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Diabetes and Cardiovascular Risk Evaluation and Management in Primary Care: Progress and Unresolved Issues

Rationale for a Nationwide Primary Care Project in Germany

Abstract

This review highlights established and more recently recognized risk factors for coronary heart disease (CHD) relevant for patients seen in primary care, emphasizing the key role of diabetes mellitus type 2. Recent trends in risk factor research as well as current methods of risk stratification, and new systemic markers are discussed. Beyond the need for more forceful public health strategies to improve early recognition and intervention, the necessity of an integrated comprehensive investigation of the overall characteristics of cardiovascular disease, especially in primary care patients as a prerequisite for future concerted actions is pointed out. Based on this, a large-scale epidemiological investigation focusing on CHD and diabetes in the primary care sector is suggested.

Key words
Coronary heart disease · type 2 diabetes mellitus · primary care · risk markers · epidemiology

Introduction

This paper will examine the current situation in cardiovascular medicine in an attempt to identify which of the established and the more recently recognized risk factors for coronary heart disease (CHD) are relevant for patients seen in primary care, emphasizing the core role of diabetes mellitus type 2. By highlighting modern concepts of risk identification and stratification and the diagnostic and therapeutic potential of systemic risk markers, different strategies of improving the current situation within the primary care sector are discussed. Unlike general population samples, samples in primary care are characterized by consider-

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ably higher proportions of subjects at high risk for cardiovascular disease (CVD), for example with regard to behavioral risk factors as well as the presence of co-morbid conditions. Due to such complex risk constellations, the search for aggregated risk score measures is of great importance because they can simplify doctors' decisions for early intervention. In this respect we will point to considerable data deficits, prompting the need for a comprehensive integrated epidemiological investigation in the primary care sector aiming at an up-to-date, overall characterization of CVD (with a focus on CHD) and diabetes-related risk constellations in primary care.

CVD is among the leading causes of death and disability with an increasing prevalence in many regions of the world, affecting all ethnic, racial, and gender groups. CVD includes common conditions such as CHD, stroke, hypertension and heart failure (HF), and less common conditions such as congenital heart disease, cardiomyopathy, and peripheral vascular disease (Benjamin et al., 2002). Worldwide, it is estimated that CHD will increase further and will be the leading cause of death and a leading cause of disability-adjusted life-years lost. Because of this projection and the high direct diagnostic and treatment costs associated, for example, with myocardial infarction (MI) in western industrialized societies, the following high priority topics are widely recognized in developed countries: prevention of CVD, research in prevention of premature CVD and death, and the extension of life expectancy and quality.

The improved survival of patients who experience such critical clinical events, rather than the decreased incidence of these events, has contributed to an observed decline in CVD mortality over recent decades, resulting in turn in an increased prevalence of chronic coronary artery disease. Further substantial reductions in coronary artery disease morbidity and mortality can be anticipated only if coronary artery disease is treated before the manifestation of clinical disease. Since coronary occlusion and myocardial infarction most frequently evolve from mild to moderate coronary stenosis (Fig. **1**), an early intervention is required (Falk et al., 1995).

An exceptional high risk of developing atherosclerosis with a marked 2- to 4-fold increase in the rate of CHD has been demonstrated for patients with diabetes (Goraya et al., 2002). Due to an expected dramatic increase in the prevalence of type 2 diabetes worldwide, this finding is of enormous importance to public health (King et al., 1998).

Modern concepts of primary prevention incorporate an individualized approach to risk assessment. Along with an increasing emphasis on a number of "new" CHD risk factors, including genetic and biological markers, increasing attention is being paid to the development of risk scores for the identification of populations at risk. Accordingly, tables and simplified algorithms, derived mostly from large clinical trials, allow the calculation of intermediate and long-term ("life-time") probabilities of cardiac events. Within this concept of primary prevention the goal is to identify subjects whose risk is as high as that of patients with clinically established CVD disease, assuming that the former individuals can then be treated efficiently. Thus, the strict distinction between primary and secondary prevention is blurred.

Risk Factors for CHD

Numerous proximal and distal risk factors that predispose to CVD have been identified. For some of these it has been shown that successful modification or alteration can result in a significant decrease of morbidity and mortality. Key observations that led to the identification of classical risk factors have come from international comparisons, such as the Seven Countries Study (Jacobs et al., 1999) performed within the US, various nations in Europe, and Japan, and the Monitoring Trends and Determinants in CVD Disease (MONICA) study (Kuulasmaa et al., 2000) performed in Europe, North America, Australia and Asia. These studies showed that differences in disease rates among these countries were directly related to blood pressure (BP), eating patterns, blood cholesterol and cigarette smoking. Convergent evidence has been provided that there are a number of proximal CHD-related and mostly behavioral risk factors with a core relevance for CVD in western industrialized countries, namely loss of or reduced physical activity, a sedentary lifestyle, malnutrition, cigarette smoking, high blood pressure and high blood cholesterol. Further research has demonstrated multiple and complex interactions between risk factors, such as the combination of inactivity on the one hand and a surplus of calories on the other hand. This combination contributes to abnormal blood lipids and

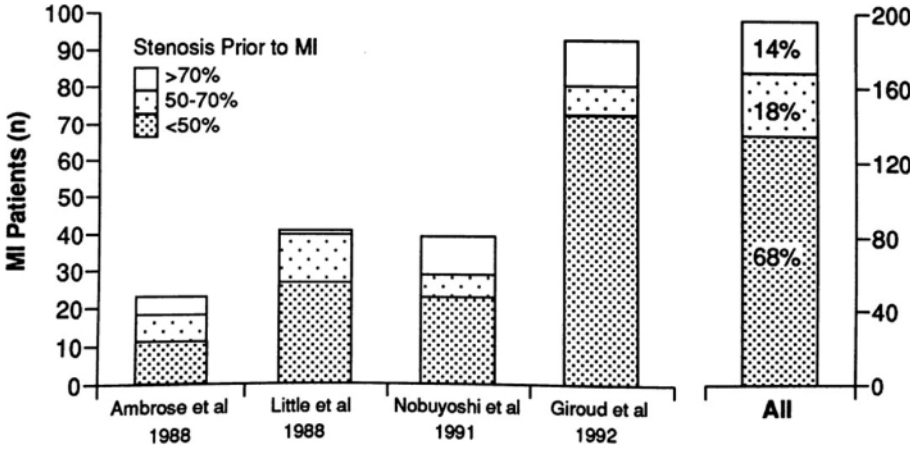

Fig. **1** Stenosis severity and associated risk of coronary occlusion and myocardial infarction as evaluated by serial angiographic examination (adapted from E. Falk, 1995).

