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Individualized Cardiovascular Risk Assessment

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1. Introduction

Cardiovascular diseases (CVD) are the main cause of death and disease burden in Europe. 48% of all deaths are from CVD: 54% of deaths in women and 43% of death in men. CVD is the main cause of death for women in Europe and also for men except France, the Netherlands and Spain (Allender et al., 2009) (Figure l). Coronary heart disease (CHD) itself is the single most common cause of death in Europe, which is followed by stroke. Overall CVD is estimated to cost EU economy €192 billion a year (Allender et al., 2009).

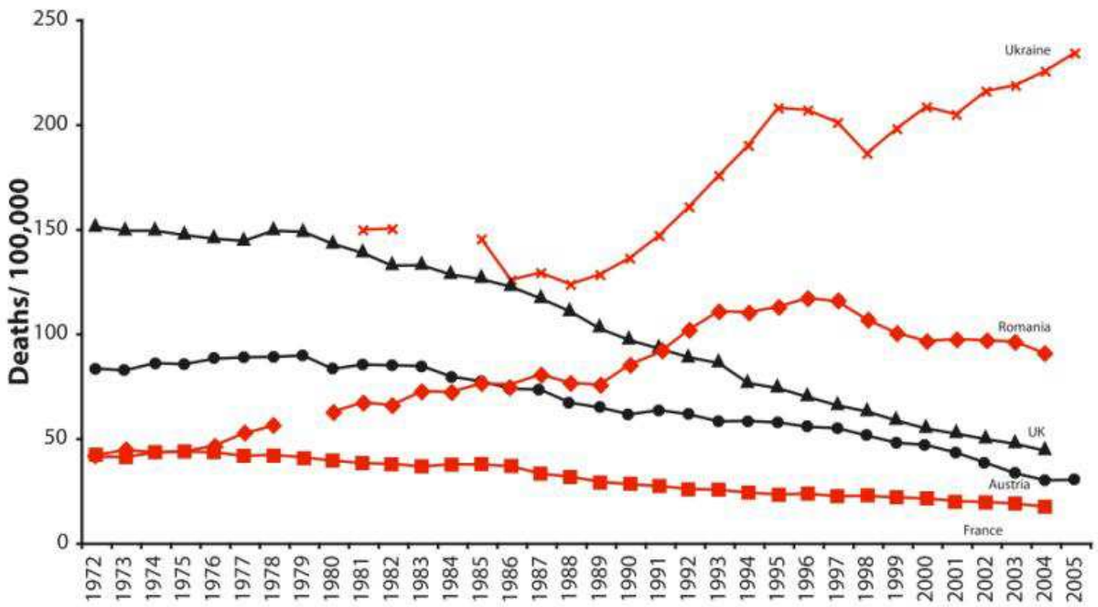

Fig. 1. Death rates from CHD, men aged under 65, 1972 to 2005, selected countries. European cardiovascular disease statistics 2008 edition (Allender et al., 2009)

Mortality rate from CHD in various countries underwent profound changes during the 20th century. While there is a trend to rapid fall in mortality rate from CHD over the past 30 years in higher-income countries, such as most Northern, Western and Southern Europe, the United States, Canada and parts of the Western Pacific, in regions with lower income,

including Central and Eastern Europe, mortality, incidence, and case fatality of CVD either not falling as fast or rising (Allender et al., 2009). Different therapeutic and preventive approaches including lifestyle changes may explain this state.

In Finland, where CHD mortality among Finnish men was the highest in the world in the late 1960s, over the 35-year period – as a result of the North Carelia Project – an 80% decline in coronary mortality in middle-aged men was observed. In this Finish model risk factor modifications (total cholesterol, blood pressure, smoking) explained a 60% reduction in CHD mortality, further 20% decline was a result of improved therapy (Vartainen et al., 2010). Similarly in Sweden, over the period of 4 decades risk factor modifications in 50-year-old men demonstrated a >50% decline in myocardial infarction (MI) rate (Wilhelmssen et al., 2008). An increased prevalence of obesity in both countries and also diabetes mellitus (DM) was observed in Swedish population over the observational period (Vartainen et al., 2010; Wilhelmssen et al., 2008), surprisingly with no influence on CVD outcome. This "obesity paradox" is probably caused by compensation of obesity associated risk with reduced overall risk due to higher rate of nonsmoking, normotension and normocholesterolaemia in population achieved by large community-based preventive and health promotion activities (Rosengren et al., 2009).

In the U.S. after peaking around 1968, over the period of 2 decades, the age-adjusted CHD death rate were cut in half (Ford et al., 2007). Approximately 44% of decline was attributed to reductions in major risk factors, including high total cholesterol, blood pressure, smoking, and physical inactivity (Hajjar & Kotchen, 2003; Johnson et al., 1993), although these reductions were partially offset by increases in the body-mass index (BMI) and the prevalence of DM (Harris et al., 1998; Hedley et al., 2004). Further 47% of this decrease was explained by evidence-based therapies including secondary preventive therapies after MI or revascularization, initial treatments for acute myocardial infarction (AMI) or unstable angina, treatments for heart failure, revascularization for chronic angina and other therapies. However, 9% of decline was unexplained (Ford et al., 2007). Similar conclusion was also found in analysis of the CHD mortality decline over the last 20-year period in UK (Unal et al., 2004). The WHO MONICA Project results (1980-1990) from 37 populations worldwide showed aorund 2/3 decline in CHD mortality by the decline in CHD incidence rates and the remaining 1/3 by the survival improvements due to better treatment (Tunstall-Pedoe et al., 1999).

Current statistical data over the past 3 decades clearly show the decline in incidence of CHD in patients aged<65 years in Europe. Alarmingly, among subjects who developed CHD <45 years, the incidence is unchanged, which may predict stagnation in CHD treatment and prevention in this population (Allender et al., 2009).

2. Active approach to the prevention of CVD: The European Heart Health Charter – The European perspective. America´s plan for better health and wellness. Action plan for non-communicable diseases

An active approach to the prevention of CHD in Europe was firstly declared in 1994 (Pyörälä et al., 1994), with the latest revision and extension to other atherosclerotic (AS) CVD in the „Fourth Task Force of the European guidelines on CVD prevention in clinical practice" (Graham et al., 2007). The current guidelines implement the previous initiatives of

major international organizations and declarations (the Osaka Declaration, 2001; the Luxembourg Declaration, 2005) regarding the necessity to achieve cardiovascular (CV) health. These guidelines do not serve as a rigid rule, they are always open for modification and should be interpreted in the clinician´s judgement with regard to national guidelines and regional differences. This document underlines the importance of preventive strategies, because: CVD mortality, morbidity, and disability is still high, their contribution to the costs of health care is escalating as well as there is increasing evidence when and how to effectively reduce CVD mortality and morbidity.

Documented secular changes in CV risk factors in high-income countries (Ford et al., 2007; O´Flaherty et al., 2008; Vartainen et al., 2010; Wilhelmsen et al., 2008) and their positive influence on CHD mortality clearly demonstrate the crucial role of risk factor modification in CV prevention. The multinational (52 countries) INTERHEART study identified the 9 major modifiable CHD risk factors associated with MI. The raised apolipoprotein B/apolipoprotein A-I ratio (ApoB/ApoA-I), smoking, hypertension, DM, abdominal obesity, combined psychosocial stressors, avoidance of any regular exercise physical activity, irregular consumption of fruits and vegetables as well as no alcohol intake accounted for 90% of MI risk worldwide in both sexes and at all ages in all regions. In this study, abnormal lipid levels showed the strongest association with MI, while daily consumption of fruits or vegetables, moderate or strenuous physical exercise ≥4 hours a week, and consumption of alcohol ≥3 times per week seemed to be protective in MI risk (Yusuf et al., 2004). The importance of modifying risk factors is supported by data from other randomised trials [blood-pressure lowering (Mancia et al., 2009), lipid lowering (CTT Collaborators, 2005; CTT Collaborators, 2008; HPS Study, 2003; Jupiter Study, 2008), dietary and life style modification (DASH Study, 2006; de Lorgeril et al., 1999; Stampfer et al., 2000)] or from observational studies (Doll et al., 2004). Some investigators have suggested that a pill that combines a statin, antihypertensive drugs, and aspirin, together with avoidance of smoking, could potentially reduce the risk of MI by 80%-90% (Wald & Law, 2003).

In spite of the improvements of CV outcome by risk factor modification, the EUROASPIRE III survey (2009) from 22 European countries showed that large proportions of coronary patients do not achieve the lifestyle, risk factor and therapeutic targets for CVD prevention: 56% had a blood pressure ≥140/90 mmHg, 53% were centrally obese, 17% of patients smoked cigarettes, 51% had a suboptimal serum total cholesterol level, and only 35% of diabetics had glycated haemoglobin A1C <6.5%. There is still considerable potential throughout Europe to raise standards of preventive care.

This findings underline the important role of lifestyle and risk factor management in CVD prevention and suggest why **to prefer primary prevention in CVD management**. Moreover, prevention of CVD should go beyond the concept of primary prevention, towards a „primordial prevention", to prevent the penetration of risk factors into the population by intervening to stop the appearance of the risk factors. The realisation of such strategic goals in everyday clinical practice requires an active approach to the CVD prevention. **The European Health Charter,** declared in 2007 in Brussels, advocates the development and implementation of comprehensive health strategies, measures and policies at European, national, regional and local level that promote cardiovascular health and

prevent CHD by the assistance of guidelines on CVD prevention (Graham et al., 2007). In June, 2011, the U.S.´s first ever **National Prevention and Health Promotion Strategy** was declared: America´s plan for better health and wellness. An active and preventive approach is postulated in several points: active living, healthy eating, tobacco as well as injury and violence free living, preventing drug and excessive alcohol use, strengthening reproductive and sexual health as well as mental and emotional well-being. The America´s National Prevention Strategy indicates a 20% reduction of both CHD and stroke mortality by 2020. Novel, global effort to promote uniform approach to risk factor reduction provides **the Non Communicable Diseases (NCD) Alliance,** launched in 2009 in Geneva as a formal alliance of four international federations representing the four main NCDs – cardiovascular disease, diabetes, cancer, and chronic respiratory disease. These conditions share common risk factors and also share common solutions.

