs most often in adults; in many cases diabetes mellitus is present, although there is usually an underlying primary disorder of triglyceride metabolism. In these two conditions of severe hypertriglyceridaemia, immediate attention must be given to lowering the triglyceride levels. Initial therapy should consist of restriction of dietary fat to less than 10% of calories for at least three days. In severe hypertriglyceridaemia unrelated to the above conditions, dietary advice given in table 32 *on page 84* should be reinforced. In addition, fish oil or drug treatment with fibrates, or nicotinic acid is recommended if conservative measures are not rapidly effective. Statins are not the drug of first choice in treating severe hypertriglyceridaemia.

HDL cholesterol levels should exceed 35 mg/dL (0.91 mmol/L)

- Certain lifestyle measures such as exercise, cessation of smoking and weight loss in overweight persons are usually associated with a 10-20% increase in HDL cholesterol levels.
- Even in patients with low HDL cholesterol levels, LDL cholesterol is the primary target for treatment.
- It is important to exclude secondary causes of low HDL cholesterol. These include: hypothyroidism, obstructive liver disease, nephrotic syndrome, and chronic renal failure. Also, certain drugs such as beta-blockers and androgens may lower HDL cholesterol.
- HDL cholesterol levels in women are usually about a third higher than in men.

Table 32: Individualised treatment of dyslipidaemia

	Therapeutic lifestyle changes	Drug treatment
General considerations		
	• Lifestyle changes are the first-line treatment if lipid targets are not met • Table 26 *on page 73*, Table 27 *on page 74*, Table 29 *on page 78*, Table 30 *on page 80*	• Consider drug treatment without delay in persons with coronary heart disease or a high risk condition (risk > 20%/10 years) • In persons free of overt coronary heart disease or at low or inter-mediate risk consider drug treatment if lipid targets are not met after 3 months of lifestyle changes • Persevere with lifestyle changes even if drugs are used
Specific considerations		
LDL cholesterol	• LDL cholesterol-lowering diet (Table 27 *on page 74*) • Regular exercise (Table 30 *on page 80*) • Weight management (Table 29 *on page 78*) • Smoking cessation (Table 26 *on page 73*)	• If lifestyle fails to reach target levels in Table 31 *on page 82*, consider drugs

	Therapeutic lifestyle changes	Drug treatment
Triglycerides	• Maintenance of normal body weight or weight reduction in overweight persons (Table 29 *on page 78*) • Regular physical activity (Table 30 *on page 80*) • Triglyceride-lowering diet - Avoid or sharply reduce intake of alcoholic drinks - Increase intake of n-3 fatty acids, principally oily fish - Limit intake of sugar, sucrose-containing foods and nutritive sweeteners (fructose, sorbitol, xylit etc.) - Patients with elevated triglycerides should also consider recommendations for a LDL cholesterol lowering diet (Table 27 *on page 74*)	• In mixed hyperlipidaemia, lowering of LDL cholesterol is the primary aim of therapy. • Triglyceride levels ≥ 500 mg/dL (5.70 mmol/L) usually require drug treatment • If LDL targets are met and triglyceride levels ≥ 200 mg/dL (2.28 mmol/L), first consider lowering of triglycerides (see Table 33 *on page 86*)
HDL cholesterol	• Maintenance of normal body weight or weight reduction in overweight persons (Table 29 *on page 78*) • Regular exercise (Table 30 *on page 80*)	• In mixed dyslipidaemia, lowering of LDL cholesterol is primary aim of therapy, since statin therapy has been shown to reduce coronary heart disease risk also in those with low HDL cholesterol • See Table 33 *on page 86* for drugs affecting HDL-cholesterol

Table 33: Drugs affecting lipoprotein metabolism

Drug Class	Agent and daily dose[1]	Lipid/Lipoprotein effects		Side effects	Contraindications
HMG-CoA reductase inhibitors (statins)	Atorvastatin (10-80 mg)[2] Fluvastatin (20-80 mg)[3] Lovastatin (20-80 mg) Pitavastatin (2-4mg)[4] Pravastatin (20-40 mg)[5] Rosuvastatin (10-40 mg)[6] Simvastatin (5-80 mg)[7]	LDL HDL TG	↓ 18-55% ↑ 5-15% ↓ 7-30%	Myopathy Incr. liver enzymes	*Absolute* •Active or chronic liver disease *Relative* •Concomitant use of certain drugs*
Bile acid sequestrants	Cholestyramine (4-16 g) Colestipol (5-20 g)	LDL HDL TG	↓ 15-30% ↑ 3-5% no change or increase	Gastrointestinal distress Constipation Decr. absorption of other drugs	*Absolute* •Dysbetalipoproteinaemia •TG > 400 mg/dL *Relative* •TG > 200 mg/dL
Nicotinic acid	Immediate rel. (1.5-3 g) Extended rel. (1-2 g) Sustained rel. (1-2 g)	LDL HDL TG	↓ 5-25% ↑ 15-35% ↓ 25-50%	Flushing Hyperglycaemia Hyperuricaemia (or gout) Upper GI distress Hepatotoxicity	*Absolute* •Chronic liver disease •Severe gout *Relative* •Diabetes mellitus •Hyperuricaemia •Peptic ulcer disease
Fibrates	Gemfibrozil (600 mg b.d.)[8] Fenofibrate (200 mg)[9] Clofibrate (1 g b.d.)	LDL HDL TG	↓ 5-20% ↑ 10-25% ↓ 20-50%	Dyspepsia Gallstones Myopathy	*Absolute* •Severe renal disease •Severe hepatic disease
Cholesterol absorption inhibitor	Ezetimibe (10 mg)[10]	LDL HDL TG	↓ 5-25% ↑ 2-3% ↓ 6-11%	Headache Abdominal pain Diarrhoea	*Relative* •Hepatic disease

1. In some countries the dosage recommendations may vary: please consult product labelling.

*Cyclosporine, macrolide antibiotics, various anti-fungal agents, and cytochrome P-450 inhibitors (e. g. fibrates and niacin) should be used with appropriate caution.

Table adapted in part from: Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-2497

2. Atorvastatin may also be of use in preventing stroke in patients with unstable angina pectoris. In a preliminary report from the Myocardial Infarction Reduction with Aggressive Cholesterol Lowering (MIRACL) study, intensive lowering of cholesterol with atorvastatin over 16 weeks in patients with acute coronary syndromes halved the incidence of thrombotic ischaemic stroke and did not increase the incidence of haemorrhagic stroke (Waters DD et al. Circulation 2002; 106: 1690-1695). Previously, the MIRACL study also reported a reduced risk for recurrent ischaemic events in the first 16 weeks for patients with acute coronary syndrome receiving atorvastatin (Schwartz GG et al. JAMA 2001 285: 1711-1718).

3. The Lescol Intervention Prevention Study (LIPS) showed beneficial effects of fluvastatin in patients with average cholesterol levels undergoing their first successful percutaneous coronary intervention. Treatment over a period of 3 to 4 years reduced the risk of major adverse cardiac events by 22% (Serruys PWJC et al. JAMA 2002; 287: 3215-3222).

4. Not available at time of going to press.

5. For a long time, the use of statins in the elderly has been controversial. The Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial was a randomised controlled trial of 40 mg pravastatin per day in 2,804 men and 3,000 women aged 70 to 82 years at high risk of coronary heart disease. Baseline total cholesterol concentrations ranged from 4 mmol/L (155 mg/dL) to 9 mmol/L (348 mg/dL). After 3 years of follow-up, LDL cholesterol was reduced by 34% in the treatment group. This was associated with a 15% reduction in the combined end-point of coronary death, myocardial infarction, or stroke. Importantly, mortality from coronary heart disease was reduced by 24% by pravastatin. An unexpected finding in this study was a 25% increase in the incidence of new cancer diagnoses in the pravastatin group. Overall PROSPER showed that treatment with statins reduces the risk of coronary heart disease and death from coronary heart disease in the elderly (Sheperd J et al. Lancet 2002; 360: 1623-1630).

6. Availability limited at time of going to press.

7. In the Heart Protection Study (HPS) adding simvastatin to existing treatments resulted in substantial additional benefits for persons without diagnosed coronary disease who had cerebrovascular disease or peripheral artery disease, persons with diabetes, for men as well for women, for those aged under or over 70 years at study entry and even those who presented with LDL cholesterol below 3 mmol/L (116mg/dL). Over a period of 5 years, treatment with simvastatin reduced the rates of myocardial infarction, of stroke, and of revascularisation by about 25%. These beneficial effects were observed irrespective of initial cholesterol concentrations, indicating that treatment benefit was at least partially due to effects other than cholesterol lowering (Heart Protection Study Collaborative Group. Lancet 2002; 360: 7-22).