elevated blood pressure and results in widespread obesity, diabetes and excessive risk of CVD (Lopez and Murray, 1998).

Classical and conditional risk factors

The classical CHD risk factors include elevated blood lipids, elevated blood pressure, smoking and diabetes. Because of their well-established causal role in the etiology of CHD they are called 'causal' risk factors (Grundy, 1999). Despite the finding that CHD, ultimately, can be found in more than 90% of patients with these risk factors (Stamler et al., 1999; Wilson et al., 1998), the predictive value of each single risk factor is low, since only a small number of patients in western countries (about 5%) are without any risk factor (Stamler et al., 1999). In fact, only 50% to 80% of the CHD cases can be explained by these "causal" risk factors (Grundy et al., 2000; Wilson et al., 1998; Khot et al., 2003). Therefore, the search has been expanded to other types of risk factors for CHD, namely conditional risk factors and predisposing risk factors. The conditional risk factors – elevated blood levels for triglycerides, lipoprotein(a), homocysteine, fibrinogen and others – reveal an increased risk for CHD in the presence of other risk or predisposing factors; however, their causal role as CHD risk factors has not yet been established. Together with the predisposing risk factors such as obesity, physical inactivity, positive family history for CHD, male sex, insulin resistance, and socioeconomic variables, these conditional factors contribute to the onset and the complexity of the disease. Age as an independent risk factor is difficult to classify since with all risk assessments it is ultimately the duration of exposure that is being measured; therefore, age contributes only vaguely to the risk estimation (Grundy et al., 1999).

Table **1** Odds ratios for cardiovascular event rates in angiographic trials of LDL-lowering therapy (adapted from NCEP ATP III Guidelines, 2002)

Trials	***Cardiovascular Event Rates Odds Ratio (Number < 1 means fewer events on therapy)***
Statins	0.67 (0.57, 0.80)* ($p < 0.0001$)[1] ($p = 0.012$)[2]
Sequestrants	0.41 (0.17, 1.00)* NS[1] NS[2]
Lifestyle	0.57 (0.23, 1.46)* NS[1] NS[2]
Combination Therapy	0.54 (0.36, 0.81)* ($p = 0.0031$)[1] ($p = 0.021$)[2]

* Confidence intervals; [1] Statistical significance compared to placebo; [2] Statistical significance compared to calcium channel blocker trials; NS = not significant

Smoking

Epidemiological data from the Seven Countries Study showed that smoking increases the risk for all-cause death (Jacobs et al., 1999). A Japanese study found a significant excess risk among current smokers (> 20 cigarettes/day) for total stroke, CHD, and total cardiovascular disease (Yamagishi et al., 2003). In a large hypertension treatment trial (HOT trial) smoking was associated with a high risk for all types of morbid and mortal events, and a particularly high risk for total mortality (Zanchetti et al., 2001). Smoking cessation has been shown to result in a reduction of cardiac event rates (Sato et al., 1992). However, a systematic review and meta-analysis of randomised controlled smoking cessation trials in workforces and in the primary care sector only observed small decreases of both total and CHD mortality. This can be attributed to fairly moderate smoking cessation success rates (net decrease rates of smoking prevalence 4.2%), and the fact that most studies relied entirely on self-report measures (Ebrahim, 1997).

Elevated blood cholesterol

Epidemiological investigations of human populations incriminate high levels of LDL cholesterol as being atherogenic. The Framingham Heart Study (Wilson et al., 1998), the Multiple Risk Factor Intervention Trial (MRFIT) (Stamler et al., 1986), and the Lipid Research Clinics (LRC) trial (LRC Program I, 1984; LRC Program II, 1984) found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new-onset CHD in men and women who were initially free of CHD. The same relation holds for recurrent coronary events in people with established CHD (Rossouw et al., 1990; Pekkanen et al., 1990; Wong et al., 1991). These findings have been confirmed by clinical endpoint trials with reductions of clinical events by diet, lifestyle changes, and lipid-lowering drug treatment (Tables **1** and **2**) (NCEP ATP III, 2002).

Recently the results of the ASCOT-LLA study, which investigated the use of a lipid-lowering statin in hypertensive patients and only normal to mildly elevated lipid levels, were published (Sever et al., 2003). This trial had to be stopped prematurely after 3.3 years of follow-up due to an overwhelming treatment benefit with reduction of the primary endpoint of non-fatal myocardial infarction and fatal CHD.

However, despite evidence from clinical trials, the implementation of guidelines for prevention of CHD is far from optimal. A retrospective analysis of data from a German secondary prevention trial in 2856 CHD patients requiring lipid-lowering medication showed that only 6.2% of the patients met the target LDL-C level of < 115 mg/dL (ESC guidelines) and only 2.7% met the target LDL-C level of < 100 mg/dL (NCEP guidelines) at baseline due to a low overall lipid-lowering treatment rate of only 34.5% and inadequate dosing (Ruof et al., 2002).

