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The Importance of Risk Factors Analysis in the Prevention of Cardiovascular Disease (CVD)

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1. Introduction

1.1 Cardiovascular disease
Cardiovascular diseases (CVD) are the number one killer of modern humankind. According to the World Health Organization (WHO) about 17.5 million people die every year from cardiovascular diseases and it is estimated this number will increase up to 20 million by 2015. Although genetic factors have a significant impact on the cardiovascular disease occurrence, their importance is often overestimated. The results of numerous clinical and epidemiological studies emphasise that cardiovascular diseases can often be predicted and therefore preventable. Accordingly, it is possible to discern several important, independent disease risk factors which can be affected to a greater or less extent.

1.1.1 Definition
Cardiovascular diseases are caused by arterial lesions characterized by local intima thickening consisting of proliferating, altered smooth muscle cells, macrophages, lipids from intracellular and extracellular serum lipoprotein deposits and proliferating connective tissue (collagen, elastin, mucopolysaccharides. Consequent arterial narrowing causes CVD, stroke, and peripheral arterial disease. The risk factors leading to the development and occurrence of cardiovascular disease are arterial hypertension, cigarette smoking, hypercholesterolemia, hypertriglyceridemia, diabetes mellitus and positive family history. Additional factors favouring the occurrence of cardiovascular disease include obesity, sedentary lifestyle (insufficient physical activity) and emotional stress. Cardiovascular diseases are associated with high morbidity and mortality rates, thus posing a major health and socioeconomic problem to modern society. CVD are the world’s the leading cause of death and severe disability. CVD or ischemic heart disease occur due to reduction of coronary blood flow, most commonly caused by coronary thrombus. This results in myocardial lesions, whose extent determine the symptomatology, clinical course and disease outcome. According to symptomatology and clinical course, ischemic heart disease is categorized into acute coronary syndrome (ST-segment elevation myocardial infarction - STEMI, non-ST-segment elevation myocardial infarction - NSTEMI and unstable angina) and stable angina pectoris. In almost 99% of cases, CVD are caused by obstructive atherosclerosis and less frequently by spasm (usually idiopathic, or caused by drugs such as cocaine). Subintimal plaques reducing or obstructing coronary blood flow characterize atherosclerosis.
Strict prevention of risk factors in patients with established CVD and those with high-risk profile can reduce the incidence and recurrence of clinical complications - coronary artery disease, stroke and peripheral arterial disease. It is crucial to focus on the prevention of disability and premature death. Coronary atherosclerosis typically develops insidiously; it is irregularly distributed through vascular bed. Acute coronary syndrome occurs due to sudden obstruction of blood flow to heart muscle, mainly due to rupture of eccentric atherosclerotic plaque. Major clinical presentations of coronary heart disease are stable angina pectoris, unstable angina and myocardial infarction. Risk factors include high levels of LDL-cholesterol, low HDL-cholesterol level, high triglyceride level, smoking, diet and lifestyle as well as systemic diseases like arterial hypertension and diabetes. The association between serum total cholesterol and LDL-cholesterol levels with risk of coronary heart disease is now well recognized and enduring. HDL-cholesterol is inversely associated with risk of coronary heart disease. Reduction of serum LDL-cholesterol slows the progression of coronary heart disease. Reduced LDL-cholesterol was also beneficial in those patients with existing coronary heart disease even if their LDL-cholesterol is within normal limits.

1.1.2 The risk factors
Division of CVD risk factors into modifiable and non-modifiable is very useful because it shows us where to direct our efforts in cardiovascular prevention. Major modifiable risk factors are: high levels of total and LDL cholesterol, low HDL-cholesterol levels, high triglyceride levels, high blood pressure, diabetes (or glucose intolerance), cigarette smoking, obesity, insufficient consumption of fruits and vegetables, lack of regular exercise, personality structure and stressful social environment. Unfortunately, we cannot affect cardiovascular risk derived from family history, age and sex. Risk factors mentioned above insidiously lead to development and occurrence of cardiovascular diseases. Hypercholesterolemia, one of the major modifiable risk factor is important in symptomatic and in asymptomatic patients. It is important to analyze total cholesterol and also its main lipoprotein particles (LDL and HDL cholesterol) which are also parameters of increased CVD risk.