8. The Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT) was conducted to investigate if raising low HDL cholesterol levels (mean at entry 32 mg/dL) in the presence of normal LDL cholesterol (mean at entry 111 mg/dL) and triglyceride (mean at entry 161 mg/dL) levels confers clinical benefit. Two thousand three hundred and thirty-one men with a mean age of 64 years were randomised to receive 1200 mg gemfibrozil or placebo for five years. A quarter of the patients had frank diabetes mellitus. In the gemfibrozil group, there was a 3.6% rise in LDL cholesterol (4% rise in controls), and a 7.5% rise in HDL cholesterol (1.8% rise in controls), while triglycerides fell by 24.5% (9.6% rise in controls). These changes were associated with a 22% drop in the predefined primary end-point of nonfatal myocardial infarction or CAD death (P = 0.006). There was also a 27% drop in the incidence of reported stroke (P = 0.05) and a 58% drop in the incidence of transient ischaemic attacks (P = 0.001) in the gemfibrozil-treated group. The effect of gemfibrozil was the same in diabetics and non-diabetics (Robins SJ et al. JAMA 2001;285:1585-1591).

9. The Diabetes Atherosclerosis Intervention Study (DAIS), conducted in co-operation with the World Health Organisation, was the first study designed to examine specifically the effect of treating lipid abnormalities on coronary atherosclerosis in patients with type 2 diabetes mellitus. In DAIS, quantitative coronary angiography was used to determine disease progression or regression. After follow-up of at least three years, treatment with fenofibrate reduced by 40% to 42% the progression of angiographic parameters considered to reflect focal disease (Diabetes Atherosclerosis Intervention Study Investigators. Lancet 2001; 357:905-910).

10. Ezetemibe co-administered with the lowest approved dose of tested statin (pravastatin, simvastatin, atorvastatin) has been shown to produce LDL-cholesterol lowering that is similar to or greater than that achieved with the highest dose of the statin used alone (Gagne C et al. Am J Cardiol 2002; 90:1084-1091; Davidson MH et al. Am Coll Cardiol 2002; 40: 2125-2134i)

Table 34: Pharmacokinetics of HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors (statins) vary widely in their pharmacokinetic properties, which has effects on the dose needed, the dosage interval, and the side-effect profile.

The following table shows the pharmacokinetic characteristics of the major statins (NA= information not available)

Parameter	Atorvastatin	Fluvastatin	Fluvastatin extended release
T_{max} (h)	2-3	0.5-1.0	4.0
C_{max} (ng/mL)	27-66	448	55
Bioavailability (%)	12	19-29	6
Lipophilicity	Yes	Yes	Yes
Protein binding (%)	80-90	> 99	> 99
Metabolism	CYP3A4	CYP2C9	CYP2C9
Metabolites	Active	Inactive	Inactive
P-glycoprotein substrates	Yes	No	No
$T_{1/2}$ (h)	15-30	0.5-2.3	4.7
Urinary excretion (%)	2	6	6
Faecal excretion (%)	70	90	90

Table 34

Parameter	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
T_{max} (h)	2.0-4.0	0.9-1.6	3	1.3-2.4
C_{max} (ng/mL)	10-20	45-55	37	10-34
Bioavailability (%)	5	18	20%	5
Lipophilicity	Yes	No	No	Yes
Protein binding (%)	> 95	43-55	88%	94-98
Metabolism	CYP3A4	Sulfation	CYP2C9, 2C19 (minor)	CYP3A4
Metabolites	Active	Active	Active (minor)	Active
P-glycoprotein substrates	Yes	Yes/No	NA	Yes
$T_{1/2}$ (h)	2.9	1.3-2.8	20.8	2-3
Urinary excretion (%)	10	20	10	13
Faecal excretion (%)	83	71	90	58

Table 35: Human cytochrome P450 enzymes known to oxidise clinically used drugs

An issue of particular concern with the use of statins is interaction with other drugs that are metabolised by the same cytochromes. This table lists the members of the P450 cytochrome complex along with the drugs that they metabolise.

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP2E1	CYP3A4
Acetaminophen	Alprenolol	Amitriptyline	Amitriptyline	Acetaminophen	Amiodarone
Amiodarone	Diclofenac	Clomipramine	Carvedilol	Ethanol	**Atorvastatin**
Caffeine	**Fluvastatin**	Diazepam	Codeine	Halothane	Chinidin
Clozapine	Hexobarbital	Mephenytoin	Debrisoquine	Paracetamol	Clarithromycin
Lansoprazole	Ibuprofen	Methylphenobarbital	Flecainide		Cyclosporine
Omeprazole	Losartan	Omeprazole	Haloperidol		Diltiazem
Paracetamol	Phenytoin	Phenytoin	Imipramine		Erythromycin
Theophylline	Tolbutamide	Proguanyl	Metoprolol		Itraconazole
	Warfarin	Propranolol	Nortriptyline		Ketoconazole
			Ondansetron		Lacidipine
			Propafenone		Lidocain
			Propranolol		**Lovastatin**
			Risperidone		Midazolam
			Sparteine		Nefazodone
			Thioridazine		Nifedipine
			Timolol		Nimodipine
			Tramadol		Protease inhibitors
			Urapidil		Quinidine
					Rapamycin
					Sildenafil
					Simvastatin
					Tacrolimus
					Terbinafine
					Theophylline
					Triazolam
					Verapamil
					Warfarin
					Zolpidem

Table 36: Inhibitors and inducers of the cytochrome P450 enzymatic pathway

CYP Substrates (Statins)	Inducers	Inhibitors	
CYP3A4 • Atorvastatin • Lovastatin • Simvastatin	• Barbiturates • Carbamazepine • Cyclophosphamide • Dexamethasone • Lansoprazole • Omeprazole • Phenytoin • Primidon • Rifampin • Troglitazone • Smoking	• Amiodarone • Cimetidine • Clarithromycin • Corticosteroids • Cyclosporine A • Dexamethasone • Diltiazem • Erythromycin • Fluconazole • Fluoxetine • Fluvoxamine • Itraconazole • Ketoconazole • Midazolam • Nefazodone • Protease inhibitors • Sertraline	• Indinavir • INH • Metronidazole • Nifedipine • Nisoldipine • Nitrendipine • Ritonavir • Tacrolimus • Tamoxifen • Tricyclic antidepressants • Valproic acid • Venlafaxine • Verapamil • Grapefruit juice
CYP2C9 • Fluvastatin • Rosuvastatin	• Phenobarbital • Phenytoin • Rifampin • Troglitazone	• Amiodarone • Azapropazone • Ketoconazole • Fluconazole • Sulfaphenazole	

Table 37: Selected drugs that may increase the risk of myopathy and rhabdomyolysis when used concomitantly with statins

Recently, cerivastatin was withdrawn from sale worldwide because of an increased risk of myopathy and rhabdomyolysis, particularly in patients also receiving gemfibrozil.

However, a wide variety of drugs in addition to fibrates may also increase the myopathy risk, as shown in this table.

CYP3A4 inhibitors/substrates	others
• Cyclosporine • Macrolide antibiotics (azithromycin, clarithromycin, erythromycin) • Azole antifungals (intraconazole, ketoconazole) • Calcium antagonists (diltiazem, verapamil) • Nefazodone • Protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir) • Sildenafil • Warfarin	• Digoxin • Fibrates (gemfibrozil) • Niacin

Table 38: LDL apheresis and other treatment options in severe refractory hypercholesterolaemia[1]

LDL Apheresis

Description: Procedure for specifically removing apo B-containing lipoproteins from the blood. Most of the commonly employed systems have utilised immunadsorption columns, dextran sulfate cellulose columns, and heparin precipitation.

Use: Approved by the U.S. Food and Drug Administration in 1996 for use in patients who despite diet and maximum tolerated drug therapy have:
- LDL cholesterol > 300mg/dL (>7.8 mmol/L) when coronary heart disease is absent
- LDL cholesterol > 200mg/dL (>5.2 mmol/L) when coronary heart disease is present

Usually performed in regional centres.

Expected lipid effects of a single treatment: 120-150 mg/dL (3.0-4.0 mmol/L) decrease in LDL cholesterol, 50-70% decrease in Lp (a), 50% decrease in VLDL cholesterol and VLDL triglycerides, small reduction in HDL cholesterol (dilutional effect)

Adverse events: Uncommon, including nausea/vomiting, flushing, and most commonly hypotension. Antihypertensive drugs need to be withheld immediately before LDL apheresis in patients at risk for hypotension. Hypotension can be severe in patients taking an ACE inhibitor.