Hypertension

The association of elevated blood pressure with cardiovascular morbidity and mortality among middle-aged and older individuals is well documented by data from epidemiological studies,

Table **2** CHD risk reduction in cholesterol trial subgroups (adapted from: NCEP ATP III Guidelines, 2002)

Intervention	*No. trials*	*No. treated*	*Person years*	*Mean cholesterol reduction (%)*	*CHD Incidence (% change)*	*CHD Mortality (% change)*
Sequestrants	3	1992	14491	9	**–21**	–32
Diet	6	1200	6356	11	**–24**	–21
Statins	12	17405	89123	20	**–30**	**–29**

Not included among these clinical trials are those employing nitrates, nicotinic acid and hormones. The major actions of fibrates and nicotinic acid are on triglyceride and HDL, whereas hormone trials have effects beyond serum lipids.

such as the Framingham study (Sytkowski et al., 1996) or the Seven Countries study (van den Hoogen et al., 2000). Meta analyses from clinical trials confirmed this finding. Antihypertensive therapy was associated with reductions in the incidence of stroke (30–39%), and reductions in the incidence of CHD and major cardiovascular events (risk reduction 20–28%). However, only a limited number of placebo-controlled trials are available, showing a significant reduction of cardiovascular and total mortality (for example the STOP or the HOPE study) (Neal et al., 2000; Lewington et al., 2002).

The concomitant manifestation of hypertension and concomitant diabetes deserves special attention. A re-analysis of data from prospective antihypertensive trials of more than 12 months duration (Syst-Eur, Syst-Chin, SHEP and HOT) revealed an approximately doubled risk of cardiovascular events in hypertensive patients with coexisting diabetes (Messerli et al., 2001).

Obesity and the metabolic syndrome

Obesity by itself plays a key role in the development of insulin resistance. Lack of physical activity and overeating lead to insulin resistance by a secretion of factors by the expanded adipose mass, in particular the visceral compartment. In addition, the lack of exercise prevents the adequate utilization of calories and reduces the insulin sensitivity of skeletal muscle. Increased adiposity, especially in the visceral compartment, leads to the well-known constellation of cardiovascular risk factors, termed the metabolic syndrome (Goldstein, 2002), that shows increasing prevalence rates throughout Europe and North America (Ginsberg and Stalenhoef, 2003).

The metabolic syndrome describes a combination of overweight, insulin resistance, elevated blood pressure, and lipid disorders. According to the US-American lipid guidelines (NCEP ATP III, 2002), the diagnosis of metabolic syndrome is made if at least three of the following five factors are present: abdominal obesity, elevated triglycerides, reduced HDL levels, elevated blood pressure and elevated fasting glucose.

The predominant importance of diabetes

From the Framingham study (Kannel and MC Gee, 1979) or the MRFIT trial (Stamler et al., 1993), we now know that diabetes by itself is associated with a marked increase in the risk of CHD by a factor of two or four (Goraya et al., 2002). Diabetes mellitus increases the rates of peripheral artery disease 2- to 4-fold (Newman et al., 1993) and the frequency of stroke 3- to 10-fold (Stamler et al., 1993; Beckman et al., 2002). Thus elevated blood glucose is regarded as an independent risk factor for CVD. The risk increases with the level of glucose. The absolute prevalence of established CVD at diagnosis of type 2 diabetes ranges from 8 to 23 percent (depending on the presence of other CVD risk factors). At least 14 prospective cohort studies have found that the risk for CVD events in diabetic men is about twice that in non-diabetic men, even after adjusting for age, hypertension, dyslipidemia, and smoking. For women, the adjusted CVD risk among diabetic individuals is elevated as much as fourfold compared with non-diabetic women. In the UKPDS cohort of diabetic patients undergoing conventional treatment, there were 17 events of myocardial infarction (MI), 5 events of stroke, and 12 events of diabetes-related deaths, respectively, per 1000 patient years (UKPDS 33, 1998).

The underlying reason for enhanced atherosclerosis in diabetic patients seems to be the abnormal metabolic state characterized mainly by hyperglycemia, dyslipidemia (increased levels of LDL and ApoB) and insulin resistance, which causes arterial dysfunction. Insulin, with its anti-inflammatory and vasodilatory functions, which are lost or even reversed in the setting of insulin resistance (Dandona et al., 2001), plays a central role in this process. In diabetic patients the function of multiple cell types, including endothelium, smooth muscle cells and platelets, is altered; in addition, diabetic patients exhibit abnormal blood coagulation. All these factors render arteries more susceptible to atherosclerosis (Beckman et al., 2002; Reusch, 2002).

Recently, cardiovascular complications associated with type 2 diabetes mellitus have attracted dramatically increased attention. A Finnish population-based registry study compared the seven-year incidence of myocardial infarction (fatal and non-fatal) among 1373 non-diabetic subjects with the incidence among 1059 diabetic subjects. This study revealed that diabetic patients without previous myocardial infarction had the same risk of myocardial infarction as non-diabetic patients with previous myocardial infarction (Haffner et al., 1998). Despite some statistical drawbacks (Evans et al., 2002), the relationship between type 2 diabetes and a marked increase in the risk of coronary artery disease is well established, for example by the population-based Health Professionals Follow-up Study (Cho et al., 2002); the 20-year follow-up Nurses' Health Study (Hu et al., 2002) and trials, which found abnormal glucose metabolism in about one-third of patients with myocardial infarction and no history of diabetes at admission (defined by impaired glucose tolerance [IGT] and undiagnosed diabetes [Norhammar et al., 2002]). Even hyperinsulinemia as a precursor state of IGT and

Table **3** Randomized, controlled trials of tight glycemic control (adapted from Harris R et al., 2003)