1.2 Atherosclerosis
Atherosclerosis is pathological process characterized by formation of subintimal plaques that can reduce or obstruct blood flow through the vessel. It is a result of normal blood vessels ageing, with initial lesion developing before age 30 (so-called fatty streaks). Risk factors that significantly accelerate this process are serum lipid impairment, hypertension, cigarette smoking, diabetes mellitus, obesity, physical inactivity and hereditary factors i.e. positive family history of cardiovascular disorders. Elevated level of low-density lipoprotein (LDL) and decreased level of high-density lipoprotein (HDL) strongly predispose the development of atherosclerosis. As mentioned above, so-called protective HDL-cholesterol is inversely proportional to the risk of CVD. Main causes of its decrease are cigarette smoking, obesity and inadequate physical activity. Premenopausal women usually have higher HDL levels than men due to hormonal effects of estrogen and therefore lower incidence of CVD. This protective effect vanishes in postmenopause. The cholesterol level and the incidence of CVD are strongly influenced by environmental factors including diet. Besides hyperlipoproteinemia, arterial hypertension is another major risk factor for the occurrence and progression of atherosclerotic lesions. The main pathophysiological
mechanism is mechanical damage to endothelial cells due to altered hemodynamics, i.e. enhanced force of the blood flow, or formation of whirls at vascular bifurcations. Arteriosclerosis is a general term describing hardening (and loss of elasticity) of medium or large arteries. Atherosclerosis is arteriosclerosis caused by atheromatous plaque. Arteriolosclerosis is a narrowing of small arteries caused by its wall thickening. In recent years, development of atherosclerosis has been elucidated (figure 1).

Fig. 1. Progression of atherosclerosis from fatty streak, formation of subintimal plaque, further lipid deposition and finally plaque rupture with subsequent thrombogenesis (Figure was produced using Servier Medical Art).

Atherosclerosis remains the major cause of death and premature disability in developed societies. It is predicted that by the year 2020, cardiovascular diseases (notably atherosclerosis) will become the leading global cause of total disease burden. Etiology of atherosclerosis is very complex, but outcome remains the same – reduction of blood flow through various organs leading to distinct clinical entities. Coronary atherosclerosis commonly causes myocardial infarction and angina pectoris. Atherosclerosis of the cerebral arteries frequently provokes strokes and transient cerebral ischemia. Atherosclerosis of the peripheral vessels causes intermittent claudicating, gangrene and mesenteric ischemia. Atherosclerosis can affect the kidneys either directly or as a frequent site of atheroembolism. Some regions are particularly susceptible to atheromatous lesions, respectively bifurcations. For example, proximal left anterior descending (LAD) coronary artery exhibits a particular predilection for developing atherosclerosis disease. Likewise, atherosclerosis preferentially
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affects the proximal portions of the renal arteries and carotid bifurcation, in the extracranial brain circulation. Not all manifestations of atherosclerosis result from stenotic, occlusive disease. Ecstasies and development of aneurismal disease (pathological widening of blood vessel), for example, frequently occur in the aorta. In addition to local, flow-limiting stenoses, non-occlusive intimal atherosclerosis also occur diffusely in affected arteries, as shown by intravascular ultrasound and postmortem studies.

Atherogenesis in human typically occurs gradually over a period of many decades. Atherosclerotic plaques growth probably does not occur in a smooth, linear fashion, but rather discontinuously, with periods of relative quiescence punctuated by periods of rapid progression. After a prolonged silent period, atherosclerosis may clinically manifest itself in acute or chronic fashion (stable angina, reproducible intermittent claudicating or acute coronary syndrome). Some people never experience clinical manifestation of arterial disease despite the presence of widespread atherosclerosis demonstrated post-mortem.

The endothelial monolayer overlying the intima contacts blood. It’s structural and functional consistency is the first dam for development of atherosclerosis. Hypercholesterolemia promotes accumulation of LDL-particles in the intimae. The lipoprotein particles then associate with constituents of the extracellular matrix, notably proteolytic enzymes. Sequestration within the intima separates lipoproteins from some plasma antioxidants and favours oxidative modification. Such modified lipoprotein particles may trigger a local inflammatory response responsible for signaling subsequent steps in lesion formation. The augmented expression of various leukocytes adhesion molecules recruits monocytes to the site of a nascent arterial lesion.