Reported benefits: Stabilisation of coronary atherosclerosis, functional improvement, reduced risk for restenosis after PTCA, reduced risk for graft vessel disease after heart transplantation, improved symptoms and stenoses in PVD

Use with statin therapy: Substantial additional LDL cholesterol lowering achieved with high-dose atorvastatin (80 mg/day) and expanded-dose simvastatin (160mg/day) in patients undergoing LDL apheresis for homozygous familial hypercholesterolaemia

Other Treatment Options

Used alone or combined with LDL apheresis: liver transplantation, portocaval shunt, plasmapheresis, partial ileal bypass surgery. Gene therapy appears to be a number of years away from routine clinical application.

1. Gotto AM Jr., Assmann G, Carmena R, Davignon J, Fernández-Cruz A, Fruchart J-C, Kastelein JJP, Paoletti R. The ILIB Lipid Handbook for Clinical Practice. Blood lipids and coronary heart disease. International Lipid Information Bureau, 2000, New York

Table 39: General guidelines for treatment of hypertension

The results of clinical trials indicate that each reduction of 12 mmHg in systolic blood pressure and 5 mmHg in diastolic blood pressure reduces risk of stroke and coronary heart disease by about 40% and 17%, respectively; the overall risk of cardiovascular events is reduced by about a third.

Blood pressure classification[1]

Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal	< 120	< 80
Normal	< 130	< 85
High normal	130-139	85-89
Grade 1 Hypertension (mild) *Subgroup: Borderline*	140-159 *140-149*	90-99 *90-94*
Grade 2 Hypertension (moderate)	160-179	100-109
Grade 3 Hypertension (severe)	≥ 180	≥ 110
Isolated Systolic Hypertension *Subgroup: Borderline*	≥ 140 *140-149*	< 90 *< 90*

When systolic blood pressure and diastolic blood pressure fall into different categories, the higher should apply.

Targets for blood pressure

- <130/85 mmHg (optimal or normal): in high-risk patients
- <140/90 mmHg (high-normal): in uncomplicated hypertension

1. In part adapted from WHO-ISH Guidelines for Management of Hypertension. J Hypertens 1999; 17: 151-183
In practise, certain systolic and diastolic blood pressures tend to go together. Thus a systolic blood pressure of 140 mmHg tends to be associated with a diastolic blood pressure of around 80 mmHg, a systolic pressure of 150 mmHg with a diastolic pressure of 90 mmHg, and a systolic pressure of 170 mmHg with a diastolic pressure of 100 mmHg.

Table 40: Requirement for therapy in hypertension[1]

Grade of hypertension	Other risk factors* and disease history**		
	no other risk factor	1 or 2 other risk factors	3 or more risk factors, disease history
1 (mild)			
2 (moderate)			
3 (severe)			

☐ Lifestyle changes, monitor blood pressure for 6 to 12 months. Begin drug therapy if SBP ≥ 150 mmHg or DBP ≥ 95 mmHg

Lifestyle changes, monitor blood pressure for 3 to 6 months. Begin drug treatment if SBP ≥ 150 mmHg or DBP ≥ 95 mmHg

Begin drug treatment immediately.

* **Risk factors:** age > 55 years in men or > 65 years in women, smoking, total cholesterol > 250 mg/dL (6.48 mmol/L), family history of premature cardiovascular disease.
Disease history: diabetes mellitus, left ventricular hypertrophy, microalbuminuria and/or slightly elevated plasma creatinine concentration (1.2-2.0 mg/dL), ultrasound or radiological evidence of atherosclerotique plaque, narrowing of retinal arteries, cerebrovascular disease, heart disease, renal disease, vascular disease, advanced hypertensive retinopathy

1. See Table 39

Table 41: Individualised treatment of hypertension

Therapeutic lifestyle changes

- Patients should cut back on or abstain from alcohol
- Encourage consumption of 5 to 9 servings of fruit and vegetables per day
- Encourage consumption of 2 to 4 servings of low-fat dairy products per day
- Patients should eat plenty of whole-grain products, poultry, fish and nuts
- Reduce intake of high-fat animal products and sucrose-containing foods and beverages
- Limit intake of salt to less than 6 g per day
- Smokers should stop smoking (Table 26 *on page 73*)
- Maintenance of normal body weight or weight reduction in overweight persons (Table 29 *on page 78*)
- Encourage patient to participate in regular physical activity (Table 30 *on page 80*)

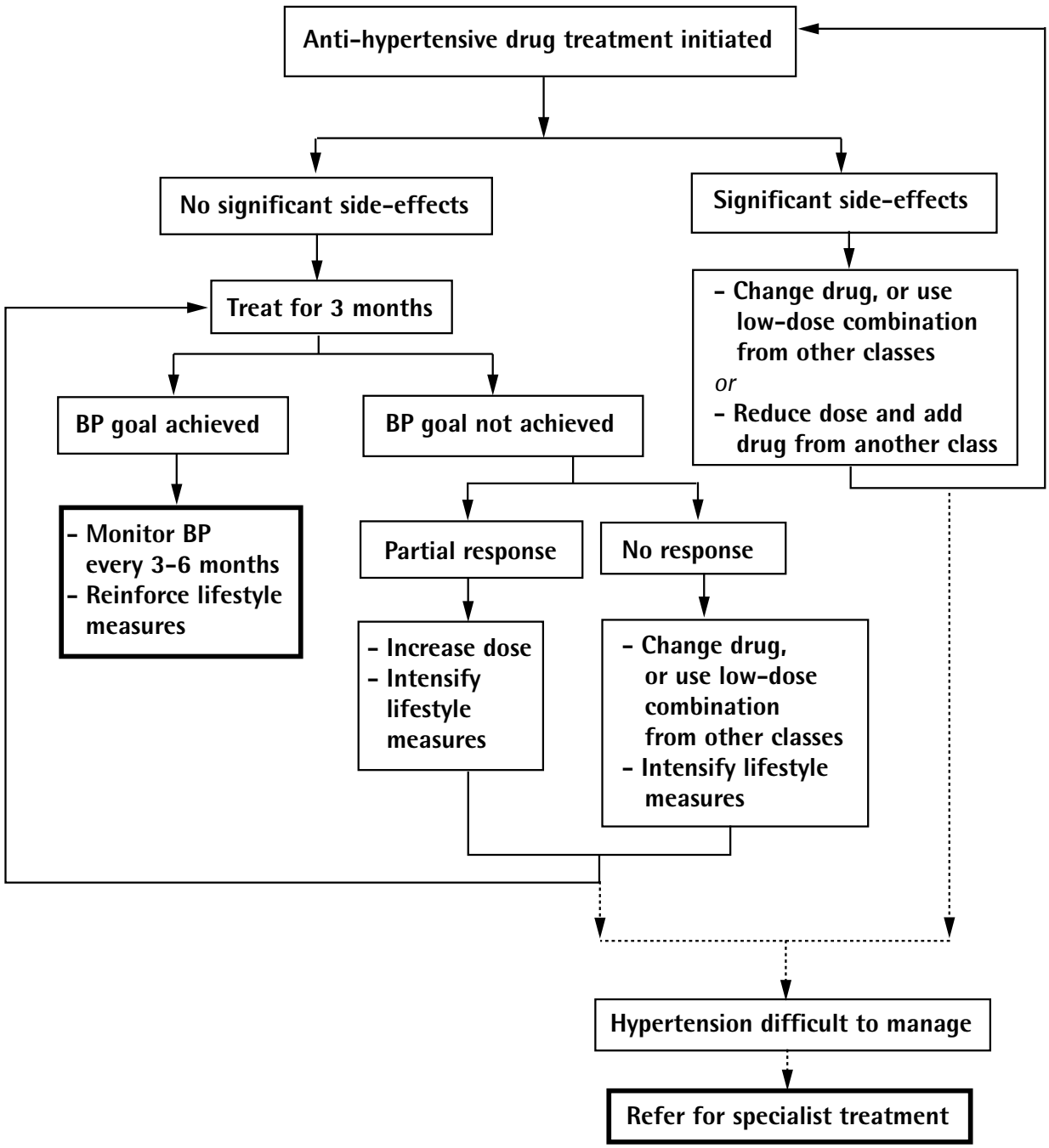
Drug treatment

- In persons with grade 1 hypertension, use of a single drug will usually reduce the systolic blood pressure by about 10 mmHg and the diastolic blood pressure by about 5 mmHg. With combination therapy, it is usually possible to achieve sustained reductions in systolic blood pressure of about 20 mmHg and in diastolic blood pressure of about 10 mmHg
- In general, begin with lowest available dose and increase dose or use appropriate drug combination as required
- Change to other drug or combination if little response or poor tolerability
- Long-acting drugs
  - provide 24-hour efficacy
  - improve compliance
  - may provide greater protection against the risk of major cardiovascular events or target organ damage
- Persevere with lifestyle changes even if drugs are required