Study, year (Reference)	*Length of study, years*	*Groups (patients)*	*Myocardial infarction*	*Stroke*	*All-cause mortality*
UGDP (Knatterud et al., 1971, 1978)	8.75	Placebo (n = 204) Insulin variable (n = 198)	20% vs. 17.6% for significant ECG abnormality (NS)	NR	26.3% vs. 24.0% (NS)
UKPDS 33, 1998	10	Conventional therapy (n = 1138) Intensive therapy (n = 2729)	16.3% vs. 14.2% ($p = 0.052$)	4.8% vs. 5.4% ($p > 0.2$)	18.7% vs. 17.9% ($p > 0.2$)
UKPDS 34, 1998	10.7	Conventional therapy, primarily diet (n = 411) Intensive therapy with metformin (n = 342)	17.8% vs. 11.4% ($p = 0.001$)	5.6% vs. 3.5% ($p = 0.13$)	21.7% vs. 14.6% ($p = 0.011$)
Kumamoto (Ohkubo et al., 1995; Shichiri et al., 2000)	8	Conventional therapy (n = 50) Intensive therapy (n = 52)	1.3 events/100 person years vs. 0.6 events/100 person years for major CVD event (NS)		NR
VA CSDM (Abraira et al., 1997; Emanuele et al., 1996; Abraira et al., 1995; Azad et al., 1999; Levin et al., 2000)	2.25	Standard therapy (n = 78) Intensive therapy (n = 75)	5.1% vs. 6.7% (NS)	2.6% vs. 6.7% (NS)	5.1% vs. 6.7% (NS)
Steno 2 (Gaede et al., 1999)	3.8	Standard therapy (n = 80) Intensive therapy (n = 80)	5.1% vs. 5.2% for non-fatal MI (NS)	10.2% vs. 1.3% for non-fatal stroke (NS)	2.6% vs. 5.2% (NS)

diabetes seems to be predictive for increased cardiovascular risk. This finding was shown in numerous prospective epidemiological studies among non-diabetic men and a case control study among non-diabetic women with postprandial hyperinsulinemia (Pyorala et al., 1998; Lempiainen et al., 1999; Baltali et al., 2003).

It is noteworthy though, that the US Preventive Services Task Force (USPSTF) recently highlighted that these are no randomized, controlled trials studying screening strategies for diabetes (Harris et al., 2003). This is a significant lack, given the evidence that feasible screening tests can detect diabetes during a preclinical phase (e.g., impaired glucose tolerance test [IGT] and impaired fasting glucose [IFG]) (Vinicor et al., 2003). Furthermore, over the 10 to 15 years after clinical diagnosis of diabetes, aggressive control of hypertension, lipid therapy and aspirin use has been shown to reduce cardiovascular events to a greater degree than did tight glycemic control (Table **3**). The impact of starting these therapies earlier in the preclinical phase of diabetes remains unclear.

Trends in obesity and diabetes

Obviously, obesity and diabetes have a major negative impact on the health status of the population and the pathogenesis of many diseases. However, in many countries rates for both disorders show further increases. Within the US the prevalence of obesity increased by 61.8% in men and 50.9% in women between the National Health and Nutrition Examination Surveys (NHANES) II (1976 – 1980) and III (1988 – 1991) (Flegal et al., 1998). Similar trends have been shown for some European countries (Inelmen et al., 2003; Galobardes et al., 2003).

The prevalence of type 2 diabetes is expected to increase considerably within the next two decades (Fig. **2**). Data from the global database collected by WHO, linked with demographic estimates and projections issued by the United Nations, revealed prevalence estimates of diabetes in adults worldwide to be 4.0% in 1995 and to rise to 5.4% by the year 2025. The estimates are higher in developed than in developing countries. Worldwide, the number of adults with diabetes is estimated to rise from 135 million in 1995 to 300 million in 2025, with a major part of this numerical increase occurring in developing countries (King et al., 1998).

Within the US alone, among individuals aged 40 – 74, the prevalence increased from 8.9% for the period 1976 – 80, to 12.3% for the period 1988 – 1994 (Harris et al., 1998). The current prevalence of obesity in the United States is likely to be even higher due to the increasing prevalence of obesity. Based on combined data from trends in diabetes prevalence rates from the National Health Interview Survey and the US Census Bureau population demographic projections, the number of Americans with diagnosed diabetes is projected to increase by 165%, from 11 million in 2000 (prevalence of 4.0%) to 29 million in 2050 (prevalence of 7.2%) (Boyle et al., 2001). A recent report from Dunston and colleagues showed more than a doubling of the prevalence of diabetes in Australia within two decades (Dunstan et al., 2002).

Risk Stratification

Modern concepts of primary prevention use an individualized approach for risk assessment. Along with an increasing emphasis on a number of "new" CHD risk factors, including genetic and biological markers, growing attention has been paid to the devel-

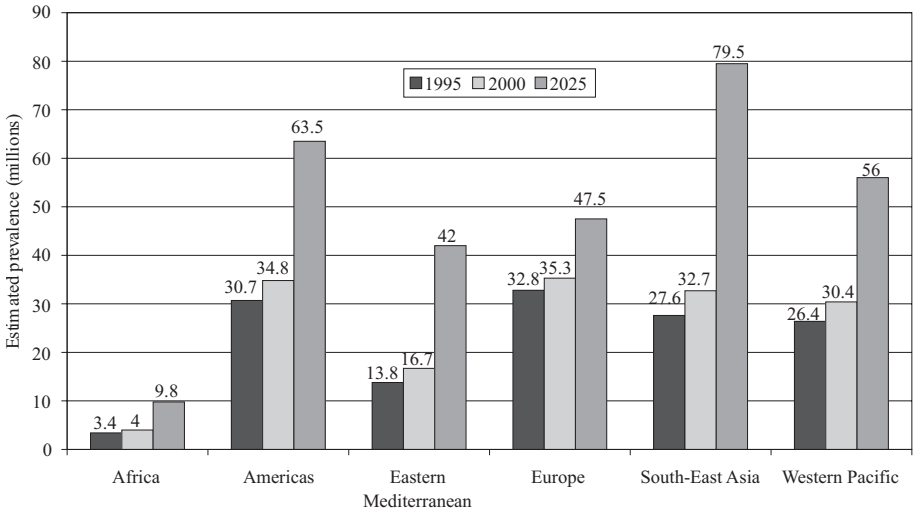

Fig. **2** Worldwide prevalence of type 2 diabetes mellitus. The prevalence of type 2 diabetes mellitus is expected to increase throughout the world in the coming years (adapted from: The World Health Report, 1997 and King et al., 1998).

opment of risk scores for the identification of populations at risk. Actual guidelines emphasize the evaluation of the overall risk with an approach that is as comprehensive as possible.