There is a real, world-wide research network for study determinants of lifestyle and its impact on risk factors and disease progression as well as to develop realistic, cost-effective strategies to reduce global burden of CVD and to face new challenges for prevention such as: a) increase of CVD in low- and middle-income countries, b) increase of diabetes and obesity, c) flattening of CHD mortality trends in the young, d) maintenance of high heart failure-incidence after MI, e) stroke.

3. Risk stratification and identification of persons at high risk of CVD has a crucial role in cardiovascular prevention

Current management of patients everywhere should provide complex program focusing on all aspects of care, including environment and lifestyle, psychosocial factors, management of risk factors, adherence to up-to-date treatment. Preventive strategies are the most effective and achievable means for improving health and may form the basis for a prevention-oriented society and health care. Preventive strategies are generally based on primordial, primary, secondary, tertiary and quaternary concepts. Due to continuous character of CVD progression, primordial, primary, and secondary preventive strategies should be implemented jointly. CV preventive strategies focus on: a) population at high risk, to reduce their morbidity and mortality, b) on the whole population at lower CVD risk, to maintain their state lifelong. Both approaches must be complementary. Paradoxically, high risk subjects develop fewer deaths compared with subjects at low risk, because they are more numerous (Rose, 1981).

Estimation of total CVD risk has been a crucial recommendation in patient management in European CVD Prevention guidelines since 1994 (Pyörälä et al., 1994). Such model assists to promote management of patients with CVD towards individual approach. **The rationale for the risk assessment is based on the following arguments**: a) risk factors are strongly associated with CVD morbidity and mortality, b) CVD is usually the product of several interacting risk factors, which may multiply the global risk, c) the possibility to reduce a risk, d) the need to treat the whole patients, not only one risk factor, e) the need for CV risk threshold to optimally manage patients, f) epidemiological data allow to estimate a global risk, g) identification of patients at high risk with most benefit from risk factor modification/treatment.

4. CVD risk assessment. Framingham risk scoring – Establishment of the 10-year absolute total risk for coronary events (fatal and non-fatal). The SCORE project – Establishment of the 10-year absolute risk for fatal CVD

The initiation of CVD prevention as well as the intensity of treatment of the individual patient depends on the patient´s risk status. Different multifactorial risk scoring systems have been developed: Framingham CHD Prediction Score 1976, Joint British Societies Coronary Risk Prediction Charts 1998, Framingham Risk Score 2002, Euroscore 2003, Procam Risk Score 2004, Progetto Cuore 2007, Qrisk 2007, Assign 2007, Framingham General CV Risk Score 2008, Predict 2008, and other systems (Lenz & Mühlhauser, 2004). A variety of risk calculators is available as charts, tables, computer programs, and web based tools. **Risk charts are intended to facilitate risk estimation in apparently healthy persons with no signs of clinical or preclinical disease.**

Because CVD is usually a result of a multiple risk factors interaction, the CVD risk should be calculated as a **global risk**, considering the global assessment of all major risk factors rather than the identification of the strength of each risk factor individually (Graham et al., 2007). Therefore**,** global risk is neither based on the simple summation of risk factors' values (risk score) nor on counting risk factors (Haq et al., 1999; Palmieri et al., 2004). One aim of primary prevention is to reduce **long-term risk** (>10 years) as well as **short-term risk** (≤10 years). Current practice in primary prevention of CVD involves estimation of short-term (typically 10-year) risk for developing CVD to identify individuals at high risk. Therapeutic goals in primary prevention depend on **absolute risk** of persons for AS CVD (i.e. the percentage chance of developing a CVD event over a given period of time). **Relative risk** is the ratio of the absolute risk of a given patient to that of a lower risk.

Equations derived from the American Framingham Heart Study are most widely used in the U.S. and have been used for many years in European countries too. Based on NCEP-ATP I and II documents, since 1988, risk stratification was provided by counting risk factors. **Framingham risk scoring** for determining the 10-year absolute total risk for developing hard coronary events (fatal – CHD death, non-fatal – myocardial infarction) was firstly used in NCEP-ATP III Recommendations (2001). To calculate risk, it used classical Framingham risk factors: age, sex, smoking, systolic blood pressure, total cholesterol, and HDL cholesterol. NCEP-ATP III defined individual absolute risk and metabolic syndrome, classified 4 patient categories: low, moderate, moderately high, and high risk as well as introduced the category of "**high CV risk**" individuals. At present, the National Heart, Lung, and Blood Institute Adult Cardiovascular Risk Reduction Guidelines effort includes both a shorter-term strategy of updating the existing guidelines for blood cholesterol, high blood pressure, and obesity as well as a longer-term strategy of developing an integrated CV risk reduction guideline. Two strategies are being undertaken because identification and management of individual risk factors, as well as a comprehensive integrated CV risk reduction approach to patients, are both important. Expected release date is 2012.

The first set of recommendations for prevention of CHD in clinical practice in Europe from 1994 included a new "risk chart" of classical Framingham risk factors for 10-year risk assessment of any CHD event, developed by Anderson et al. (1991). A 10-year ≥20% risk was used arbitrarily as a threshold for intensified risk factor intervention.

Endorsed by the Third Joint Task Force in 2003, a new risk chart was constructed: the **SCORE project** (Systematic COronary Risk Evaluation). 12 European cohort studies provided a scientific background to the development of this model for the estimation of a 10-year absolute fatal CVD in population based on the following risk factors: age, gender, smoking, systolic blood pressure, and either total cholesterol or total cholesterol/HDL cholesterol ratio. Separate charts were produced for total cholesterol/HDL cholesterol ratio as well as for low (Belgium, France, Greece, Italy, Luxembourg, Spain, Switzerland, Portugal, and countries with recently experienced substantial lowering of the CV mortality rates) and high risk regions (all other European countries). **The Third Joint Task Force** shifted the prevention from CHD to CVD, introduced the multifactorial SCORE model for risk assessment, continued in CV prevention focusing to determine high risk subjects, identified subclinical AS and other conditions as higher CV risk than indicated in the chart. Changing mortality trends in various countries required the recalibration of risk chart, which resulted in construction of national guidance enforced by **Fourth Joint Task Force** in 2007. Introduction of relative risk chart, its use in conjunction with the absolute SCORE chart, revised approach to the effect of other risk factors and organ damage on total CV events and mortality, the nomenclature of increased risk instead of high risk as well as introduction of fatal and nonfatal instead of only fatal risk estimation were other new features in the latest Task Force. SCORE model allows the estimation of absolute CVD death risk, its extrapolation to age 60 years as well as the estimation of a relative risk. The following risk categories can be differentiated by SCORE model: low, moderate, increased, and markedly increased. Risk ≥5% is considered increased/high (Figure 2, 3).

An update version of this latest guidelines will become available in 2012, but at the present time the new **ESC/EAS guidelines on management of dyslipidaemias** modify in several ways the current CVD risk assessment (Reiner et al., 2011): redefine risk categories; introduce very high risk category; determine persons at automatically high or very high CV risk adding chronic kidney disease and documented CVD by invasive or non-invasive methods to the previously automatically determined diseases; modify the relative risk of diabetes; indicate multipliers to convert fatal to total (fatal + non-fatal) CVD risk; refine the HeartScore by entering actual HDL cholesterol level instead of the combined HDL/LDL cholesterol level (www.escardio.org/guidelines), "fast track" calculator of BMI in the unavailability of blood pressure and cholesterol inputs as well as „risk age" function to determine the theoretical age of a person. **The primacy of managing total risk rather than focusing on individual risk factors is stressed in all latest European preventive documents with definition of desirable levels of individual risk factors. The threshold for high total CVD risk is arbitrary, but targets to initiate pharmacological interventions are open** because the risk is a continuum and there is a need for continuous up-to-date modification.

The main difference between the 2 major scoring systems – Framingham Risk Score vs. SCORE – is expressed in some aspects: a) population based: 5000 Americans vs. 200,000 Europeans, b) prediction: coronary events vs. AS CVD, c) end points: composite including also non-fatal events vs. fatal events, d) adjustment: impossibility for national variations vs. possibility to be customized using national statistics.

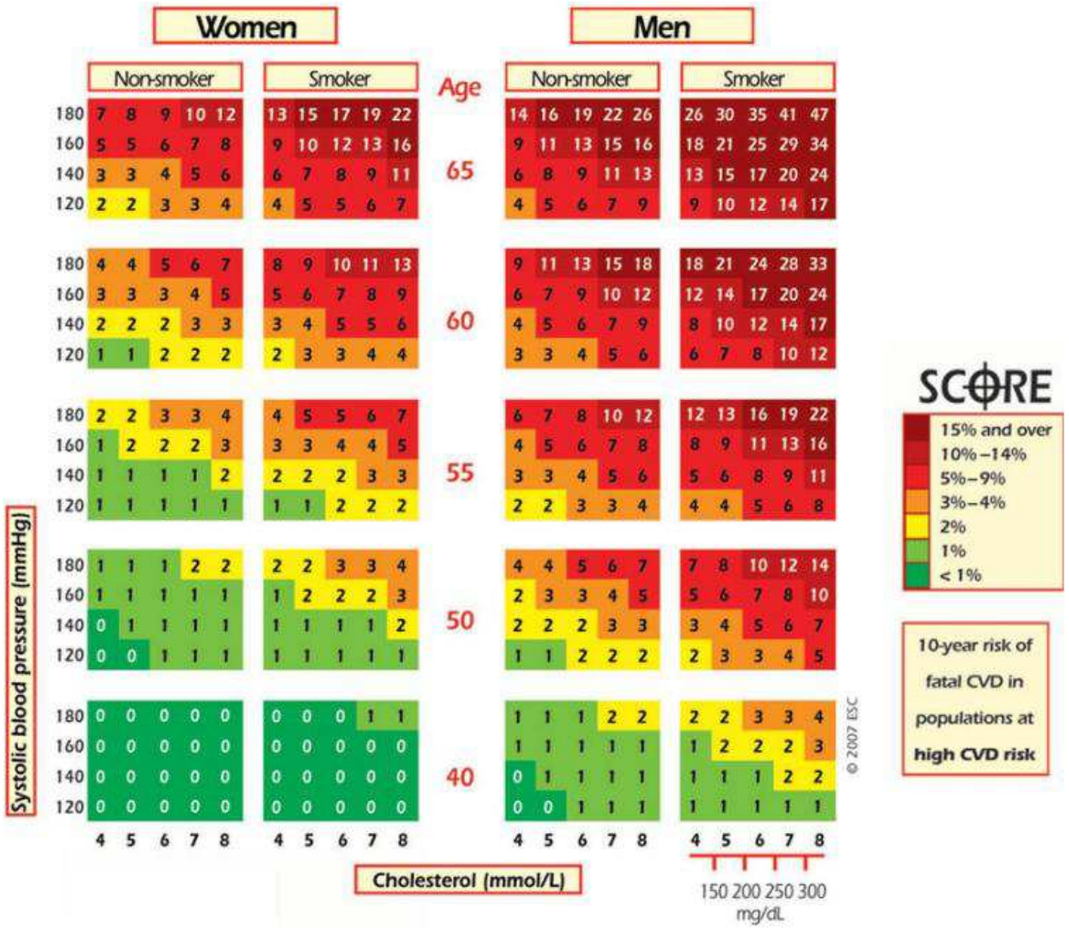

Fig. 2. SCORE chart: 10-year risk of fatal CVD in populations at high CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. ©The European Society of Cardiology