Causes of refractory hypertension

- Unsuspected secondary cause, e.g. of renal or endocrine origin
- Poor compliance
- Intake of blood pressure-raising drugs, in particular non-steroidal anti-inflammatory drugs
- Adverse lifestyle factors such as weight gain or heavy alcohol intake, in particular binge drinking
- Volume overload due to inadequate diuretic therapy, progressive kidney failure or high salt intake
- Spurious, due to "white coat" effect or use of too small a blood pressure cuff

Fig. 16: Flow-chart for managing anti-hypertensive therapy[1]



1. WHO-ISH Guidelines for Management of Hypertension. J Hypertens 1999; 17: 151-183

Table 42: Indications and contraindications for anti-hypertensive drugs[1]

Drug Class	Indications	Contraindications
Diuretics[2]	*Compelling* • Heart failure • Elderly patients • Systolic hypertension *Possible* • Diabetes mellitus	*Compelling* • Gout *Possible* • Dyslipidaemia • Sexually active males
Beta-blockers	*Compelling* • Angina • After myocardial infarction • Tachyarrhythmias *Possible* • Heart failure • Pregnancy • Diabetes mellitus[3]	*Compelling* • Asthma and chronic obstructive pulmonary disease • Heart block[4] *Possible* • Dyslipidaemia • Athletes and physically active patients • Peripheral vascular disease
Angiotensin-converting enzyme (ACE) inhibitors[5]	*Compelling* • Heart failure • Left ventricular dysfunction • After myocardial infarction • Diabetes mellitus	*Compelling* • Pregnancy • Hyperkalaemia • Bilateral renal artery stenosis
Calcium antagonists	*Compelling* • Elderly patients • Systolic hypertension *Possible* • Peripheral vascular disease	*Compelling* • Heart block[6] *Possible* • Congestive heart failure[7]

Table 42

Drug Class	Indications	Contraindications
Alpha-blockers	*Compelling* • Prostatic hypertrophy *Possible* • Glucose intolerance • Dyslipidaemia	*Possible* • Orthostatic hypotension
Angiotensin II antagonists	*Compelling* • ACE inhibitor cough *Possible:* • Heart failure • Diabetes mellitus • Left ventricular hypertrophy	*Compelling* • Pregnancy • Bilateral renal artery stenosis • Hyperkalaemia

1. Adapted from WHO-ISH Guidelines for Management of Hypertension. J Hypertens 1999; 17:151-183

2. The results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial clearly show that thiazide diuretics are the drug of the first choice in the initial treatment of arterial hypertension. They are less expensive than alternative forms of first-step therapy such as calcium channel blockers and inhibitors or angiotensin converting enzyme, and are also superior in preventing cardiovascular disease. Although ALLHAT did not compare a beta-blocker to a thiazide diuretic, previous studies have suggested equivalence of these two agents. After the ALLHAT trial was designed, newer agents such as angiotensin receptor blockers and selective aldosterone antagonists have become available. Note further that 35% of the study population were black, who have poorer blood pressure response with ACE inhibitors. (The ALLHAT Officers and Coordinators of the ALLHAT Collaborative Research Group. JAMA 2002; 288: 2981-2997).

3. Some beta-blockers may interfere with glucose tolerance

4. Grade 2 or 3 atrioventricular block

5. Trials of agents blocking the angiotensin pathway have indicated that treatment with both angiotensin-converting enzyme inhibitors and antagonists of the type 1 angiotensin II receptor may have substantial beneficial effects that go beyond a simple lowering of blood pressure. In the Heart Outcomes Prevention Evaluation (HOPE) Study, treatment of patients aged at least 55 years with either vascular disease or diabetes mellitus + one other risk factor with the angiotensin-converting enzyme inhibitor ramipril resulted in a 22% reduction in a composite end-point of myocardial infarction, stroke or cardiovascular death. This benefit was seen in patients who were already taking aspirin, beta-blockers, and/or lipid-lowering agents, indicating that inhibition of angiotensin-converting enzyme confers benefit over and above that already shown for these agents (HOPE Investigators, N Engl J Med 2000; 342: 143-153).
   More recently, the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study showed that, compared to beta-blockade with atenolol, selective antagonism of the type 1 angiotensin II receptor with losartan prevented about 13% more primary cardiovascular events (death, myocardial infarction, stroke) for a similar reduction in blood pressure, indicating that the effects of the agent extended beyond simple blood pressure lowering. This effect was particularly marked in patients with diabetes mellitus and signs of left ventricular hypertrophy. Moreover, there was a 25% lower incidence of new-onset diabetes mellitus in the losartan-treated than in the atenolol-treated group. Losartan was also more effective than atenolol at reversing left ventricular hypertrophy (Dahlöf B et al. Lancet 2002; 359: 995-1003, Lindholm LH et al. Lancet 2002; 359: 1004-1010).

6. Grade 2 or 3 atrioventricular block with verapamil or diltiazem

7. Verapamil or diltiazem.

Table 43: Anti-thrombotic therapy

Anti-platelet therapy

- In high-risk patients and in patients with established atherosclerotic disease, anti-platelet therapy should be prescribed consisting of
  - Acetyl salicylic acid (see below)
    or
  - Clopidogrel 75 mg/day
- Doses of 75-160 mg/day of acetyl salicylic acid are as effective as higher doses[1].
- Contraindications for use of acetyl salicylic acid: Do not use in patients with intolerance for acetyl salicylic acid. Low-dose use increases risk for gastrointestinal bleeding and haemorrhagic stroke. Do not use in persons at increased risk for these diseases. However, benefits of cardiovascular risk reduction outweigh these risks in most patients at higher coronary risk[1]

Anti-coagulation therapy

- For patients with chronic or intermittent atrial fibrillation, warfarin should be used, except for those in whom warfarin is contraindicated or in those aged < 65 years without high risk. These patients may be treated with acetyl salicylic acid
- After myocardial infarction, when antiplatelet drugs are contraindicated, warfarin should be prescribed
  - Warfarin: target international normalised ratio (INR): 2.5 (range 2.0-3.0)

1. Pearson TA et al. Circulation 2002; 106: 388-391

Table 44: Factors producing a hypercoagulable state

As shown in this table, a wide range of inherited and acquired factors may contribute to a hypercoagulable state. These include the presence of certain single-nucleotide polymorphisms (SNPs) in the genes encoding glycoproteins on the surface of patelets, increases in the levels of circulating clotting factors, or mutations in the genes encoding these factors, and reduced circulating levels of fibrinolytic factors or mutations in the genes for these factors. Other causes are the presence of anticardiolipin antibodies and transient factors such as dehydration.

Blood factors involved in hypercoagulability
• Increased platelet activation (e.g. SNPs of GP IIb/IIIa and Ib/IX)
• Increased coagulation factors (e.g. clotting of factors V, VII, VIII, vWF, XIII)
• Decreased anti-coagulation factors (e.g. proteins S, C, thrombomodulin, AT III)
• Prothrombin mutation (G20210A)
• Decreased endogenous fibrinolysis (e.g. reduced t-PA, increased PAI-1, PAI-1 SNPs)
• Other factors (e.g. anti-cardiolipin AB)
• Transient hypercoagulaemia (e.g. dehydration, adrenergic surge, postprandial)

C. Special issues

Table 45: Treatment of emerging risk factors

Lifestyle changes form the cornerstone of treatment of emerging risk factors.
Treatment of hyperhomocysteinaemia is dealt with separately in Figure 17 *on page 105*.

- Administer anti-platelet treatment to all high-risk patients with a pro-thrombotic state (Table 43 *on page 102*)
- Elevated Lp(a): No specific therapy exists. Some authorities suggest more aggressive lowering of LDL cholesterol; consider hormone replacement therapy in post-menopausal women
- Pro-inflammatory state: reduce weight (Table 29 *on page 78*), consider acetyl salicylic acid

1. Shlipak MG et al. JAMA 2000; 283: 1845-1852

Fig. 17: Measurement and treatment of elevated homocysteine

Determination of homocysteine levels are recommended for patients with a personal or family history of atherosclerosis as well as in patients who are likely to have high homocysteine levels, e.g. patients with renal insufficiency, smokers and patients under treatment with drugs causing elevated homocysteine (e.g. fibrates, theophyllin, methotrexate, or anti-epileptic drugs).