For risk categorization of individuals, several guidelines and scores have been developed; all of them refer to data of the Framingham study. The current US-American National Cholesterol Education Program (NCEP ATP III) is using categorical risk factors as well as the 10-year risk calculation derived from the Framingham group to define goals in the treatment of elevated lipid levels. Categorical major risk factors include smoking, hypertension, low HDL cholesterol, family history of CHD, and age. In addition, so called "CHD risk equivalents" are defined; these risk equivalents are atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm and symptomatic carotid artery disease), diabetes and multiple risk factors that confer a 10-year risk for CHD > 20% (NCEP ATP III, 2002).

The guidelines from the Framingham group (Wilson et al., 1998) as well as from European groups (Wood et al., 1998) are less categorical than the NCEP ATP III Guidelines. The Prospective Cardiovascular Münster (PROCAM) study is a risk stratification program (Assmann and Schulte, 1988; Assmann et al., 2002), which builds on the following 8 independent risk variables, ranked in order of importance: age, LDL cholesterol, smoking, HDL cholesterol, systolic blood pressure, family history of premature myocardial infarction, diabetes mellitus, and triglycerides. A certain limitation of all these guidelines and risk stratification programs is that they are validated only for in part highly selected populations. The Framingham study is based on clinical data from 5209 individuals (55% were female) from Framingham, USA, and the PROCAM study is based on the data of 5389 men from local companies and government authorities around Münster, Germany. Besides the fact that some of these data were collected many years ago, this also raises concerns regarding the applicability of these programs to other populations. A different approach has been undertaken by the SCORE project group, who recently published a new European risk stratification program for CVD in Europe. This score is based on a pool of datasets from 12 European cohort studies, covering 205178 persons, including 3968 participants from the MONICA Augsburg cohort study (Conroy et al., 2003).

A different method to predict cardiovascular health outcomes has been introduced by the MacArthur studies of successful aging. These studies promote the concept of "allostatic load" (AL) as a new conceptualization of the cumulative biological burden exacted on the body through attempts to adapt to life's demands. This model uses assessments of 10 biological parameters that reflect functioning of the hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system, cardiovascular system, and metabolic processes. The results of this 7-year survey of 1189 men and women aged 70 – 79 showed that AL was a better predictor of mortality than the metabolic syndrome. However, due to the small number of cases the results for incident CVD achieved only marginal significance (Seeman et al., 2001).

A more comprehensive approach for individualized risk assessment requires permanent development of its diagnostic tools. There are a number of "new" promising systemic risk markers, which could contribute tremendously to the current risk assessment procedures.

Systemic Risk Markers

The process of atherosclerosis is characterized by a complex activation of numerous pathways and involves different kinds of cells, e.g., monocytes, platelets and lymphocytes as well as many different cytokines (e.g., IL-1, IL-6, TNF-Alpha), adhesion-molecules (e.g., ICAM-1, VCAM-1, E-selectin) and various acute-phase proteins. In recent years there has emerged an abundance of evidence that inflammatory mechanisms play a central role in atherogenesis and its clinical sequelae. Pathophysiologically, the classical risk factors (e.g., smoking, obesity and diabetes), which act as pro-inflammatory stimuli, trigger the generation of cytokines; this generation by itself induces the production in the liver of acute-phase proteins such as hs-CRP or fibrinogen. In contrast to hs-CRP, fibrinogen is directly involved in the coagulation process. It affects hemostasis, increases blood viscosity and leuko-

cyte adhesion and is up-regulated by a number of cytokines (Lind, 2003).

Numerous proteins and other mediators are released from endothelial cells and other cells, contributing to the atherogenic process (Ross, 1999). These findings from basic atherosclerosis research have been supported by results from prospective clinical trials among patients with atherosclerosis, indicating a strong and independent association between elevated concentrations of particular markers of systemic inflammation and the numbers of cardiovascular events in apparently healthy men and women as well as in patients with stable angina, with unstable angina, and after coronary events (Ridker et al., 1997; Ridker et al., 1998; Haverkate et al., 1997; Biasucci et al., 1999). Certain markers of systemic inflammation are powerful predictors of cardiovascular events, such as fibrinogen, high-sensitivity C-reactive protein (hs-CRP), and cytokines. In addition, several cardiovascular risk factors (e.g., smoking, obesity, diabetes) are associated with high levels of fibrinogen and hs-CRP (Rosenson and Koenig, 2003). Moreover, CRP is elevated in patients with metabolic syndrome (Froehlich et al., 2000). The IRAS study showed in non-diabetic patients that elevated levels of hs-CRP and fibrinogen are associated with insulin resistance and elevated fasting insulin, however the association for both was relatively stronger with CRP than with fibrinogen levels (Festa et al., 2000). This clearly supports the hypothesis of a common cause of both diseases, diabetes and atherosclerosis. The association of later cardiovascular events and elevated levels of fibrinogen, hs-CRP, and leukocytes has been investigated in numerous case-control studies as well as in prospective studies, with consistent results for hs-CRP; however only a limited number of case-control studies evaluating leukocyte count or fibrinogen as predictors in unstable angina have been reported with some contradictory results (Lind, 2003).