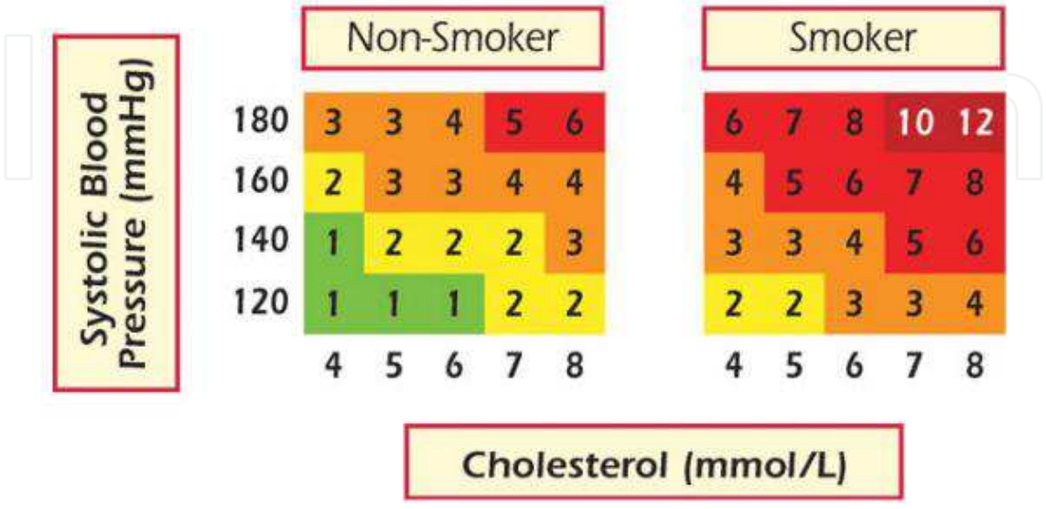

Fig. 3. Relative risk chart. ©The European Society of Cardiology

5. High /very high risk groups. FRAMINGHAM (NCEP-ATP III Update, 2004) high risk: 10-year total (fatal or non-fatal) hard CHD risk >20%. SCORE (ESC/EAS 2011) high /very high risk: 10-year fatal CVD risk ≥5%/10%

5.1 Determined high /very high risk groups (without estimation)

NCEP-ATP III described the high CV risk individuals with 10-year risk >20%: those with the presence of CHD or CHD equivalent. According to ESC/EAS 2011 guidelines, subjects at high or very high risk are as follows: a) subjects with known CVD, b) asymptomatic patients**:** with DM2, DM1 with target organ damage such as microalbuminuria, markedly elevated level of individual risk factors with /without target organ damage, c) chronic kidney disease (CKD). **These subjects are automatically at high/very high total/fatal CVD risk and need intensive management of all risk factors, for all other people a risk estimation is recommended using Framingham/SCORE system.**

5.2 Framingham risk categories

NCEP-ATP III identified the following 10-year CV risk categories: a) low risk: (<10%: 0-1 risk factor, b) moderate risk: (<10%): ≥2 risk factors, c) moderately high risk: (10-20%): ≥2 risk factors, d) high risk: (>20%): presence of CHD or CHD equivalent. CHD risk equivalents include clinical manifestations of noncoronary forms of AS disease [peripheral arterial disease (PAD), abdominal aortic aneurysm, and carotid artery disease (transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery)], DM, and ≥2 risk factors with 10-year risk for hard CHD >20%. According to NCEP-ATP III panel, major risk factors (exclusive of high LDL cholesterol) modifying the risk include: cigarette smoking, hypertension [blood pressure (BP) ≥140/90 mmHg or antihypertensive medication], low HDL cholesterol (<40 mg/dl), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years). The NCEP-ATP III Update document introduced the "very high risk" category, i.e. patients with acute coronary syndromes (ACS) or with CVD and a) DM, b) severe and poorly controlled risk factors, c) metabolic syndrome (MS).

5.3 SCORE risk categories

According to SCORE chart, the 10-year absolute total risk of CVD death ≥5% is considered as high/increased risk. **The European Third Joint Task Force Guidelines on CVD Prevention** (De Backer et al., 2003) determined high risk patients as follows: 1) patients with established AS CVD, 2) asymptomatic subjects at high risk for AS CVD because of: a) multiple risk factors with a 10-year risk ≥5%, b) markedly increased levels of single risk factors: cholesterol ≥8 mmol/l (320 mg/dl), LDL cholesterol ≥6 mmol/l (240 mg/dl), BP ≥180/110 mmHg, c) DM type 2 or DM type 1 with microalbuminuria, 3) close relatives of a) patients with early onset AS disease, b) asymptomatic subjects at particularly high risk. **The Fourth Joint Task Force** (Graham et al., 2007) selected four 10-year fatal CVD risk categories: a) low (<1%); b) moderate (1-4%); c) increased (5-9%); d) very increased risk (≥10%). It confirmed the same high-risk patient groups as the Third Task Force, but reclassified they as increased-risk groups as well as endorsed an increased risk in those subjects with markedly elevated level of single risk factors, especially in association with end-organ damage.

The new **ESC/EAS guidelines on management of dyslipidaemias** classify the following risk categories (Reiner et al., 2011): 1) very high risk: patients with any of the following: a) documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous MI, ACS, coronary revascularization (percutaneous coronary intervention, coronary artery bypass graft) and other arterial revascularizations, ischaemic stroke, PAD, b) patients with DM2, DM1 with target organ damage such as microalbuminuria, c) patients with moderate to severe CKD [glomerular filtration rate (GFR) <60 ml/min/1.73 m²], d) calculated 10-year risk SCORE ≥10%, 2) high risk: subjects with markedly elevated single risk factor with /without target organ damage or a calculated risk ≥5% SCORE <10%, 3) moderate risk: subjects with ≥1% SCORE <5%, 4) low risk: subjects with SCORE <1%. Calculated risk may underestimate the real risk in various conditions.

The 10-year fatal CVD risk ≥5% (high/increased risk) is equated approximately to 10-year total (fatal and non-fatal) CHD risk ≥20% according to previous European risk charts based on the Framingham Heart Study results (De Backer et al., 2003) and to 10-year total fatal and non-fatal CVD risk about ≥15% according to the latest ESC/EAS guidelines, considering also data from FINRISK MONICA; the multiplier is slightly higher in women and lower in older persons (Reiner et al., 2011; Vartiainen et al., 2000).

6. Limitations of a current system. Underestimation of a real 10-year CHD/CVD risk in various clinical conditions

The most frequently used risk models (Framingham, SCORE) have also limitations such as: 1) may overestimate the risk in low risk regions or in countries with a falling CVD mortality rate and underestimate it in high risk ones or if the risk is rising, 2) may underestimate the individual risk, 3) at any given age, the estimated risk is lower in women than men because it is deferred by 10 years, 4) the risk algorithms do not include several risk factors strongly associated with CVD mortality with higher real than calculated CV risk, 5) short-term risk prediction.

Despite the availability of several validated risk prediction algorithms, their use has lagged in primary care. One potential reason for physician inertia in using risk prediction instruments is the multiplicity of such algorithms, each for predicting an individual CVD component, e.g. hard coronary event, stroke, fatal CVD, etc. There is a need in primary care for risk scoring of developing any major AS CVD event using a single, general CVD risk assessment tool, enabling physicians to identify high-risk candidates for any and all initial AS CVD events using measurements readily available. A sex-specific multivariable risk factor algorithm (D´Agostino et al., 2008) can be conveniently used to assess absolute general CVD risk and risk of individual CVD events (coronary, cerebrovascular, PAD, and heart failure).

Current practice in primary prevention of CVD involves estimation of short-term (typically 10-year) risk for developing CVD to identify individuals at high risk, resulting in treatment only for older individuals with substantial risk factor burden. Younger and middle-age individuals with clearly adverse risk factor levels may have low short-term but substantial lifetime risks for development of CVD. The estimated lifetime risks for CVD and median survival are associated with different clinical strata of individual risk factors and with

aggregate risk factor burden at 50 years of age. Compared with participants with ≥2 major risk factors at 50 years of age, those with optimal levels had substantially lower lifetime risks (5.2% vs. 68.9% in men, 8.2% vs. 50.2% in women) and markedly longer median survivals (>39 vs. 28 years in men, >39 vs. 31 years in women). The presence of diabetes at 50 years of age conferred the highest lifetime risk for CVD of any single risk factor (Lloyd-Jones et al., 2006) (Figure 4).