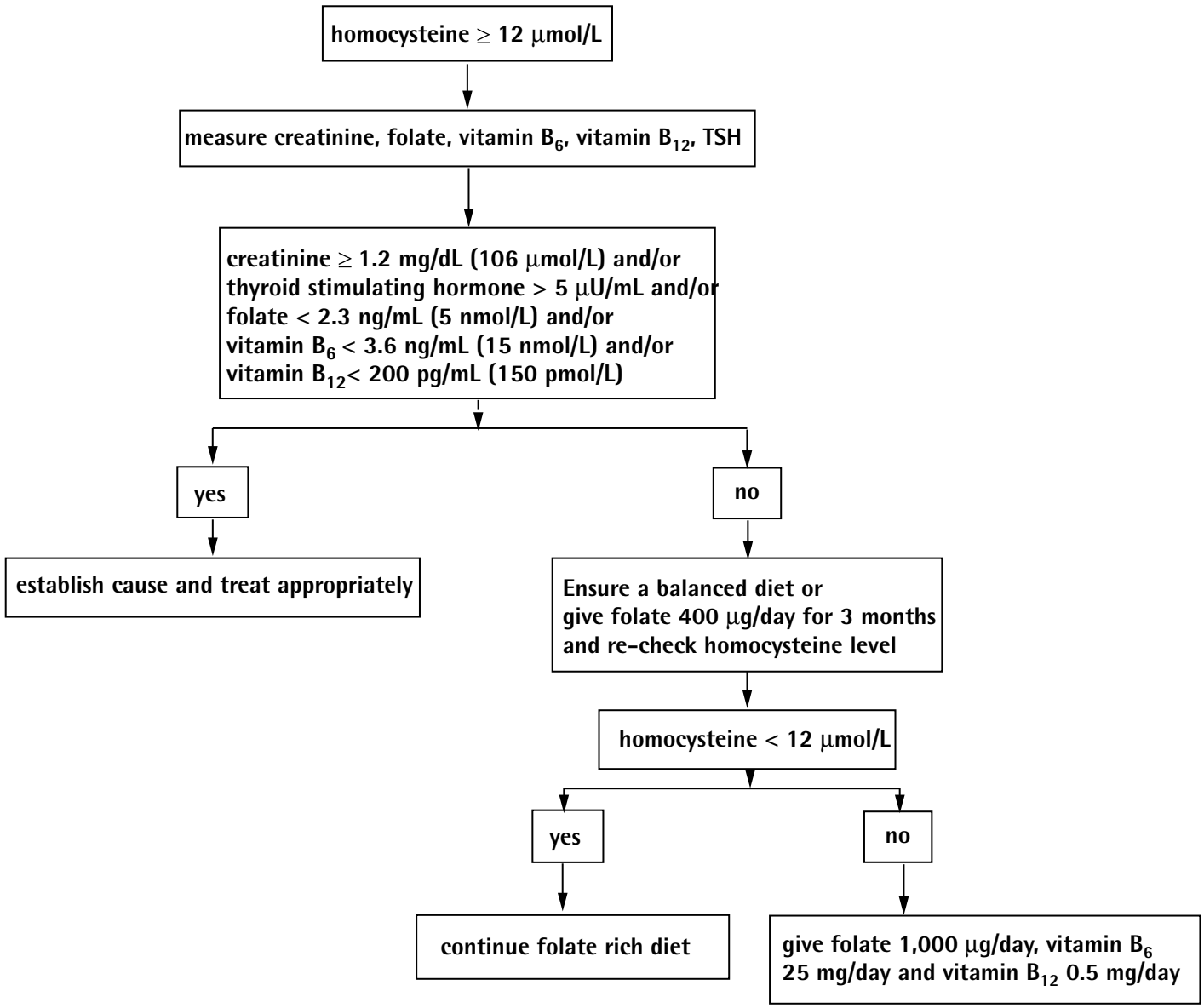


Table 46: Reducing coronary risk in patients with diabetes mellitus and impaired glucose tolerance / impaired fasting glucose

As explained elsewhere in this guide (Table 18 *on page 59*), type 2 diabetes mellitus is an independent risk factor for coronary heart disease. In the past, the importance of diabetes mellitus for coronary heart disease has been underestimated. Equally, the importance of checking for signs of coronary heart disease and coronary risk factors in diabetic patients has not always received the attention it deserves. Diabetes mellitus is a growing problem of epidemic proportions:

- The prevalence of type 2 diabetes mellitus is increasing rapidly and already exceeds 5% of the population in almost all developed and many less developed countries
- Only about half of all cases of type 2 diabetes mellitus have been diagnosed, indicating a total prevalence of up to 10%
- Previously undiagnosed diabetes mellitus and impaired glucose tolerance are common in patients with myocardial infarction
- Type 2 diabetes mellitus is always preceded by a prolonged period of impaired glucose tolerance lasting months or years. The metabolic syndrome is often also a precursor of type 2 diabetes mellitus
- Algorithms have been developed that allow calculation of the chance of developing frank type 2 diabetes mellitus in the future based on the risk factors age, blood glucose, BMI, HDL cholesterol, hypertension and family history of type 2 diabetes mellitus[1]
- Impaired glucose tolerance can be reversible with conservative treatment, in particular aerobic exercise and normalisation of body weight
- Recent trials have indicated that add-on treatment with the alpha-glucosidase inhibitor acarbose[2], with with the biguanide anti-diabetic drug metformin[3], with the statin pravastatin[4], with the angiotensin converting enzyme inhibitor ramipril[5], or with the angiotensin receptor blocker losartan[6] may in some cases delay or prevent the onset of type 2 diabetes mellitus.

1. Incidence = 1/(1+ exp(-y), where y = -18.5694
   + 0.0258 x age in years
   + 6.461163 x 10^{-3} x glucose in mmol/L
   + 0.108 x BMI in kg/m^2
   - 0.4585 x 10^{-3} x HDL cholesterol in mmol/L
   + 0.4190 x family history of type 2 diabetes mellitus (no = 0, yes = 1)
   + 0.1713 x hypertension (no = 0, borderline = 1, manifest = 2)

   (Calculated among 3,737 men aged 36 to 60 years in the PROCAM study with a mean follow-up of 6.3 years. von Eckardstein A et al. J Clin Endo Metab 2000; 85: 3101-3108)

2. In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), 100 mg/day of the alpha-glucosidase inhibitor acarbose for a mean of 3.3 years reduced by 25% the progression of impaired glucose tolerance to frank diabetes mellitus, and also increased the incidence of reversion of impaired glucose tolerance to normoglycaemia (Chiasson J-L et al. Lancet 2002; 359: 2072-2077).

3. In the Diabetes Prevention Program (DPP), treatment with metformin reduced the incidence of type 2 diabetes mellitus in patients with impaired glucose tolerance by 31% (Diabetes Prevention Program Research Group. N Engl J Med 2002; 346: 393-403).

4. The West of Scotland Coronary Prevention Study showed that pravastatin treatment of 45 to 64 year old non-diabetic men resulted in a 30% reduction in the hazard of developing type 2 diabetes mellitus (Freeman DJ et al. Circulation 2001; 103: 357-362).