The question arises, which marker is the best indicator to predict cardiovascular events. CRP appears to have several advantages over fibrinogen. In contrast to the coagulation proteins (e.g. fibrinogen) and most other major acute-phase proteins, the clearance rate of CRP is not altered by inflammatory disorders, so that plasma concentrations of CRP are directly related to the rate of synthesis. In prospective studies of fibrinogen and CVD there are only small absolute differences in fibrinogen concentrations between disease and disease-free groups, which is a concern because of measurement errors in functional assays estimating the fibrinogen concentration by the thrombin clotting time. The different measurement methods for fibrinogen concentration (Clauss method and immunoassay) seem to differ regarding their predictive potential. Fibrinogen levels determined by immunoassay may have a stronger association with CVD than those obtained by the Clauss method (Stec et al., 2000). In contrast to this, the established WHO International Reference Standard for CRP permits precise assays with one method. Besides that, other limitations are encountered in the routine measurement of fibrinogen such as preanalytic sources of error from prolonged tourniquet application and delayed sample processing (Rosenson et al. 1998). Overall, it seems that hs-CRP measurements are more reproducible than plasma fibrinogen measurements and potentially less influenced by preanalytic sources of method error (Rosenson and Koenig, 2003).

Recent trials have suggested that hs-CRP may not only be a marker of the atherogenic situation, but might be directly involved in the pathogenesis of atherosclerosis itself at the endothelial level (Pasceri et al., 2000) by inducing MCP-1 production (Pasceri et al., 2001). Hs-CRP may also act indirectly by promoting the uptake of oxidized low density lipoprotein by macrophages (Zwaka et al., 2001); inducing the expression of adhesion molecules (E-selectin, VCAM-1, ICAM-1) in endothelial cells (Pasceri et al., 2000); decoying monocytes from the blood (Torzewski et al., 2000); promoting thrombus generation via stimulation of tissue factor (TF) in monocytes (Cermak et al., 1993); and possibly by the activation of complement (Buono et al., 2002).

To conclude, there are some advantages of using measurements of hs-CRP levels instead of fibrinogen levels in daily routine for the prediction of cardiovascular risk. Thus, presently, CRP, described the first time by Tillet and Francis (Tillet and Francis, 1930), seems to be the best-studied and most promising marker of inflammation correlated with atherosclerotic vascular disease (Van Wissen et al., 2002) and appears to be the inflammatory-marker of choice to predict vascular risk.

High-sensitivity C-reactive-protein (hs-CRP)

Since hs-CRP by itself seems to be an atherogenic factor, the key question now is whether reduction of hs-CRP reduces cardiovascular risk. Behavioral influences such as weight reduction (Tchernof et al., 2002), physical activity, cardio-respiratory fitness (LaMonte et al., 2002) and the modest consumption of alcohol (Imhof et al., 2001) are known to reduce hs-CRP levels; such reductions could contribute to the preventive effect of these measures. Regarding drug treatment, the most comprehensive set of data exists for the HMG-CoA reductase inhibitors, the statins. Data from the post-hoc analysis of the AFCAPS/TexCAPS studies (Ridker et al., 2001), the CARE-study (Jialal et al., 2001), the PRINCE study (Albert et al., 2001) and the ASAP study (Van Wissen et al., 2002) showed that statins reduced hs-CRP levels for approximately 15 – 25 % of subjects, independently of the extent of the low density lipoprotein (LDL). A recent evaluation of 27,939 apparently healthy American women, followed for a mean of eight years, suggested that the C-reactive protein level is an even stronger predictor of cardiovascular events than the LDL cholesterol level and that it adds prognostic information to that conveyed by the Framingham risk score (Ridker et al., 2002).

CRP, the classical acute-phase protein, is synthesized in the liver. Recent reports suggest that CRP also might be synthesized within the atherosclerotic plaque (Yasojima et al., 2001). CRP is a highly sensitive marker of inflammation and increases 1000-fold within 24 – 48 hours after acute injury, infection or other inflammatory stimuli (Gabay and Kushner, 1999). Its mean plasma elimination half-life is short (19 hours), but stable under all conditions, meaning that the synthesis rate in the liver is the only determinant of its plasma concentration. Robust assays for CRP measurement have been established (Hutchinson et al., 2000; Rifai et al., 1999). Since 1996 at least 15 published, epidemiological, longitudinal studies have indicated a positive correlation between slightly increased levels of CRP and the incidence of acute myocardial infarction. A recent meta-analysis of 11 of these studies found that patients with CRP levels within the upper ter-

tile (CRP > 3 mg/L) had a more than 2-fold increased risk for future coronary events, compared with patients from the lowest tertile (CRP < 1 mg/L; relative risk [RR] 2.0; 95%-confidence-interval [CI] 1.6 to 2.5) (Danesh et al., 2000).

A preliminary answer to the question of whether treatment of elevated hs-CRP levels has therapeutic implications has been given from a study of 388 consecutive patients undergoing coronary stent implantation. Here statin therapy significantly attenuated the increased risk for major adverse cardiac events (MACE) in patients with elevated levels of hs-CRP (> 0.6 mg/dl) (Walter et al., 2001).

Other risk markers

Besides C-reactive protein and systemic inflammation, other factors (coagulation factors, oxidative stress, ventricular hypertrophy and various dyslipidemia subtypes) have been identified as potential contributors for CVD (Grundy et al., 1999; Harjai, 1999). An increase in total plasma homocysteine (tHcy) is one of these new factors, as shown by observational studies (Welch and Loscalzo, 1998; Bostom et al., 1999; Graham et al., 1997). An elevated level of homocysteine was first suspected to be associated with atherogenic and thrombogenic tendencies in patients with classic homocysteinuria (Sebastio et al., 1995; Mudd et al., 1985). Data from a meta-analysis suggest that lowering homocysteine concentrations by 3 µmol/l from current levels by increasing folic acid intake would reduce the risk of ischemic heart disease by 16%, deep vein thrombosis by 25% and stroke by 24% (Wald et al., 2002). Despite a huge body of epidemiological, experimental and clinical data it remains to be proven that an elevated level of tHcy is an independent risk factor for CVD. There are several ongoing, controlled clinical trials, which will try to demonstrate that a reduction in serum tHcy levels by vitamin supplementation will reduce cardiovascular morbidity and mortality (Eikelboom et al., 1999). Interestingly, the association between elevated levels of tHcy and the cardiovascular outcome in diabetes patients (all types) was stronger than in non-diabetic individuals for all types of studies, as shown in a large MEDLINE database search (Audelin and Genest, 2001).