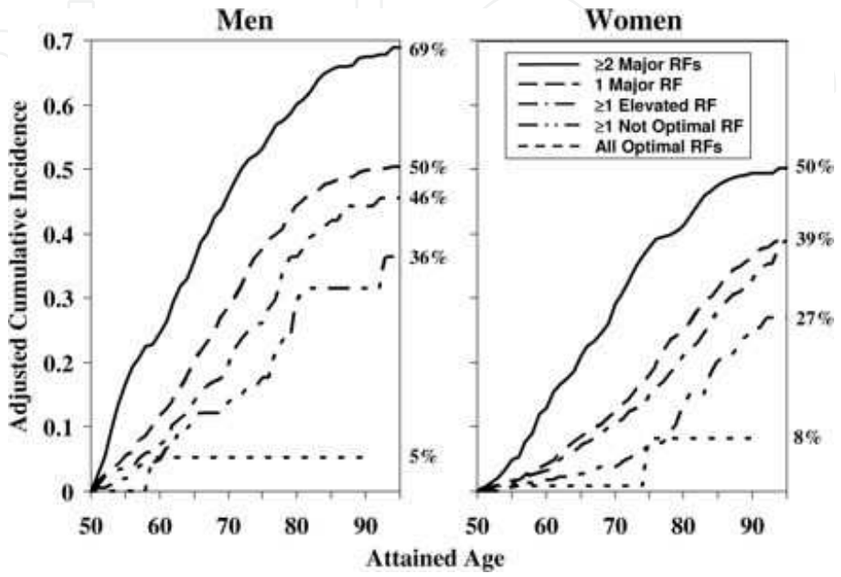

Fig. 4. Lifetime risk. Prediction of lifetime risk for CVD by risk factor burden at 50 years of age (Lloyd-Jones et al., 2006)

7. Population groups with increasing evidence of high CV risk (similarly to those with automatically determined high risk according to NCEP-ATP III 2004 and ESC/EAS 2011 guidelines)

7.1 Subjects with established subclinical atherosclerosis

The total CVD risk may be higher than indicated in the Framingham/SCORE chart (Reiner et al., 2011) **mainly in the following situations (qualifiers):** a) preclinical AS, particularly evidence of vascular wall morphological abnormalities detected by imagine methods such as ultrasonography [(plaques, increased carotid intima-media thickness (CIMT)], CT scanning, assessment of coronary artery calcium, etc., as well as detection of functional abnormalities of vascular wall, for example, ankle-brachial index (ABI), decreased flow mediated vasodilation (FMD), etc.; increasing role in detection of preclinical AS is attributed to biochemical markers of preclinical AS, mainly high sensitivity C-reactive protein (hs-CRP) (Greenland et al., 2010), b) renal impairment, c) DM, d) severe abnormalities of single risk factors, e) obesity, especially with central type (waist circumference [International Diabetes Federation (IDF), 2005]: ≥94 cm in men and ≥80 cm in women), physical inactivity, unhealthy diet, f) social deprivation, g) low HDL cholesterol or apoA-I in SCORE, increased triglycerides (TG), fibrinogen, homocysteine, apoB, lipoprotein(a) (Lp(a)), familial hypercholesterolaemia, increased hs-CRP; these factors indicate a higher level of risk in both genders, all age groups and at all levels of risk, h)

strong positive family history of premature CVD. From these, **renal impairment, DM, and severe abnormalities of single risk factors are classified similarly to documented CVD as determined high/very high risk condition, without need to calculate it.**

DM is associated with 5x higher CVD risk in women and 3x higher in men in comparison with those without DM. Epidemiological data documented progressive rise (20-30x) of CVD risk from microalbuminuria with preserved GFR to end-stage renal disease. Recently a KDIGO report has suggested a new global guideline to assess all-cause and CV mortality, end-stage renal disease, acute kidney injury, and progressive chronic kidney disease based on estimated GFR (eGFR) and level of albuminuria. As the data have indicated, those at lower level of eGFR and higher levels of albuminuria were at increased risk for all outcomes, including CV (Levey et al., 2010).

7.2 Subjects with elevated heart rate

Beyond qualifiers recommended by the European guidelines to check while calculating the 10-year fatal CVD risk, another clinical conditions have been shown to be associated with high CV risk, e.g. elevated heart rate. Elevated heart rate (>70/min) is strongly, gradually, and independently of other factors associated with increased risk of all-cause and CV mortality as well as development of CVD in general population, hypertensives, diabetics, and those with pre-existing CHD (Diaz et al., 2005; INVEST Study, 2008; Kannel et al., 1987; OPERA registry, 2007; TNT Study, 2006; WOSCOPS Study, 1995). Risk of sudden death in men is particularly associated with elevated resting heart rate, but in women and the elderly this association is not so strong (Shaper et al., 1993). Arterial hypertension (AH) in conjunction with elevated heart rate is associated with the worst prognosis (Levy, 1945). Heart rate >80/min, left ventricular mass >270 g, and increased pulse pressure are considered as negative prognostic markers of plaque rupture. Elevated heart rate is a frequent symptom of physical inactivity and associated obesity, diabetes and MS, excessive use of psychostimulants, psychological stress and associated hypertension as well as smoking. Up-to now, elevated heart rate as a part of a pathophysiological pathway of most traditional modifiable risk factors is declared neither as a separate high CV risk state nor as a qualifier. Pharmacological reduction of heart rate is not recommended in asymptomatic population.

8. Personalized CV prevention. Identification of subjects at high CV risk among those without determined or calculated high risk

To identify patients at high risk with most benefit from risk factor modification or specific pharmacological treatment is a crucial step in primary prevention. Current guidelines based on the most frequently used Framingham and SCORE model determine subjects at high/very high 10-year total CHD/fatal CVD risk without necessity to calculate it. To identify other subjects at high risk, risk stratification is recommended. The AS CV continuum is a multiple interaction of a wide spectrum of risk factors, but **available risk charts based on the set of a few risk factors have limitations to asses a real CVD risk, thus sometimes the calculated risk underestimates the real one.** Epidemiological data from studies (Belcaro et al., 1996; Postley et al., 2009), which failed in prediction CV risk assessed by risk charts, based on classical risk factors. Only 40% of patients with high risk developed CV event, while 70% of those with low risk. **To document high risk condition in those**

without determined or calculated high risk is a target for individualized risk stratification. According to the latest guidelines, **two main subclinical CV pathologies are strongly associated with the increased CV risk: a) subclinical AS** (either early or advanced stage), **and b) end-organ damage.** Thus personalized prevention aims to focus on active search for these conditions. Sometimes a physician would like to target risk assessment and preventive measures to a specific CV end point such as MI or stroke depending, for example, on an individual patient's family history, age, diabetic status, or predisposition to a particular outcome by valve disease. If calculation does not indicate high risk, the individual risk assessment is recommended.

Up to now there is no strict recommendation for individual risk assessment: whom, when, and how to investigate. Because screening of the whole population is extremely time-consuming, expensive, and ineffective, much more effective way with better cost/benefit ratio might be the selection of either subjects, time, or screening tools for individualized risk stratification. **Personalized CV prevention may be useful mainly at the time of expected acceleration of AS** (age risk, in the onset of multiple risk factors with multiplicative interactions, in various comorbidities). We do not know with certainty what changes are typical for accelerated AS (dynamics of morphological changes, presence of specific markers, highly increased level of some markers, etc.). Identification of AS acceleration could serve as an indicator to start with pharmacotherapy in asymptomatic patients in whom benefits of treatment could outweigh its adverse effects, cost, burden of staff, and stress from "health loss".

9. Beyond the SCORE chart. Personalized risk assessment in Europe. Whom, when, and how?

9.1 Whom?

Persons, who are not classified automatically as high CV risk and are not at high but moderate calculated risk with the presence of:

1. obesity, dyslipoproteinaemia (low HDL cholesterol or apoA-I, high TG, fibrinogen, homocysteine, apoB, Lp(a), hs-CRP),
2. positive family history,
3. psychosocial factors,
4. multiple risk factors (mostly modifiable),
5. specific comorbidities, mainly associated with inflammation, but also with cardiometabolic risk: (autoimmune chronic inflammatory diseases: rheumatic diseases, vasculitides, psoriasis; infections associated with AS; organ transplantations; sleep apnoea, chronic obstructive lung disease; some endocrinopaties, hormonal substitution; etc.).

Certain clinical states are recognized at higher 10-year fatal CVD risk than indicated in the SCORE chart (with rationale for individualized risk stratification): sedentary or obese subjects, especially with central obesity, with low HDL cholesterol or apoA-I, raised TG, fibrinogen, homocysteine, apoB, Lp(a), hs-CRP, with strong family history of premature CVD, in social deprivation, but increasing data suggest the need for screening also in the setting of multiple risk factors with <5% 10-year fatal CVD risk as well as in the presence of specific comorbidities.

9.1.1 Sedentary lifestyle and associated risk factors

Sedentary lifestyle doubles the risk of premature death and increases the risk for CVD (Paffenbarger et al., 1993; Rosengren & Wilhelmsen, 1997). Obesity, a worldwide epidemic in both children and adults (Poirier et al., 2006) is considered as an insulin resistant, pro-inflammatory, and prothrombotic state. Fat is associated with hypersecretion of free fatty acids, hyperinsulinaemia, insulin resistance, hypertension and dyslipidaemia (Carr & Brunzell, 2004; Wajchenberg, 2000). Excess central fat is strongly associated with metabolic and CVD risk (Despres et al., 1990). It has been shown that body weight increases CV risk by its adverse effect on many risk factors such as blood pressure, total, LDL, and HDL cholesterol, waist circumference, sleep apnoea, etc. (Graham et al., 2007). The association between increasing BMI, waist circumference as well as waist–to hip ratio (WHR) and greater CVD risk has been also demonstrated (Larsson et al., 1984). Taking into account known associations between increasing waist circumference/WHR and other cardiometabolic risk factors and cost/benefit relations, screening for the presence of preclinical AS or end-organ damage is highly indicated in patients with MS. In spite of the fact that MS represents an increased risk of developing CVD and DM type 2, it does not indicate a priori high risk similar to those with CVD and diabetes.