5. The Heart Outcomes Prevention Evaluation Study. (The HOPE Investigators. N Engl J Med 2000; 342: 143-153)

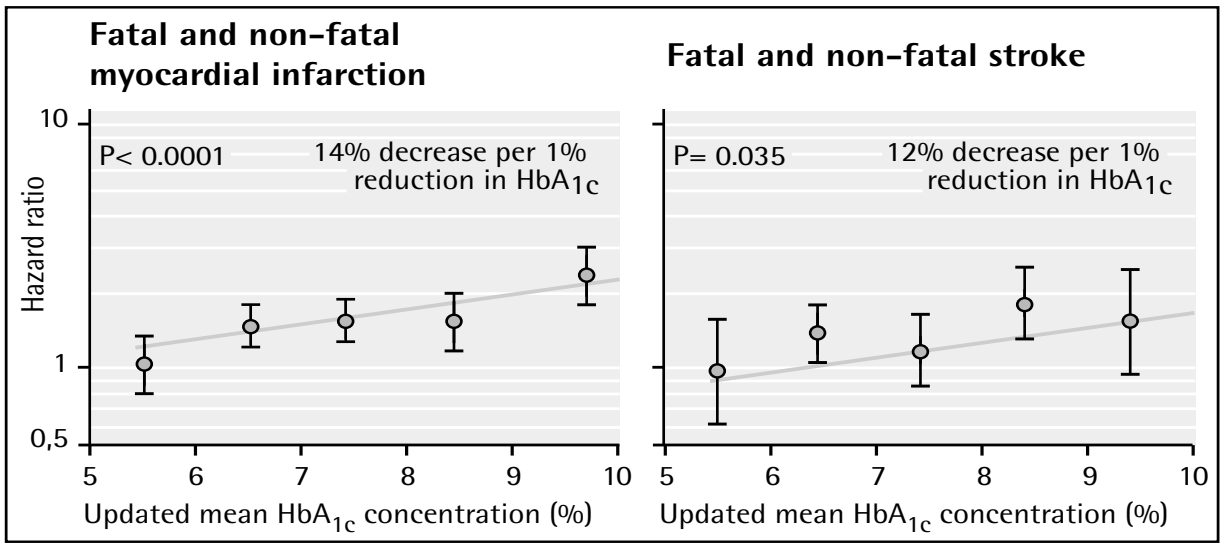
6. Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE Study). (Dahlöf B et al. Lancet 2002; 359: 995-1003)

Table 47: Coronary heart disease prevention approaches in type 2 diabetes mellitus

- Weight reduction is the cornerstone of treatment in the overweight (Table 29 *on page 78*)
- Increased physical activity in physically inactive (Table 30 *on page 80*)
- Smoking cessation in smokers (Table 26 *on page 73*)
- Anti-hyperglycaemic therapy (oral anti-hyperglycaemic agents or insulin)
- Anti-hypertensive treatment (Table 39 *on page 94*, Table 41 *on page 96*, Figure 16 *on page 98*)
- Treatment of dyslipidaemias (Table 31 *on page 82*)
  - Lowering of elevated LDL cholesterol levels
  - Lowering of elevated triglyceride levels
  - Raising of low HDL cholesterol levels
- Anti-thrombotic therapy (Table 43 *on page 102*)

Fig. 18: Effect of lowering glycosylated haemoglobin level on risk of cardiovascular disease

In the United Kingdom Prospective Diabetes Study, relative risk analyses were performed on 3,642 white, Asian, Indian, and Afro-Caribbean patients with type 2 diabetes mellitus[1]. After a median follow-up of 10 years, the incidence of clinical complications was significantly associated with glycaemia. Each 1% reduction in the mean level of glycosylated haemoglobin (HbA_{1c}) was associated with a reduction in risk of 21% for any complication related to diabetes mellitus, 21% for deaths related to diabetes mellitus, 14% for myocardial infarction, and 37% for microvascular complications. Furthermore, no threshold of risk was observed for any end point. The following graph shows the reduction in fatal and non-fatal myocardial infarction and in fatal and non-fatal stroke that may be expected with each 1% lowering in the HbA_{1c} level.



1. Stratton IM et al. for the UKPDS group. BMJ 2000; 321: 405-411

Fig. 19: Flow-chart for diagnosis of impaired glucose tolerance and diabetes mellitus

This flow-chart is intended to assist in making the diagnosis of diabetes mellitus. Diabetes mellitus is a life-long condition and carries prognostic implications of the same gravity as some malignant conditions.

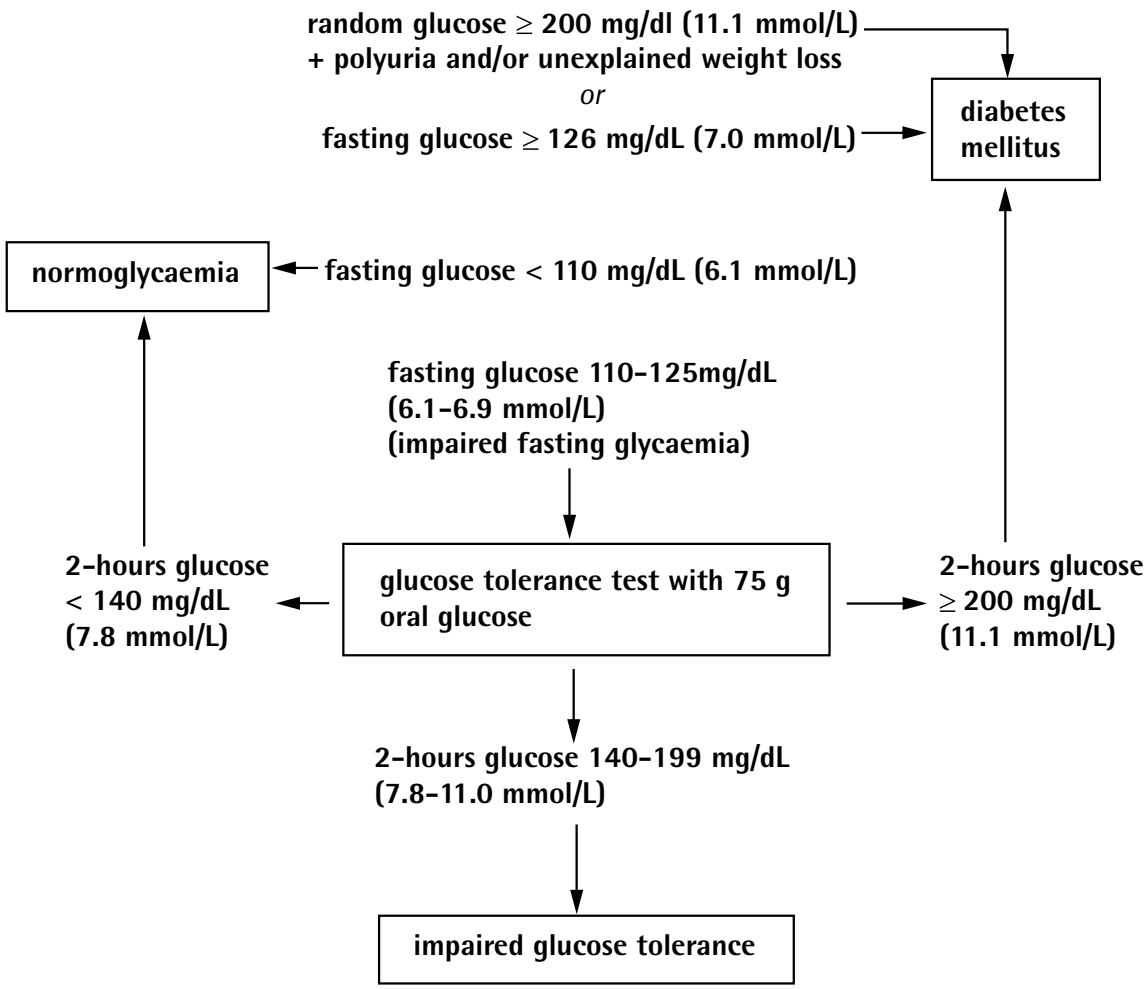


Table 48: Atherosclerosis in women

Contrary to popular belief, atherosclerosis is by no means rare in women, particularly in women after the menopause. In fact, more women than men die of atherosclerotic disease, albeit at a later age.

- The same risk factors for coronary heart disease operate in women as in men
- The absolute risk of coronary heart disease in post-menopausal women (45-65 years) is between one-quarter and one-half that of men of the same age with the same risk factor profile; with advancing years the risk in women approaches that of men of the same age
- Recent randomised trials have not shown that hormone replacement therapy is effective in preventing coronary heart disease in women. The decision to prescribe hormone replacement should therefore be based on menopausal symptoms and the need for osteoporosis prophylaxis[1]
- The major risk factors in women appear to be hypertension and diabetes mellitus
- Women with diabetes mellitus have the same risk of coronary heart disease as diabetic men of the same age
- Coronary heart disease in women is often diagnosed later than in men with a consequent worsening of prognosis
- Physicians should be alert to the possibility of metabolic syndrome in women

1. In the Women's Health Initiative, overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2 year follow-up among healthy postmenopausal women (Women's Health Initiative. JAMA 2002; 288: 321-333). Furthermore, in the Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II), hormone replacement therapy did not reduce the risk of cardiovascular events in women with established coronary heart disease (Grady G et al. JAMA 2002; 288: 49-57).