Another challenging factor is the soluble CD40 ligand, which is expressed in many cell-types and is actively released from platelets after their stimulation. It is a pro-inflammatory factor that promotes coagulation. There is growing evidence that this factor plays an important role in the pathophysiology of acute coronary syndromes, with evidence for a clear correlation between elevated levels of the soluble CD40 ligand and an increased risk of coronary events in patients with unstable coronary artery disease (Heeschen et al., 2003). In another study, elevated levels of CD40 ligand were found in patients with familial hypercholesterolemia (FH). Treatment of these patients with a statin led to a marked decrease of the elevated CD40 levels; the decrease was independent of the degree of reduction in cholesterol levels (Semb et al., 2003).

Other developments are upcoming changes in the appraisal of well-known risk indicators such as apolipoprotein B and apolipoprotein A-1. In the large Apolipoprotein-Related Mortality Risk Study (AMORIS) the strongest univariate predictor of cardiovascular risk was the apolipoprotein B/apolipoprotein A-1 ratio. Four large prospective studies have shown that apolipoprotein B is superior to total cholesterol or LDL in the prediction of cardiovascular risk and that the ratio of apolipoprotein B/apolipoprotein A-1 is superior to total cholesterol/HDL cholesterol as an overall index of risk (Sniderman et al., 2003).

There is accumulating evidence that low levels of insulin-like growth factor (IGF-I) play a pathogenetic role in the development of CVD and type 2 diabetes. IGF-I, a peptide with structural and functional homologies with insulin, typically shows low levels in diabetes type 2, and may play a role in the regulation of cardiovascular function and development of myocardial infarction in patients without type 2 diabetes. In the Rotterdam Study, the genetic polymorphism of the IGF-I gene and the relationship of the polymorphism with type 2 diabetes and myocardial infarction were examined. In noncarriers of the suggested wild-type allele (12% of the population), an increased relative risk for type 2 diabetes and for myocardial infarction was found, suggesting that a genetically determined exposure to relatively low IGF-I levels is associated with an increased risk for type 2 diabetes and myocardial infarction (Vaessen et al., 2001).

In the future, complex genetic assays might facilitate insight into the individual cardiovascular risk profile and provide better prophylactic and therapeutic targets; until then, the use of individual risk-stratification procedures based on the summing and weighing of all the known different markers and factors of risk will be the only way to explore individual cardiovascular risk and optimize intervention efforts.

Strategies for Improving Public Health

Whereas the incidence of CVD is rapidly increasing, not only in Western countries but also in other regions such as the Western Pacific and Asia, most of these diseases still remain undertreated. Their economic burden is huge and still increasing tremendously, generating a clear need for prevention, early detection and treatment of these conditions. Assuming that sedentary behavior increases the risk of CVD 1.9-fold, $ 6.4 billion could be saved if, for example, all Americans began to walk regularly (Fletcher, 2002). The question is raised as to whether a society can afford the costs for prevention. (The answer to that question might be influenced by cost-benefit analysis, which is the most often used approach for economic evaluation of differing medical or health care strategies.) These rising costs are pressuring purchasers of healthcare to ask more frequently (1) whether new therapeutic methods actually work in broader populations as compared to the target populations of randomized clinical trials, and (2) whether these treatments provide benefits that are worth their additional costs and are considered important by physicians and patients. Risk stratification to address the target therapy in order to limit health care costs is needed. Whereas methods of risk stratification in patients with unstable coronary syndromes are widely used (e.g., TIMI risk score [Antman et al., 2000], TIMI STEMI risk score [Morrow et al., 2000], GUSTO score [Califf et al., 1997] and the PURSUIT score [Boersma et al., 2000]), a broadly accepted and used comprehensive method for risk stratification within the primary care sector is still missing.

Identification of risk factors with subsequent follow-up and treatment of populations at risk is one important approach to improve public health. An impressive example of a targeted approach was the recently published Steno-2 Study of patients with diabetes type 2. Here a targeted, intensified, multi-factorial intervention yielded major improvements compared to a conventional treatment of modifiable risk factors for cardiovascular outcomes (Gaede et al., 2003).

The identification of proximal causes of CHD – major CHD risk factors such as high blood cholesterol, high blood pressure, cigarette smoking and physical inactivity – which satisfy public health criteria explain at least 75% of new cases. The search for "new" CHD risk factors such as thrombotic factors, inflammation factors, homocysteine levels, infectious agents, estrogen deficiency, early life exposure and prenatal factors, genetic influences and the role of the psychosocial environment continues. There may be some advantages of the "new factors" such as clear cutoff points or simplicity of measurements, but the importance of these factors for public health in comparison to the established factors, requires further investigation. Thus research into unexplained variations in the occurrence of CHD, into life course influences and socio-economic inequalities may provide additional leads. Of special interest is research on the social and economic determinants of CHD, prevention policies, and program effectiveness. The feasibility and effectiveness of population-wide prevention provides another possibility for increasing public health (Beaglehole et al., 2002).

Another approach is given by non-invasive imaging techniques of the atherosclerotic plaque itself, especially of the disruption-prone plaque. There are different techniques available such as Electron Beam CT (EBCT), Multidetector-Row CT (MDCT) and Magnetic Resonance Imaging (MRI), which compete for temporal and spatial resolution as determinants of the imaging quality (Fayad et al., 2002). The relevance of these techniques for cardiovascular risk prediction is currently under investigation.

Despite these stratification strategies the enormous economic burden and dramatic increase of CVD require a broader use of primary prevention, including strategies that address proper exercise and diet, focusing on early school years.