The causal relationship between total and LDL cholesterol and CVD risk is generally known, beyond the "standard risk assessment" there is no recommendation for further risk screening (CTT Collaborators, 2005). While treatment goals are clearly declared for total and LDL cholesterol, no specific ones are documented for HDL cholesterol and triglycerides. The benefits of statins are proven for both genders and age except for in healthy, asymptomatic women (HPS Study, 2003). Current ESC/EAS guidelines modify indications for lipid analysis (Reiner et al., 2011).

9.1.2 Positive family history for early CHD

A positive family history of early CHD is an independent risk factor for CHD. The risk of CHD increases in a first, second, and third degree relatives, as the number of family members with CHD increases and the younger the age at which family members develop CHD (Graham et al., 2007). Impact of risk factors on the development of AS is influenced by environmental and genetic factors. Relatively high level of heritability for many CHD phenotypes may partially explain a strong genetic determination (Pankow et al., 2001; Worns et al., 2006). The identification of **new genetic polymorphisms** associated with CV phenotypes opened novel perspectives in AS research. Polymorphisms of chromosomal loci (9p21, 1p13, 1q41, 10q11, 21q22, 6p24, 2q33 and 3q22) were associated with development of AS and its complications in genome wide association studies (GWAS) published in 2007-2009. 9p21 locus showed the strongest association with stroke, peripheral artery disease, aortic and cerebral artery aneurysm and sudden cardiac death. Significant but relatively low effect on CV risk is documented for variants of genes involved in lipid metabolism, coagulation, and various aspects of endothelial function (Pankow et al., 2001; Worns et al., 2006).

In spite of the suggestive results, population screening for genetic polymorphism is currently not yet realistic (Casas et al., 2006; Purcell et al., 2003). Individual stratification of CVR could be an alternative bridging tool between use of risk algorithm based on classical

risk factors with low predictive value and population screening for presence of genetic polymorphisms. Genetic screening may promote in the future search for individuals at high CVD risk as well as individual therapeutic approaches according to the individual genetic make-up. Subjects with positive family history may gain from further risk stratification.

9.1.3 Psychosocial factors

Psychosocial factors increase the risk of the first event and also a worsening of CHD prognosis (Rozanski et al., 2005). Besides the presence of smoking and unhealthy diet as risk factors, endocrine, autonomic and inflammatory changes contribute in promoting CHD. Beyond the CHD risk they show problematic management and no active approach of subjects to lifestyle modification. The following types are involved in CHD risk: low socio-economic status, social isolation and lack of social support, stress at work and in family life, negative emotions including depression and hostility. For non-compliance there is no strict rule for screening these patients for subclinical AS or end-organ damage.

9.1.4 Multiple risk factors

Markedly increased levels of single risk factors: total cholesterol ≥8 mmol/l (320 mg/dl), LDL cholesterol ≥6 mmol/l (240 mg/dl), BP ≥180/110 mmHg, severe continuous smoking are automatically high risk conditions.

Management of patients with **arterial hypertension**, particularly the initiation of pharmacological treatment, depends not only on the BP level but also on total CV risk assessment, including identification of a) associated clinical condition: established CVD, renal impairment (plasma creatinine >133 umol/l in men, >124 umol/l in women, proteinuria >300 mg/24h), as well as advanced retinopathy (haemorrhages, exudates or papilloedema), b) coexistence of other CV risk factors, i.e. high pulse pressure, c) the presence of subclinical end-organ damage such as: electrocardiographic or echocardiographic left ventricular hypertrophy, carotid-wall thickening (CIMT ≥0.9 mm) or plaque, abnormal pulse-wave velocity (carotid-femoral ≥12 m/s), pathological ankle-brachial index (ABI <0.9), slight increase of plasma creatinine (115-133 umol/l in men, 107-124 umol/l in women), low eGFR (<60 ml/min/1.73m^2 MDRD; <60ml/min Cockroft-Gault) or microalbuminuria (30-300 mg/24h). Associated clinical condition represents a very high and subclinical organ damage a high CV risk (Graham et al., 2007). ESH Task Force (Mancia et al., 2009) recommends a search for subclinical organ damage in hypertension. **Active and passive smoking** increase the risk of CHD and smoking-related diseases. The adverse effect of smoking is related to the amount of tobacco smoked daily and to the duration of smoking. Smoking interact synergistically in the presence of other CVD risk factors such as age gender, AH, and DM (Law et al., 1997; US Department of Health and Human Services, 2004). Individualized risk stratification in smoking is of great importance in a cluster with other risk factors.

9.1.5 Specific comorbidities associated with inflammation or cardiometabolic risk

Evidence suggests that enhanced AS causes premature CV events in some autoimmune diseases. Patients with **rheumatoid arthritis** (RA) have a 2-5 times increased risk of developing premature CV event that shortens life expectancy by 5-10 years. Indeed, low-

grade inflammation and endothelial dysfunction play pivotal roles in enhanced atherogenesis in rheumatic diseases. The joint influence of CV risk factors and inflammation causes expression of adhesion molecules [selectins, vascular cell and intracellular adhesion molecules (VCAM-1, ICAM-1)] induced by pro-inflammatory cytokines [interleukin (IL)-1β and tumor necrosis factor-α (TNF-α)] as well as by CRP and CD40/CD40 ligand interactions that promote the adherence of monocytes (Gasparyan et al., 2010). In addition, coagulation factors [increased levels of tissue factor, van Willebrand factor (vWF), and plasminogen activator inhibitor-1 (PAI-1)] as well as proteolytic enzymes [matrix metalloproteinases (MMPs)] with their role in destruction, destabilization, and rupture of vulnerable atherosclerotic plaques are also important (Hürlimann et al., 2004). Advanced glycation end-products (AGE), their receptors (RAGE) as well as antiphospholipid antibodies and other inflammation propagating factors may be contributed to accelerated AS during the course of different systemic inflammatory diseases.

Remarkably, relatively few studies have been published on the occurrence of accelerated AS in patients with **vasculitis**. In giant cell arteritis, mortality because of ischaemic heart disease is not increased. During active stage of Takayasu arteritis (large vessel vasculitis), Kawasaki disease (medium-sized vessel vasculitis) as well as in small vessel vasculitis (anti-neutrophil cytoplasmic autoantibodies-associated) accelerated AS has been well documented. Several risk factors, such as DM and AH are present more often in patients with vasculitis in comparison with healthy controls. In addition, steroid therapy, impaired renal function, persistent proteinuria, increased levels of CRP and autoantibodies, enhanced oxidation processes, activated T-cells as well as inhibited regulatory T-cells documented in these patients are well-known risk factors for acceleration of AS (Tervaert, 2009).

According to various authors, the hypothesis of a **relationship between infection and AS** is still alive, recently an answer is required about whether the atherogenic process is triggered, accelerated, or both by infection (Gurfinkel, 2006). The association of Chlamydia pneumoniae, Helicobacter pylori, cytomegalovirus, Epstein-Barr virus as well as other viruses and parasites with AS lesions are generally known. Infective agents act through the tool like receptors, having crucial role in natural defence against microbial pathogens (Ekesbo et al., 2001). Human immunodeficiency virus **(HIV)-infected patients** are at a significantly higher risk from CHD and MI compared to gender- and age-matched non-infected individuals. Antiretroviral therapy induces metabolic abnormalities in HIV-infected patients that are linked to inflammation, probably also via visceral adipose tissue activation affecting the liver function, followed by pro-atherogenic dyslipidaemia. Pro-inflammatory cytokines released by adipocytes are responsible for worsening insulin sensitivity and hyperglycaemia. As a result of nuclear factor-kappa B (NFκB) activation, hs-CRP up-regulates cytokines that contribute to MI by recruiting leukocytes and promoting thrombosis (De Lorenzo et al., 2008).

Both CRP (marker of systemic inflammation) and asymmetric dimethylarginine (ADMA – endogenous inhibitor of NO-synthase) have been shown to be associated with increased incidence and progression of AS lesions in carotid arteries as well as to be important risk factors for CVD and mortality in the **end-stage renal disease** population (Rattazzi et al., 2003).

The accelerated AS in **transplanted kidneys and hearts** has a complex pathogenesis, which includes both immunological and nonimmunological factors. Hypertension is one such factor, which has been claimed to be an independent risk factor for chronic renal transplant dysfunction, usually characterised by transplant AS (Fellström et al., 1989). Recent experimental and clinical data suggest accelerated AS occurs following bone marrow mobilisation or intracoronary haematopoietic stem cell therapy (Vanderheyden et al., 2005).

Obstructive sleep apnoea (OSA) may accelerate AS by exacerbating key atherogenic risk factors (secondary hypertension, insulin resistance, diabetes, dyslipidaemia) (Szabóová et al., 2008). In addition, clinical data and experimental evidence in animal models suggest that OSA can have direct proatherogenic effects inducing systemic inflammation, oxidative stress, vascular smooth cell activation, increased adhesion molecule expression, monocyte/lymphocyte activation, increased lipid loading in macrophages, lipid peroxidation, and endothelial dysfunction (Drager et al., 2011). Several cross-sectional studies have shown consistently that OSA is independently associated with surrogate markers of premature AS, most of them in the carotid bed (Szabóová et al., 2007). Moreover, OSA treatment with continuous positive airway pressure may attenuate carotid AS, as has been shown in a randomized clinical trial. High prevalence of CIMT and increased CVD risk as assessed by carotid ultrasonography in **chronic obstructive pulmonary diseases** with a broad spectrum of airway obstruction severity has been shown in a recent study (Pobeha et al., 2011).

It is generally known, that some **endocrinopaties** may increase the cardiometabolic risk (e.g. acromegaly, thyreopathies, hyperparathyreosis, adrenal hyperfunction as well as hormonal treatment associated with cardiometabolic and thrombogenic risk such as corticosteroid therapy, hormone substitution/replacement therapy, oral contraceptive use, etc.). Because of high incidence, the greatest clinical significance is linked to hypothyreosis as well as hormone replacement therapy in perimenopausal women.

Active risk screening in above-mentioned clinical conditions may add to the overall precision of CV risk quantification.