Table 49: Coronary heart disease in the elderly

- Because of the high incidence of coronary heart disease in the elderly, even a small lowering of risk translates into a considerable reduction in the number of coronary heart disease events
- Treatment of coronary heart disease risk factors in the elderly requires particular care:
  - Quality of life is of special importance and should be reflected in any therapeutic decision
  - Dietary change should take food preferences and eating difficulties into account and must maintain a nutritionally sound combination of foods
  - The treatment of hypertension in older persons is of established benefit
  - Drug treatment to lower cholesterol is indicated in high-risk persons aged over 60 years
  - Beyond age 85 years, high plasma cholesterol concentrations are associated with increased life expectancy, because undiagnosed cancers and infections lower cholesterol. The effects of cholesterol-lowering therapy have yet to be assessed in this age group
  - Differences in drug metabolism may necessitate lower drug dosage in the elderly
  - Drug costs can be a source of difficulty in older patients
- Because of the large number of drugs used by older persons, drug interactions are of special concern

Table 50: Notes on treatment of dyslipidaemia in the elderly[1]

Therapy	Considerations
Lifestyle modification	Carefully individualise diet to ensure adequacy of nutrition. Regular physical activity if appropriate
Drug therapy	Use particular caution in proceeding to drug therapy, because the elderly may be particular susceptible to adverse effects. Statins, fibrates and cholesterol absorption inhibitors are well tolerated
Statins	Most cases of severe myopathy have occured in older patients, particularly those with coexisting disease, e.g., renal insufficiency
Resins	Associated constipation may be a particular problem. Absorption of other drugs may be decreased
Fibrates	Occurrence of gallstones may be increased; cholecystectomy carries more risk in older patients. Other possible side effects are GI distress, impotence, and, in patients with renal insufficiency, myopathy
Niacin	Common side effects may be more pronounced, e.g., flushing, dry skin, dry mouth. Impaired glucose tolerance may be aggravated. Niacin raises uric acid concentrations and may precipitate gout

1. Adapted from Gotto AM Jr., Assmann G, Carmena R, Davignon J, Fernández-Cruz A, Fruchart J-C, Kastelein JJP, Paoletti R. The ILIB Lipid Handbook for Clinical Practice. Blood lipids and coronary heart disease. International Lipid Information Bureau, 2000, New York

Table 51: Coronary heart disease risk factors in childhood

- Cardiovascular risk factors affect arteries from an early age
- Ensure a healthy pattern of eating and physical activity
- Encourage adolescents not to start smoking
- In children with a first-degree relative who suffered coronary heart disease before the age of 60 years, assess risk factors and consider measurement of LDL cholesterol, HDL cholesterol and fasting triglyceride levels
- Measure lipids in all children with diabetes mellitus
- In children with hyperlipidaemia and/or hypertension, perform a careful screen for secondary causes and familial disorders
- Consider pharmacological therapy to lower lipids only in children above the age of 10 years in whom persistent conservative measures have failed to lower LDL cholesterol level to < 130 mg/dL (< 3.37 mmol/dL)

Table 52: Selected considerations in blood sampling

Consideration	Notes
Nonfasting vs. fasting	Total cholesterol and HDL cholesterol: Nonfasting acceptable in follow-up Triglycerides: Fasting always required (12- to 14-hour fast; water and calorie-free liquids permitted, including tea or coffee without whitener)
Fingertip vs. venous	Screening (total cholesterol, HDL cholesterol, triglycerides): Fingertip blood and dry chemistry techniques may be used Decision making: Follow-up testing with venous blood required
Serum vs. plasma	Standardise sample type from one test date to the next: Plasma lipid values are about 4% lower than serum values Serum: Preferably, collect blood in tubes without anticoagulant Plasma: Tubes containing EDTA may be used
Establishing baseline values	Establish baseline values by using several blood samples over 1-3 months, for estimate of variability, and use for evaluation of treatment Cholesterol values normally fluctuate day to day by 3% or more. Note that seasonal variations also occur, e.g. cholesterol values modestly increase in spring and modestly decrease in autumn Fluctuations from day to day of > 30% occur in fasting triglycerides independent of meal pattern

.....continued

Consideration	Notes
Concurrent illness or other condition	Myocardial infarction: Determine lipid values within 24 hours of the onset of chest pain. Beginning about 12 hours after a myocardial infarction, LDL cholesterol values decrease for up to 12 weeks. However, decreases in lipid values generally do not exceed 10% during the first 24 hours; decreases > 10% generally do not occur until ≥ 48 hours after admission. All patients admitted with a myocardial infarction or suspected myocardial infarction are fasting at some point during the first 24 hours, and fasting lipid values should be determined during that window of opportunity. After this period, deferral of diagnostic lipid evaluation for 4-6 weeks is customary Other major illness or surgery. Defer for 3 months. Minor illness: Defer for 3 weeks. Pregnancy: Associated with physiologic hyperlipidaemia; defer testing until after delivery, but test patients with history of hypertriglyceridaemia (pregnancy could elevate triglycerides to pancreatitis range). During pregnancy, LDL cholesterol, HDL cholesterol, and triglycerides rise
Diet	Patient followed current diet for 3 weeks and maintained constant weight

.....continued

Consideration	Notes
Posture	Standardise patient posture because posture can alter cholesterol values by changing plasma volume; patient seated for 5-10 minutes convenient. If patient lies down for 10 or 15 minutes before blood sampling, the lipid values may be lower than they otherwise would be. Triglycerides and total cholesterol are 9-19% higher when the patient is erect rather than recumbent
Phlebotomy technique	Draw venous sample without prolonged stasis; use tourniquet as briefly as possible before inserting needle and release before drawing sample
Laboratory	Use same laboratory for consistency over time Seek a laboratory that participates in a reliable standardisation programme - in the United States, preferably one that has its lipid assays standardised through one of the National Network Laboratories of the Centers for Disease Control and Prevention Rapid capillary blood (fingerstick) methodology for total cholesterol, triglycerides, and HDL cholesterol can produce satisfactory results provided determinations are standardised in the same fashion as venous serum or plasma determinations

.....continued

Consideration	Notes
Recognition of chylomicro-naemia	Refrigerate fasting serum or plasma for 12 hours. Finding of creamy supernatant indicates presence of chylomicrons. Rule of thumb: triglycerides > 300 mg/dL (> 3.4 mmol/L) confers turbidity to plasma
Non-HDL-C	Some investigators have suggested that non-HDL cholesterol -i.e., LDL cholesterol + IDL cholesterol + VLDL cholesterol, a measure of all lipoproteins that contain apo B - is a better representation of "atherogenic cholesterol" than is LDL cholesterol. In fasted plasma (from which chylomicrons are usually absent), apo B concentrations may serve as a marker of the number of atherogenic particles, and it has been recognised as a clinical coronary heart disease predictor. The clinician may wish to be familiar with these research issues
Limitations	At present, routine laboratory measurements cannot identify small, dense LDL, nor can they distinguish whether hypertriglyceridaemia is caused by small or large particles. IDL, VLDL, and small, dense LDL may be associated with increased risk for atherosclerosis. (Rule of thumb: A preponderance of small, dense LDL in the LDL fraction is likely when fasting triglycerides exceeds 190 mg/dL (2.1 mmol/L); normal LDL size is likely when fasting triglycerides is below 105 mg/dL (1.2 mmol/L))

Gotto AM Jr., Assmann G, Carmena R, Davignon J, Fernández-Cruz A, Fruchart J-C, Kastelein JJP, Paoletti R. The ILIB Lipid Handbook for Clinical Practice. Blood lipids and coronary heart disease. International Lipid Information Bureau, 2000, New York

Table 53: Genetic polymorphisms

In addition to assessment of conventional risk factors and imaging techniques, a great deal of effort in recent years has been put into the investigation of the influence of genetic polymorphisms on coronary risk. This research has been fraught with problems, chiefly due to the effects of confounding factors that make it very difficult to collect study and control populations of sufficient size, especially when several polymorphisms are being investigated simultaneously. The possibility of confounding is particularly relevant in view of the fact that most of polymorphisms studied have been associated with modest relative risk estimates that pale by comparison with the 40-fold risk differentiation possible by means of conventional algorithms.

Nevertheless, progress is being made in this field that indicates that use of genetic polymorphisms may become relevant to improve risk stratification in the future. For example, in a recent interesting study, 112 polymorphisms in 71 candidate genes were investigated in 2003 Japanese men and 816 Japanese women with myocardial infarction and in 1,306 male and 936 female controls.[1,2] In a two-step selection process, logistic regression analysis revealed significant associations with polymorphisms in the connexin 37 gene in men and the plasminogen activator inhibitor and stromelysin genes in women, after adjustment for age, BMI, smoking, hypertension, diabetes mellitus, hypercholesterolaemia and hyperuricaemia.