The Situation Within the Primary Care Sector

The primary care sector holds a special responsibility for the detection and treatment of CVD, as well as for prevention and delay of concomitant and related subsequent diseases. Despite the presence of evidence-based guidelines remarkable quality problems persist. In particular, CVD-related primary and secondary lifestyle-factor prevention is rarely practiced, presumably due to suboptimal implementation, time and financial barriers, and poor compliance on the patients' side.

Studies and their deficits

Only a few studies are available that recognize and take into account the extent, complexity and critical importance of the overall high risk constellations for CVD found in primary care and routine care in general. Most of these studies are clinical studies that are based on selected patient groups (e.g., UKPDS study [UKPDS 38, 1998]).

Similarly, the recommendations from guidelines and reviews for the diagnosis and treatment of these CVD are based on the results of controlled clinical trials. As mentioned above, these results have been obtained from selected patient groups (e.g., groups that excluded multi-morbid and co-medicated patients, very old patients and [in practice] women of child-bearing age); in addition, the research was performed under highly standardized, artificial conditions. Therefore, the results cannot be extrapolated directly to the situation in primary care. As sound data from the primary care sector is lacking so far, attention must be drawn to the danger that the knowledge and conclusions obtained from these selected patient groups might be of limited relevance for routine care and the general practitioner sector.

Although in recent years these problems have been increasingly discussed, investigated and confirmed on the basis of clinico-epidemiological studies (cf. Concerted Action in the Health Service 2002, MONICA [Bothig, 1998; Tunstall-Pedoe et al., 1994], German Cardiovascular Study [Helmert and Shea, 1997], Federal Health Authority Survey [Hoffmeister et al., 1994], Euro Heart Survey with its projects EUROASPIRE I and II [EUROASPIRE II Study Group, 2001], Euro Heart Survey ACS [Hasdai et al., 2002], Euro-HF [Cleland et al., 2000], GRACE [The GRACE Investigators, 2001], HYDRA [Wittchen et al., 2003 and PROCAM [Assmann and Schulte, 1988]), the studies so far have addressed only a few segments of the overall problem (selected groups of patients with coronary syndromes, data from selected centers or investigations of the general public). Furthermore, the research might be regarded as being out of date with regard to current care situations and structures, as well as treatment options. Moreover, the reports available so far are generally limited in their value with respect to the technical effort expended on investigation, as they seldom show a satisfactory representativeness – in spite of high numbers of cases – with respect to region, care sector, spectrum of diseases and care characteristics.

In view of the existing multiple therapeutic options, it can be seen on the basis of health care-oriented investigations that only a fraction of the existing therapeutic options are used optimally in routine care. Furthermore, it is apparent that the integration and patient-related fine-tuning of the therapeutic plan (disease management) are deficient, as recent care studies have shown (e.g., HYDRA [Sharma et al., 2003, 2004] and Concerted Action in the Health Service 2002).

Due to the complexity of the influencing factors to be considered (e.g., age, sex, disease stage, comorbidity pattern, current and previous interventions, start of initial therapy in primary medical or specialist sectors) on the one hand and outcome indicators of interest on the other hand (e.g., treatment success, costs, degree of care provision), such clinico-epidemiological studies require enormous numbers of cases in order to produce informative results on the basis of adequate statistical models.

The considerable additional expenditure of money needed for the measurement of clinico-chemical indicators represents a fur-

ther important challenge, which would explain the absence of comprehensive epidemiological studies of this problem.

Conclusion

A public health approach for CHD prevention and therapy is needed and may require public policy changes and aggressive marketing to the public. The need for such a concerted action is pressing, especially in light of the fact that most developed systems are currently facing restructuring, the introduction of disease management programs (DMPs), and the integration of new treatment methods and strategies. Such extensive measures require rational planning data. These data ideally should simultaneously take into account, in the context of coordinated and rational improvements in the quality of care, various data and planning perspectives: (a) the perspective of the patient and his or her individual illness, (b) the perspective of the immediate social environment (e.g., family), (c) the perspective of the care provider (e.g., doctors, care system) and (d) the structural properties and rules of the system.

Which data do we need?

We need actual data regarding prevalence, type and severity of manifest CVD and diabetes, associated subsequent diseases and high-risk constellations. We need to know about medical detection and diagnosis rates as well as diagnostic and therapeutic strategies, including the extent of their over-, under- and misuse; especially from the primary care sector. We need an assessment of the quality of treatment and the extent of adherence to current diagnostic and treatment guidelines. We need to know about the existence of predictors (physicians, patients, system variables) for appropriate diagnosis and intervention rates. We need an assessment of the overall extent of medical care and how we could improve the quality of care. We would like to identify typical problems and care provision problems in selected high-risk groups of patients. In addition, we need to get actual data about the co-morbidity of depression and CVD as well as the co-morbidity of sexual disorders and CVD. We need to know more about the taking behaviors and treatment compliance of medically prescribed interventions. We also need a comprehensive dataset of laboratory markers that permit prediction of unfavorable courses and complications and, especially, markers that detect high-risk constellations.

The foregoing scenario requires an integrated investigation in the primary medical care sector on the basis of clinical epidemiological principles to define a comprehensive, overall characterization of CVD (with a focus on CHD) and diabetes. This need prompted us to design and launch a nationwide, epidemiological study in unselected, consecutive primary care attenders (general practice and internal medicine) in Germany. This study program includes several waves of investigation. First, practice data from the participating physicians are collected. Second, unselected patients complete a standardized self-report questionnaire followed by a standardized clinical doctor evaluation, including additional laboratory tests in a random subset of patients. The third step will be a 12-month follow-up. This study has been launched in September 2003, involving 3500 practices with over 80 000 patients. The complex design of this study as well as some baseline data will be published elsewhere. Preliminary results of the evaluation will be available in mid-2004.

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