9.1.6 Personal opinion

A. Patients are a priori at high/very high risk, no additional testing, but aggressive management is recommended in:

1. known CVD,
2. DM type 2/DM type 1 with end-organ damage (microalbuminuria),
3. renal impairment,
4. very high level of single risk factor with /without target organ damage,
5. presence of multiple risk factors with calculated 10-year risk ≥5%.

B. Individual stratification seems to be useful for identification of other high-risk patients, particularly, in those at moderate calculated risk with:

1. metabolic syndrome (involving obesity and dyslipoproteinaemia),
2. arterial hypertension,
3. positive family history,
4. presence of ≥2 risk factors, especially smoking in cluster with other risk factors,
5. specific comorbidities with suspected acceleration of AS.

9.2 When?

The probability to detect preclinical AS/end-organ damage is higher at the time with possible acceleration of AS:

1. risky age,
2. the onset of multiple risk factors,
3. the onset of specific comorbidity.

9.2.1 Risky age

Age ≥45 years in men and ≥55 years in women is considered as non-modifiable risk factor. CVD risk in women is deferred by 10 years. More older women die than men from CVD. The actual incidence of CVD is increased in older women, which further support the specific age-related risk for CVD in women (Stramba-Badiale et al., 2006). The age-related worsening of classical risk factors in women may be explained by: increased incidence of systolic hypertension, cholesterol peak, obesity, diabetes, oral contraceptive use in combination with smoking.

9.2.2 The onset of multiple risk factors

Detectability of following markers for accelerated AS is extremely important: biochemical (classical, novel: specific vascular proteomes, combination of various cell, tissue, and plasma proteomes), functional, and morphological markers. Various emerging risk factors are involved in the regulation of crucial pathways of AS development such as endothelial dysfunction, inflammation, lipid metabolism, haemostasis, etc. Multiple risk factors may accelerate the development of AS. **In diabetics** a cluster of potent CV risk factors is present, which explains an extremely high risk for future CV event. Well documented is a specific role of inflammation in the development of macrovascular (AS) complications of DM. The following pathophysiological steps are stressed: a) activation of NFκB (potent pro-inflammatory and pro-atherosclerotic mediator), b) expression of AGE, reactive oxygen species with promoting AS, c) hyperglycaemia-induced vascular cell changes (loss of non-adhesivity of endothelial cells, adhesion of monocytes to endothelial surface, promotion of oxidative stress, decreased expression of NO, activation of matrix metalloproteinases (involved in plaque rupture and vascular remodeling) in smooth muscle cells, stimulation of smooth muscle cells to proliferation/migration/changed reactivity, d) hyperglycaemia-induced vascular inflammation by activation of cytokines from monocytes (IL-1β, IL-6, etc.) and lymphocytes resulting in acceleration of AS.

A strong association was documented between **inflammatory markers** and **obesity** as well as **insulin resistance** (TNF-α, adiponectin) (Rask-Madsen et al., 2003; Tsuchiya et al., 2007), between inflammatory markers, haemostasis, and the development of MI as well as between haemostatic factors and incidence of CHD (Ridker et al., 2000; Scarabin et al., 2003).

Lower HDL cholesterol levels, positive family history of CHD, and elevated fibrinogen concentrations were found as independent predictors for future CV events in a recent study (Rizzo et al., 2008). Lower HDL cholesterol levels may potentially accelerate the progression from subclinical lesions [CIMT, asymptomatic atherosclerotic carotid plaque (ACP)] to clinical events. Fibrinogen as a glycoprotein is involved in a number of mechanisms with a

crucial role of early formation and growth of atheroma (Coppola et al., 2006; Maresca et al., 1999; Wilhelmsen et al., 1984; Woodward et al., 1997). In a recent study a significant inverse correlation between HDL cholesterol levels and fibrinogen concentrations has been shown, suggesting a possible "synergistic" role of low HDL cholesterol and inflammation on the atherosclerotic disease progression from subclinical lesions to clinical events **(**Rizzo et al., 2008). **The presence of subclinical carotid AS together with low HDL cholesterol concentrations points to a category of subjects at "high" CV risk**. This effect could be due to the up-regulation of the inflammatory pathway: HDL cholesterol may promote inflammation in the acute phase.

9.2.3 The onset of specific comorbidity

Histologically is well documented a vascular AS calcification in most patients with **severe CKD** as part of cholesterol crystallization within AS lesions. Prominent AS medial calcification has been previously identified as Mönckeberg's sclerosis. A unifying concept supported by the preponderance of pathologic evidence contends that Mönckeberg's sclerosis is a manifestation of accelerated AS in patients with CKD. Factors that seem to promote the osteoblastic transformation of vascular smooth muscle cells and enhance deposition of calcium hydroxyapatite crystals include phosphorus activation of the Pit-1 receptor, bone morphogenic proteins 2 and 4, leptin, endogenous 1,25 dihydroxyvitamin D, vascular calcification activating factor, and oxidative stress (McCullough et al., 2008).

9.3 How?

Detection of preclinical AS increases the CV risk. Preclinical markers of AS are related to the presence of AS risk factors, to multifocal AS, and to the severity of coronary artery stenosis assessed by intravascular ultrasound (IVUS) or angiographically (Amato et al., 2007). They are classified as:

1. biochemical,
2. genetic,
3. functional,
4. morphological markers.

In assessing risk is recommended to follow standard diagnostic steps: history taking including family history, physical examination (blood pressure, heart and lung examination, heart rate, foot pulses, BMI, waist circumference), laboratory tests (urine for glucose and protein, total, HDL, LDL cholesterol, triglycerides, glucose, creatinine, eGFR), ECG and exercise ECG if angina suspected, ECG/echocardiogram in young or severely hypertensive persons, hsCRP, Lp(a), fibrinogen, or homocysteine in positive family history (Graham et al., 2007).

9.3.1 Biochemical markers of preclinical AS

A. Markers of endothelial dysfunction

- **adhesion molecules:** ICAM-1, VCAM-1, E-selectin, P-selectin, platelet-endothelial cell adhesion molecule PECAM-1, endoglin, vascular endothelial (VE)-Cadherin, S-Endo-1 antigen, CD40 L,

- **cytokines:** IL-6, IL-18, TNF-α, 8-iso-prostaglandin F2α, endothelin-1 (ET-1), metalloproteinases,
- **others**: endothelial-derived microparticles, progenitor cells, glycocalyx measurements (invasively, non-invasively), microalbuminuria (Nieuwdorp et al., 2006; Romanens et al., 2010).

B. Inflammatory markers: hs-CRP, fibrinogen, serum amyloid A, dimethylamine (DMA), asymmetrical dimethylarginine (ADMA), oxLDL, lipoprotein-associated phospholipase A2.

C. Factors of haemostasis: vWf, tissue plasminogen activator (t-PA), PAI-1, factor VII (F VII), F V, prothrombin, plasminogen, D-dimers, Lp(a).

Endothelial dysfunction is consistently associated with CV risk factors and predicts higher risk of CV event. Endothelial dysfunction is the first, functionally important stage of AS, detected far before the structural changes of arterial wall. Any endothelial damage may trigger inflammatory response involving endothelial cells by several mechanisms: expression of adhesion molecules, production of cytokines, transmigration of leukocytes, and angiogenesis. Microalbuminuria as a biochemical parameter of endothelial dysfunction is recommended in hypertesives and diabetics to detect end-organ damage as well as to predict overall and CV risk in chronic kidney disease. Increasing evidence is for its role in the population screening in the future (Kalaitzidis & Bakris, 2009; Levey et al., 2010).

A strong correlation has been detected between **hs-CRP** and CV risk, moreover hs-CRP predicts destabilisation of the AS plaque (Burke et al., 2002; Ridker, 2001). The rationale for incorporation of biochemical markers (especially CRP) into prediction risk model is accentuated with findings from recent trials (JUPITER, 2008; MARS, 2010), where CRP level ≥2 mg/l appears as an effective tool for identification of subjects with increased risk independently from LDL cholesterol. The utility of hs-CRP in risk assessment is weakened by: a possible reverse causality and findings from recent genetic analysis, which failed to support association between CRP genotypes coding higher CRP levels with CVD or risk factors. Interestingly, genetic analysis of haemostatic factors documented an moderate association of factor V gene and prothrombin gene with CHD risk (Ye et al., 2006). In spite of strong arguments based on numerous meta-analyses from epidemiological trials **there is still no joint consensus on the use of inflammatory markers (especially CRP) in risk evaluation in Europe, but not so in the U.S.**

Biochemical markers of haemostasis. High Lp(a) predicts risk of early AS similar to high level of LDL cholesterol. Lp(a) is a risk factor for advanced AS independent of LDL cholesterol that indicates a risk for plaque thrombosis. High heritability may signalize its role in person with positive family history and with high risk for sudden cardiac death (Nordestgaard et al., 2010). Fibrinogen has been identified in large prospective studies as an independent risk factor for CHD (Wilhelmsen et al., 1984; Woodward et al., 1997) and strong predictor for CV events (Coppola et al., 2006; Maresca et al., 1999). There is no joint consensus on the use of haemostatic markers in risk evaluation, except some specific indications mainly in subjects with positive family history.

9.3.2 Genetic markers of subclinical AS

A. Markers of lipid metabolism: apolipoprotein E, B, B-100 (ApoE, ApoB, ApoB-100), lipoprotein lipase (LPL), cholesterol-ester transferprotein, PCSK9 for proprotein convertase

subtilisin/kexin type 9, USF-1 for upstream transcription factor-1, Lp(a), LDL-receptor for familial defective ApoB-100 (FDB).

B. Markers of coagulation: PAI-1, t-PA, glycoprotein IIb/IIIa, F V, vWF, methylene-tetrahydropholate reductase, homocysteine, prothrombin.

C. Markers of endothelial function: endothelial nitric oxid synthase (eNOS), angiotensin converting enzyme (ACE), preproendothelin-1 (PPET-1), endothelin converting enzyme-1 (ECE-1), endothelin B receptor, NFκB, ICAM-1, VCAM-1, E-selectin, adrenomedullin, C-type natriuretic peptide (CNP), p22phox for NAD(P)H oxidase, superoxide dismutase, leptin receptor, a-adducin, caveolin, MEF2A (15q26.3) for myocyte-specific enhancer factor 2A, LTA (6p21.3) for lymphotoxin alpha, LGALS2 (22q12-q13) for galectin-2, ALOX5AP for 5-lipoxygenase, PDE4D (5q12) for phosphodiesterase 4D (Casas et al., 2006; Purcell et al., 2003).