Thus, while at the moment use of genetic polymorphisms cannot be recommended as part of the initial screen of cardiovascular risk, this situation may change as more and better information becomes available.

1. Yamada Y et al. N Engl J Med 2002; 347: 1916-1923

2. Peters RJ, Boekholdt SM. N Engl J Med 2002; 347: 1963-1965

D. Appendix

Table 54: Selected internet resources

Organisation	Address	Content
American College of Cardiology	www.acc.org	•clinical guidelines •pocket guidelines
American Diabetes Association	www.diabetes.org	•aspects of diabetes
American Dietetic Association	www.eatright.org	•nutritional aspects
American Heart Association	www.americanheart.org	•information on prevention and treatment of cardiac diseases •encyclopaedia
American Stroke Association	www.strokeassociation.org	•aspects of stroke
British Heart Foundation	www.bhf.org.uk	•information for patient education
European Stroke Initiative	www.eusi-stroke.com	•guidelines for stroke management •slide kits
International Atherosclerosis Society	www.athero.org	•aspects of atherosclerosis
International Diabetes Federation	www.idf.org	•aspects of diabetes
International Obesity Task Force	www.iotf.org	•aspects of obesity
International Task Force for Prevention of Coronary Heart Disease	www.chd-taskforce.com	•PROCAM interactive CHD risk score and calculator •clinical recommendations and practical advice for management and prevention of risk factors •slide kits •scientific news on prevention of CHD •guidelines for CHD prevention

Organisation	Address	Content
International Union of Nutritional Sciences	www.iuns.org	•nutritional aspects
The Living Heart	www.livingheart.com	•information for patient education
National Guideline Clearinghouse	www.guideline.gov	•evidence-based clinical practice guidelines
National Lipid Education Council	www.lipidhealth.org	•information on lipids
UK risk score by age	www.riskscore.org.uk	•distribution of risk score in UK population by age
U.S. Agency for Health Care Policy and Research	www.ahcpr.gov	•smoking cessation guide for primary-care physicians
U.S. Centers for Disease Control and Prevention	www.cdc.gov	•U.S. Surgeon General's reports on physical activity and smoking
U.S. National Heart, Lung, and Blood Institute	www.nhlbi.nih.gov	•clinical guidelines and practical advice for treatment of overweight and obesity
World Heart Federation	www.worldheart.org	•aspects of heart health
World Health Organization	www.who.int	•health aspects from A to Z

Note: Many of the selected sites contain links to other national and international sites of interest.

Table 55: Selected literature

American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002; 25: 213-229

The ALLHAT Officers and Coordinators of the ALLHAT Collaborative Research Group. Major out-comes in high-risk hypertensive patients randomised to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288: 2981-2997

Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Münster (PROCAM) Study. Circulation 2002; 105: 310-315

Campbell B, Bradrick T, Flatman R, Kanowski D. Limited clinical utility of high-sensitivity plasma C-reactive protein assays. Ann Clin Biochem 2002; 39: 85-88

Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for The STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002; 359: 2072-2077

Dahlöf B, Devereux RB, Kjeldsen SE et al. for the LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359: 995-1003

Davidson MH, McGarry T, Bettis R et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. Am Coll Cardiol 2002; 40: 2125-2134i

Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet 2001; 357: 905-910

Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403

Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-2497

Freeman DJ, Norrie J, Sattar N et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001; 103: 357-362

Gagné C, Bays HE, Weiss SR et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002; 90: 1084-1091

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Gotto AM Jr., Assmann G, Carmena R, Davignon J, Fernández-Cruz A, Fruchart J-C, Kastelein JJP, Paoletti R. The ILIB Lipid Handbook for Clinical Practice. Blood lipids and coronary heart disease. International Lipid Information Bureau, 2000, New York

Grady G, Herrington D, Bittner V et al. for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/Progestin Replacement Study. Follow-up (HERS II) JAMA 2002; 288: 49-57

Guidelines Committee. 1999 World Health Organization - International Society of Hypertension Guidelines for the management of hypertension. J Hypertens 1999; 17: 151-183

Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000; 342: 145-153

Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22

International Task Force for Prevention of Coronary Heart Disease. Coronary heart disease: Reducing the risk. The scientific background for primary and secondary prevention of coronary heart disease. A worldwide view. Nutr Metab Cardiovasc Dis 1998; 8: 205-271

Janus ED Postiglione A, Singh RB, Lewis B. The modernization of Asia. Implications for coronary heart disease. Council on Atherosclerosis of the International Society and Federation of Cardiology. Circulation 1996; 94: 2671-2673

Krauss RM, Eckel RH, Howard B et al. AHA dietary guidelines. Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Circulation 2000; 102: 2284-2299

Lindholm LH, Ibsen H, Dahlöf B et al. for the LIFE study group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002; 359: 1004-1010

Mancini JGB, Pitt B on behalf of the PREVENT Investigation. Coronary angiographic changes in patients with cardiac events in the prospective randomized evaluation of the vascular effects of Norvasc trial (PREVENT). Am J Cardiol 2002; 90: 776-778

National Institutes of Health. Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults. Bethesda, MD; National Institutes of Health, 1998

NIH Consensus Development Panel on Physical Activity and Cardiovascular Health. Physical activity and cardiovascular health. JAMA 1995; 276: 241-246

NIH/NHLBI Obesity Education Initiative: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Executive summary. 1998. http://www.nhlbi.nih.gov/guidelines/obesity/ob_xsum.htm

Pearson TA, Blair SN, Daniels SR et al. AHA Guidelines for primary prevention of cardiovascular disease and stroke: 2002 update. Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. Circulation 2002; 106: 388-391

Peters RJ, Boekholdt SM. Gene polymorphisms and the risk of myocardial infarction-an emerging relation. N Engl J Med 2002; 347: 1963-1965

Robins SJ, Collins D, Wittes JT et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA 2001; 285: 1585-1591

Schwartz GG, Olsson AG, Ezekowitz MD et al. for the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL study: a randomized controlled trial. JAMA 2001; 285: 1711-1718

Serruys PWJC, de Feyter P, Macaya C et al. for the Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following a first successfull percutaneous coronary intervention. A randomized controlled trial. JAMA 2002; 287: 3215-3222

Shepherd J, Blauw GJ, Murphy MB et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623-1630

Shlipak MG, Simon JA, Vittinghoff E, et al. Estrogen and progestin, lipoprotein (a), and the risk of recurrent coronary heart disease events after menopause. JAMA 2000, 283: 1845-1852

Smith SC Jr., Blair SN, Bonow RO et al. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. J Am Coll Cardiol 2001; 38: 1581-1583.

Smith SC Jr., Greenland P, Grundy SM. AHA Conference Proceedings. Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: executive summary. American Heart Association. Circulation 2000; 101: 111-116

Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci 2001; 101: 617-679

Stratton IM, Adler AI, Neil HAW et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-412

Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P, for the WHO MONICA (monitoring trends and determinants in cardiovascular disease) Project. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA Project populations. Lancet 1999; 353: 1547-1557

U.S. Department of Health and Human Services, Public Health Services: Treating tobacco use and dependence. A clinical practice guideline. June 2000. http://www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf

von Eckardstein A, Schulte H, Cullen P, Assmann G. Lipoprotein (a) further increases the risk of coronary events in men with high global cardiovascular risk. J Am Coll Cardiol. 2001, 37: 434-439

von Eckardstein A, Schulte H, Assmann G. Risk for diabetes mellitus in middle-aged caucasian male participatns of the PROCAM Study: Implications for the definition of impaired fasting glucose by the American Diabetes Association. J Clin Endocrinol Metab 2000; 85: 3101-3108

Voss R, Cullen P, Schulte H, Assmann G. Prediction of risk of coronary events in middle-aged men in the Prospective Cardiovascular Münster Study (PROCAM), using neural networks. Int J Epidemiol 2002; 31: 1253-1262

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For further information resources consult the website of the International Task Force for Prevention of Coronary Heart Disease: **http://www.chd-taskforce.com**

Table 56: Sample form for calculating absolute 10-year risk of fatal or non-fatal myocardial infarction or sudden cardiac death

Name of patient:

Risk factor	Level of risk factor		Point score for risk factor	
Age				
LDL cholesterol				
HDL cholesterol				
Triglycerides				
Cigarette smoking	Yes	No	8	0
Diabetes	Yes	No	6	0
Family history of myocardial infarction	Yes	No	4	0
Systolic blood pressure				
Total score				**points**
Absolute 10-year CHD risk (men)				**% in 10 yr**
Post-menopausal, non-diabetic women			*divide absolute risk for men by 4*	
Absolute 10-year risk (women)				**% in 10 yr**