Once adherent, some white blood cells will migrate to the intimae attracted by the factors including modified lipoprotein particles themselves and chemo attractant cytokines, such as the chemokine macrophage chemo attractant protein-1 produced by vascular wall cells in response to modified lipoproteins. Leukocytes in the evolving fatty streak can divide and exhibit augmented expression of receptors for modified lipoproteins. These mononuclear phagocytes ingest lipids and become foam cells, represented by a cytoplasm filled with lipid droplets. As the fatty streak evolves into a more complicated atherosclerotic lesion, smooth-muscle cells migrate through the internal elastic membrane and accumulate within the expanding intimae where they lay down extracellular matrix that forms the bulk of the advanced lesion. Depending on the lipid compound, plaques are divided into stable and unstable. Stable plaques contain smaller amount of ingested lipids covered with thick fibrous layer thus preventing its rupture. On the other hand, unstable plaques with high lipid content and thin fibrous cap are very vulnerable and their rupture initiates acute ischemic event.

2. Modifiable risk factors

2.1 Blood pressure (BP)

High blood pressure is the arterial pressure of above normal limits (traditionally 140/90 mmHg). It is commonly called the silent killer because it damages vital organs (brain, heart, kidneys) without causing any early symptoms. Untreated hypertension increases the risk of heart failure, heart attack (myocardial infarction), stroke, aneurysms, kidney failure and damage to retinal blood vessels. Hypertension is marked by rise in blood pressure regardless of the cause, and is divided into primary (essential) and secondary hypertension. In most (95%) cases etiology is multifactorial and incompletely understood and this is called
primary or essential hypertension. Secondary hypertension (5%) results from damage of organs involved in regulation of blood pressure, endocrine disorders and drug toxicity. Children and adolescents have significantly lower blood pressure than adults do. Blood pressure naturally exhibits diurnal variation. Physiologically blood pressure varies throughout day with the highest values in the morning and lowest during sleep at night. Arterial blood pressure usually progressively increases with age because great arteries lose their natural elasticity and become rigid. There are two basic mechanisms of increased blood pressure - vasoconstriction (contraction of the arteries) usually caused by hormones or stress and the increase in total blood circulating volume. Obesity, sedentary lifestyle, stress, excessive alcohol and fatty foods intake have an important role in hypertension. These causes are potentially modifiable and by doing so hypertension can be avoided unless, there is a hereditary, constitutional cause of hypertension. Stress temporary increases blood pressure by activating biochemical processes that cause vasoconstriction of blood vessels. This can partly explain the mechanism of hypertension.

A diagnosis of arterial hypertension and all treatment decisions rely on the correct measurement of arterial blood pressure. The clinical measurement of arterial pressure using a calibrated mercury sphygmomanometer is still the main method in everyday clinical practice but it demands compliance with certain rules and recommendations. Because of the latest knowledge, and particularly chronobiology, we are increasingly aware of this method’s limitations, primarily due to the characteristics of the measurement variable itself. A more comprehensive picture from arterial pressure (AP) values can be obtained by an intermittent 24-hour measurement of arterial pressure, and mean values obtained with this method are the closest to real values. Self-measurement of the arterial pressure cannot fully replace the intermittent arterial pressure measurement, but it can represent an additional source of information in diagnostic procedures and treatment decisions. Patient education and certified sphygmanometers are mandatory to avoid false positive and negative measurements. Both intermittent AP measurement and self-measurement have shown to be superior in the prediction of target organ damage and its progression to clinical measurement. When applying these methods, it is important to use devices authorized by international professional societies. The appropriate combination of more measurement methods is the only proper way to make an accurate diagnosis of arterial hypertension, assess total cardiovascular risk, and make the safest decision on treatment method.

Arterial hypertension is an important risk factor for both cardiovascular and renal disease. Blood pressure control is important to prevent complications that may attribute to elevated blood pressure.

Treatment of arterial hypertension is based on two important principles: application of non-pharmacological measures or lifestyle changes, and pharmacotherapy. The new ESH/ESC (European Society of Hypertension/European Society of Cardiology) guidelines for arterial hypertension diagnosis and treatment emphasize the importance of total cardiovascular risk assessment in addition to blood pressure values. This means that a person with normal mean blood pressure can have higher cardiovascular risk than hypertensive person without additional risk factors. New laboratory tests and diagnostic procedures have been introduced in order to stratify cardiovascular risk of hypertensive patients. Routine assessment of target organ damage (especially heart, kidney and retina) now includes, among others, microalbuminuria and measurement or estimation of glomerular filtration rate.
Main treatment goals are reduction of target organ damage and prevention of cardiovascular events. Lifestyle changes are recommended to all patients and represent main stem of therapy in spite of wide spectrum of medications. The Guidelines have kept their educational and advisory character, emphasizing individual approach to patients, thus trying to improve implementation in everyday practice.