Population screening for genetic polymorphism is currently not yet realistic.

9.3.3 Functional changes of the vascular wall (Lekakis et al., 2011)

Diagnostic modalities of endothelial dysfunction include assessment of epicardial and microvascular coronary endothelial function, local vasodilation by venous occlusion plethysmography, flow-mediated dilatation, arterial pulse wave analysis and pulse amplitude tonometry as well as microvascular blood flow assessment by laser Doppler flowmetry. Asymptomatic but advanced AS may be detected by ankle-brachial index (ABI). **These methods are widely used for identification of preclicnial AS in different studies, but only some of them seem to be recommended as screening tool (ABI for subclinical AS, parameters of arterial stiffness for end-organ damage).**

Quantitative coronary angiography (QCA) measures epicardial coronary vasodilatation either invasively [after intracoronary pharmacological stimuli, such as acetylcholine (ACh), metacholine, or papaverine] or non-invasively [using computed tomography (CT) or magnetic resonance imaging (MRI)] (Husmann et al., 2008). **Microvascular coronary endothelial function** is assessed by non-invasive methods, such as MRI and positron emission tomography (PET).

Venous occlusion plethysmography estimates the dose–response forearm blood flow (FBF) due to the local endothelium-dependent vasodilation (Joyner et al., 2001). An impaired endothelium-dependent relaxation (low ACh-induced FBF) has been documented in patients with CV risk factors at the level of microcirculation (Chowienczyk et al., 1992; Panza et al., 1990). **Brachial artery flow-mediated dilatation (FMD**) is evaluated through an ultrasound assessment of brachial artery diameter in basal condition and after 5 minutes of suprasystolic occlusion determined reactive hyperaemia, causing vasodilation. FMD is associated with a traditional risk factors for AS, it predicts CV risk and seems to be an independent prognostic marker of advanced AS. A low FMD is a marker of multifocal AS and disease extension (Coretti et al., 2002; Landmesser et al., 2004; Schroeder et al., 1999). Due to high interindividual variations of measurements, time-consuming character, and complicated technique, FMD is not recommended for population screening.

Parameters of arterial stiffness [aortic pulse wave velocity (PWV), augmentation index of a. brachialis (Aix)] are also associated with traditional risk factors for AS as well as are

independent predictors of CV risk, mainly in patients with AH, DM, end-stage chronic renal failure, and in the elderly hospitalized patients (Hansen al., 2006; Safar &, O´ Rourke, 2006). Abnormal values of arterial stiffness identify early AS and according to some authors may confirm endothelial dysfunction. Pulse wave registration is performed by various methods using different principles, such as piezoelectric, oscillometry, or applanation tonometry.

Measurement of peripheral vasodilator response with fingertip **peripheral arterial tonometry** (PAT) technology is emerging as a useful method for assessing endothelium-dependent vascular function (Kuvin et al., 2003). In response to hyperaemic flow, the digital pulse amplitude increases (Nohria et al., 2006). Patients at low Framingham Risk Score but with endothelial dysfunction are at a higher actual risk than patients with high Framingham Risk Score but normal endothelial function. Furthermore, endothelial dysfunction was found to be an independent risk factor for a future major adverse cardiovascular event (Rubinshtein et al., 2010).

Non-invasive **laser doppler flowmetry** enables the monitoring of skin microvascular blood flow, a window towards the responses that should be observed in other vascular beds, using various techniques (i.e. direct delivery of Ach, adrenaline, insuline, sodium nitroprusside, etc.) through iontophoresis, micro-dialysis, post-occlusive hyperaemia, or local skin heating (Fredriksson et al., 2009; Ozbebit et al., 2004).

Ankle-brachial systolic pressure index can reflect altered pressure values in PAO, most frequently of AS origin (Hirsh et al., 2001). Some authors define 5 ABI categories (McDermott et al., 2005): a) definite peripheral PAD: ABI <0.90, b) borderline ABI: 0.90–0.99, c) low-normal ABI: 1.00–1.09, d) normal ABI: 1.10–1.29, e) high ABI (possibly indicative of medial arterial calcinosis): >1.30. The optimal upper limit of normal ABI is unknown, recently ABI >1.30 has been suggested as the upper limit of normal for ABI (Hiatt, 2001). ABI is a marker of subclinical and advanced AS and correlates well with risk factors for AS. A strong correlation between decreased ABI, carotid or coronary AS and future cardiac or cerebrovascular events was demonstrated in different studies (Diehm et al., 2006; Dormandy & Creager, 1999; Fowkes et al., 1991; Ostergren et al., 2004). ABI <0.9 is linked with 2-4 fold increase of relative risk of CV events and mortality (Ankle Brachial Index Collaboration, 2008). Recently, an association had been found between ABI >1.4 and CV mortality (Resnick et al., 2004).

9.3.4 Morphological changes of the vascular wall

Morphological changes of the vascular wall are mostly detected by imaging techniques, such as ultrasound (IMT, AS plaque), IVUS, multiple detector–row (MDCT) coronarography, coronary Ca-scoring, MRI, PET, selective coronarography, etc. **AS changes of the arterial wall detected by any imaging techniques** (except for pathological ABI, "functional abnormality", that may prone also asymptomatic but advanced changes of peripheral arteries) clearly **confirm preclinical AS as a condition with increased CVD risk** (Graham et al., 2007).

Diagnosis of **coronary artery disease** is based generally on the confirmation of ischaemia by non-invasive functional tests (exercise ECG testing, stress echocardiography, or radionuclide scintigraphy), which are not suitable for population screening. Selective coronarography is a gold standard for visualization of coronary artery morphology, but

cost-benefit relations do not favour its use as screening tool. Nowadays, new imaging techniques are available (MRI, multi-slice CT for detecting coronary artery lesions and coronary calcium, as well as IVUS capable to provide a virtual histology from the coronary artery wall). Up to now, they have little significance as screening tools.

Due to the correlation between the severity of AS in one arterial territory and involvement of other arteries, it appears logical to examine non-invasively **peripheral arteries** (carotid) instead of coronary or intra-cerebral arteries. Ultrasound is relatively cheep, widely available, low-cost, and non-invasive method with good reproducibility. It may serve as a screening tool for morphological assessment of arterial wall (IMT or presence of AS plaque). IMT (carotid, femoral) shows a remarkable correlation with traditional RF, as well as their number, intensity, or duration. Moreover, IMT is associated with endothelial dysfunction (Corrado et al., 2006; Corrado et al., 2005; Novo et al., 1997). CIMT indicates multifocal AS as well as predicts target organ damage (CIMT ≥0.9 mm) and coronary artery disease (CIMT ≥0.85 mm) (Touboul et al., 2005). CIMT is also an independent predictor of future stroke and MI (ARIC Study, 2000; Rotterdam Study, 1997). A recent meta-analysis of 8 population studies [ARIC Study, 2000; Cardiovascular Health Study (CHS), 1999; Carotid Atherosclerosis Progression Study (CAPS), 2006; Kitamura Study, 2004; Kuopio Ischemic Heart Disease Risk Factor Study (KIHD RF), 1993; Longitudinal Investigation for the Longevity and Aging in Hokkaido Country (LILAC), 2005; Malmo Diet and Cancer Study (MDCS), 2005; Rotterdam Study, 1997] registered an increased rate of myocardial infarction (15%) and stroke (18%) for every increase of 0.1 mm in the CIMT value (Matthias et al., 2007). According to this data, IMT may be a "more powerful" predictor than other traditional risk factors. Significant carotid artery stenosis increases coronary risk about 6 times to those without AS lesion. Plaque characteristics appear to be crucial in prediction of cerebrovascular events (The ACSRS Study, 2005). Complex ultrasound evaluation of vascular wall morphology (carotid, femoral, and popliteal) has a higher predictive value for future CV in comparison with IMT (Belcaro et al., 1996). Detection of AS by ultrasound or other imaging methods indicates a high-risk condition.

10. Personalized CV risk assessment – Cost/benefit relations

Personalized CV risk assessment means identification of subjects with accelerated AS by evidence-based, non-invasive, widely available, cheap, and preferably objective method with good reproducibility. CVD risk should be known in every subject.

If there is a known CHD or CHD equivalent (Framingham), as well as CVD, type 2 DM or type 1 DM with end-organ damage such as microalbuminuria, renal impairment, or very high levels of individual risk factors with/without end-organ damage (SCORE), the risk estimation is not necessary, because patients are already in high/increased CVD risk and need aggressive management of all risk factors.

If the risk in not evident, should be estimated:

1. in countries using Framingham score, dominantly if ≥2 risk factors are present,
2. in European countries using ScoreCard, in every other patient.

If the calculated risk is ≤20% (Framingham) or <5% (SCORE), an individual risk assessment should be considered.

How to assess the absolute CVD risk quickly and easily?

ATP III Update:

1. patients with acute coronary syndromes or with CVD + DM are at very high risk,
2. patients with CHD or CHD equivalents are at high risk,
3. in every other patient – count the risk factors (see further a. and b.):
   3.1. calculate the number of points for each risk factor,
   3.2. estimate the global risk score by adding together the points for each risk factor,
   3.3. assess for each score the corresponding total risk for suffering a hard (fatal or nonfatal) CHD event within the next 10 years.
   a. if ≤1 risk factor is present, Framingham scoring is not necessary, patient is at low risk,
   b. if ≥2 risk factors are present, according to the Framingham Global Risk Point Score, 3 categories of CHD risk are possible: high (>20%), moderately high (10-20%), and moderate (<10%).

SCORE chart (table) (the risk can be read directly without any calculation):

1. choose a low or high risk chart,
2. in a table for one´s gender, smoking status, and age find the cell nearest to the ones´s systolic blood pressure and total cholesterol, use the HDL cholesterol table to refine the risk,
3. read directly the 10-year risk from the chart without any calculation,
4. to establish individual risk, check qualifiers listed in the latest preventive guidelines,
5. to project the risk to higher age, simply shift the found table cell upward to the desired age,
6. to project the relative risk, shift the found cell within the gender-age table downward and to the left to find the corresponding normal systolic BP and total cholesterol level, finally, shift this relative cell to the non-smoking table,
7. estimating the relative risk is simpler by using the relative risk chart,
8. to convert the risk for fatal CVD to the risk for total (fatal+nonfatal) hard CVD, multiply by 3 in men, and 4 in women, and slightly <3 in old people (ESC/EAS Guidelines, 2011).

There are no strictly recommended methods for population screening. No data are available about the validity of different methods in screening for subclinical AS. They should be evidence-based, non-invasive, objective, widely available, reproducible, cheap, and quick (Criqui et al., 2008). A recent paper has documented a 42% prevalence of functional markers of subclinical AS in a sample of primary prevention subjects from a high-risk Eastern region of Central Europe (Szabóová et al., 2010). Rigorous expert analysis of the available data documenting benefits and risks of therapies and procedures can improve the effectiveness of care, optimize patient outcomes, and favourably affect the cost of care by focusing resources on the most effective strategies.

11. Current guidelines modifying CV risk assessment. ACCF/AHA Guideline, 2010; ESH Task Force Document, 2009; ESC/EAS Guidelines, 2011

ACCF/AHA guideline (Greenland et al., 2010) for assessment of CV risk in asymptomatic adults differs from those used in Europe and recommend:

1. Risk assessment in all asymptomatic adults without a clinical history of CHD,
2. Family history of atherothrombotic CVD should be obtained in all asymptomatic adults,
3. CRP measurement is indicated:
   a. in the selection of patients for statin therapy: in men aged ≥50 years or women aged ≥60 years with LDL cholesterol <130 mg/dl (not on lipid-lowering, hormone replacement, or immunosuppressant therapy; without clinical CHD, DM, chronic kidney disease, severe inflammatory conditions, or contraindications to statins),
   b. in asymptomatic intermediate-risk men aged ≤50 years or women aged ≤60 years,
4. Hemoglobin A1C in patients with/without DM,
5. Microalbuminuria in asymptomatic hypertensives or diabetics as well as in asymptomatic adults at intermediate risk without AH or DM,
6. Lipoprotein-associated phospholipase A2 in intermediate-risk,
7. A resting ECG in asymptomatic adults with/without AH or DM,
8. Echocardiography to detect left ventricular hypertrophy in asymptomatic adults with AH,
9. Measurement of carotid artery IMT at intermediate risk,
10. Measurement of ABI at intermediate risk,
11. Exercise ECG in intermediate risk,
12. Stress myocardial perfusion imaging (MPI) in diabetics or asymptomatic adults with a strong family history of CHD or when previous risk assessment testing suggests high risk of CHD, such as a coronary artery calcium (CAC) score of ≥ 400,
13. Measurement of CAC at intermediate (10-20%) as well as low to intermediate risk (6-10%) 10-year risk,
14. In asymptomatic adults with DM aged ≥40 years: measurement of CAC,
15. Hemoglobin A1C may be considered for CV risk assessment in asymptomatic diabetics,
16. Stress MPI in asymptomatic adults with DM or when previous risk assessment testing suggests a high risk of CHD, such as a CAC score of ≥400.

ACCF/AHA guideline in asymptomatic adults does not recommend:

a) genotype testing for CHD risk, b) measurement of lipid parameters beyond a standard fasting lipid profile, c) natriuretic peptides, d) CRP neither in asymptomatic high-, nor low-risk men aged <50 years or women aged <60 years, e) FMD, arterial stiffness, stress echocardiography in low- or intermediate-risk, echocardiography without hypertension, stress MPI in low- or intermediate-risk, measurement of CAC in low-risk, coronary CT angiography, MRI coronary angiography.

Reappraisal of European guidelines on hypertension management (2009) modify the CV risk assessment in hypertension:

1. Total CV risk assessment must include a search for subclinical organ damage (SOD),
2. The presence of SOD in hypertension represents a high CV risk,
3. Simple, widely available, and low-cost measures are suitable for routine use: urinary protein excretion (including microalbuminuria), eGFR [Modification of Diet in Renal Disease (MDRD) formula], and ECG; cardiac and vascular ultrasound are more and more encouraged in Europe,
4. SOD should be assessed in screening and during the treatment.

ESC/EAS guidelines for the management of dyslipidaemias (2011) recommend the following evaluation of laboratory lipid and apolipoprotein parameters:

Lipid profile may be considered in:

1. Type2 DM, established CVD, hypertension, smoking, BMI ≥30 kg/m², waist circumference >94 (90 cm for Asian) males or 80 cm for women, family history of premature CVD or familial dyslipidaemia, chronic inflammatory diseases, chronic kidney disease,
2. Adult men ≥40 years and women ≥50 years of age or post-menopausal, particularly in the presence of other risk factor.

Recommendations for lipid analyses for screening for CVD risk:

1. Total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), TG (I/C),
2. Non-HDL-C as well as apoB as alternative risk markers in combined hyperlipidaemias, DM, MS, or CKD; Lp(a) in selected cases at high risk and in subjects with a positive family history of CVD (IIa/C),
3. apoB/apoA-1 ratio as well as non-HDL-C/HDL-C ratio as alternative parameters for risk analysis (IIIb/C).

Recommendations for lipid analyses of dyslipidaemias before treatment:

1. LDL-C, HDL-C, TG (I/C),
2. Non-HDL-C as well as apoB in combined hyperlipidaemias, DM, MS, CKD; Lp(a) in selected cases at high risk and in subjects with a positive family history of CVD (IIa/C),
3. TC may be considered but is usually not enough (IIb/C) before initiation of treatment.

Recommendations for lipid analyses as treatment target in the CVD prevention:

1. LDL-C (I/A),
2. TC if other analysis is not available; TG in hypertriglyceridaemias; non-HDL-C as well as apoB as secondary target in combined hyperlipidaemias, DM, MS, CKD (IIa/B),
3. HDL-C, apoB/apoA-1 ratio are not recommended (III/C).

12. Management of patients at high CVD risk

The management of patients, including type and intensity of treatment, is based on the CVD risk category. Persons at low risk do not require further testing for risk assessment, those already documented to be at high/very high risk are already candidates for intensive preventive interventions, so that added testing will not provide benefit.

Aggressive control of risk factors:

Epidemiological data suggest that eating fruit and vegetables, taking exercise, and avoiding smoking could lead to about 80% lower relative risk for myocardial infarction (Yusuf et al., 2004). Thus, lifestyle modification is of substantial importance in both men and women, at all ages, in individuals from all geographic regions of the world. **Luxembourg Declaration defined the characteristics for achievement of CV health as follows: 0-3-5-140-90-5-3-0** (avoidance of tobacco – adequate physical activity avoiding overweight (3 km walking at least 30 min per day) – 5 daily portions of fruit and vegetables – BP <140/90 mmHg – total

cholesterol <5 mmol/l – LDL cholesterol <3 mmol/l) (Ryden et al., 2007). Among individuals with ≥1 intermediate or major risk factors at 50 years of age, data suggest that aggressive global risk factor modification should be considered, given the associated high lifetime risks for CVD. Much more intensive lifestyle changes and aggressive risk factor modifications are needed in subjects at high risk (Yusuf et al., 2004).

Current recommendations of the European guidelines on disease prevention in clinical practice: Fourth Joint Task Force (Graham et al., 2007**) for management of patients at high risk,** updated according to Reappraisal of European guidelines on hypertension management (Mancia et al., 2009) and ESC/EAS guidelines for the management of dyslipidaemias (2011) underline the need for achievement of most rigorous risk factor control:

1. blood pressure 130-139/80-85 mmHg for all hypertensive patients, if possible, close or slightly below to lower values in this range for very high risk category,
2. total cholesterol <4.5 mmol/l (175 mg/dl) with an option of <4 mmol/l (155 mg/dl), if possible,
3. LDL-C <1.8 mmol/l (70 mg/dl) and/or ≥50% LDL-C reduction when target level cannot be reached in very high risk; LDL-C <2.5 mmol/l (100 mg/dl) in high risk; LDL-C <3.0 mmol/l (115 mg/dl) in moderate risk,
4. fasting glucose <6 mmol/l (110 mg/dl) and HbA1C <6.5%, if possible,
5. hs-CRP as a secondary target is not recommended for everybody, may be useful in people close to high risk category, for those hs-CRP <2mg/l.

The use of cardioprotective drugs (aspirin, ACE inhibitors, statins, beta-blockers, anticoagulants) mainly depends on the type and severity of organ involvement and is guided by evidence-based recommendations.

13. Further studies are needed to achieve an optimal approach to CV risk assessment in communities

Implementation of novel biomarkers and new methods into clinical practice will further promote the CV research and thus the assessment of CV risk. Based on new data from ongoing trials and scientific research, guidelines are continuously modified. In the near future, proteomic and genetic analyses may help to target vulnerable patients and monitor the beneficial effects of pharmacologic agents.

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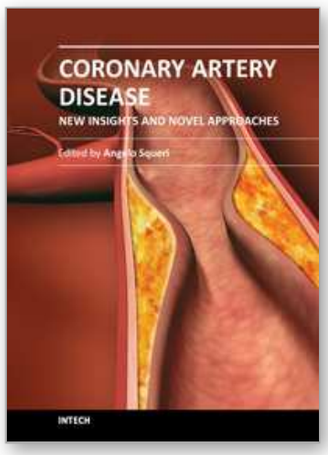

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Coronary Artery disease is one of the leading causes of death in industrialized countries and is responsible for one out of every six deaths in the United States. Remarkably, coronary artery disease is also largely preventable. The biggest challenge in the next years is to reduce the incidence of coronary artery disease worldwide. A complete knowledge of the mechanisms responsible for the development of ischaemic heart disease is an essential prerequisite to a better management of this pathology improving prevention and therapy. This book has been written with the intention of providing new concepts about coronary artery disease pathogenesis that may link various aspects of the disease, going beyond the traditional risk factors.

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