2.1.1 Isolated systolic hypertension
Introduction of isolated systolic hypertension as a separate entity confirmed the importance of systolic blood pressure as cardiovascular risk factors, indicating the need to treat this form of hypertension particularly prevalent in elderly and very elderly patients. It is defined as systolic blood pressure above 140 mmHg, with diastolic values below 90 mmHg. The goal of therapy for more patients is BP under 140/90 mmHg, but for diabetic patients and individuals at high or very high total CVD risk, the BP threshold should be lower (130/80 mmHg). In patients with established CVD, the BP goal is < 130/85 mmHg and the choice of antihypertensive drugs depends on the underlying cardiovascular disease, concomitant disease, and the presence or absence of other cardiovascular risk factors. In asymptomatic individuals, the decision to start treatment depends on not only the level of BP, but also the assessment of total cardiovascular risk and the presence or absence of subclinical target organ damage. BP reduction should generally be obtained gradually. Elevated BP, whether systolic or diastolic, is established as a strong, independent risk factor for renal disease and for several cardiovascular (CV) disorders—including coronary heart disease (CVD), stroke, heart failure and peripheral arterial disease.

2.1.2 Definition and classification of hypertension
From a prognostic point of view, there is no clear cut-off value to define hypertension because BP distribution in population follows Gaussian curve. This has major implications for definition of hypertension particularly since there is no distinctive BP level at which risk of CV or renal disorder starts. On the contrary, CV risk is continuous and graded across the whole BP range and hence from a prognostic viewpoint the definition of hypertension is arbitrary. Nevertheless, for practical and communication purposes hypertension is considered and defined as a separate entity, as if it were a dichotomous (present/absent) variable. The pragmatic determinant of the definition of hypertension should be that level of BP at which investigation and management do more good than harm as determined by randomizes clinical trial (RCT) evidence. In fact, evidence supporting current definition of hypertension most commonly used around the world is not based on RCT evidence but rather based on overall evidence. Nevertheless, the current definitions still seem reasonable. Whilst the definition of hypertension (systolic BP>140 mmHg and/or, diastolic BP 90>mmHg) is universally accepted for the classification of BP (Table 1 and 2). The importance of raised BP lies in the fact that it is one of the major risk factors for current global mortality. Indeed raised BP, here defined as a systolic BP> 115 mmHg, is current the biggest single contributor to death around the world. Prevalence of hypertension, defined as a systolic BP>140 mmHg and/or a diastolic BP >90 mmHg varies around the world. Hypertensions rates also vary with age and sex. BP tend to rise with age in both men and women once populations have become exposed to the adverse environmental factors associated with development of hypertension (i.e. advanced age, excess salt, calories, saturated fat and alcohol intakes with reduced intake of fresh fruit.
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<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic</th>
<th>Diastolic</th>
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<td>Optimal</td>
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<td>&lt;80</td>
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<tr>
<td>Normal</td>
<td>120 - 129</td>
<td>80 - 84</td>
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<td>High normal</td>
<td>130 - 139</td>
<td>85 - 89</td>
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<td>Grade 1 hypertension (mild)</td>
<td>140 - 159</td>
<td>90 - 99</td>
</tr>
<tr>
<td>Grade 2 hypertension (moderate)</td>
<td>160 - 179</td>
<td>100 - 109</td>
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<tr>
<td>Grade 3 hypertension (severe)</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>&lt;90</td>
</tr>
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</table>

Table 1. Classification of BP levels: European Guidelines

<table>
<thead>
<tr>
<th>BP classification</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120 - 139</td>
<td>80 - 89</td>
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<td>Stage 1 hypertension</td>
<td>140 - 159</td>
<td>90 - 99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>≥110</td>
</tr>
</tbody>
</table>

Table 2. Classification of BP levels: American Guidelines

and vegetables and reduced exercise output). Until the age of 60, hypertension is usually more common in men than women but after then even higher rates are apparent among women. It is also clear than in many parts of the world including the established market economies, hypertension affects the majority of adults over the age of 60 years and presents a major public health issue.

By contrast, in several remote uncultivated populations around the world BP levels show the natural relationship between BP an increased age. These data taken from the Intersalt study showed no increase in systolic or diastolic BP across the age range 20 to 60 years in populations around the world that were not exposed to adverse environment factors.

Future prospects for the prevalence of hypertension: Because 80% of the world’s population is in the process of development, humongous increase in hypertension prevalence is expected. It is therefore even more important that optimal BP management is determined and put into practice.

Why will the prevalence of hypertension increase? The absolute number of people affected by raised blood pressure will rise over the next 2 decades in part because the world population is increasing and the mean age of the world’s population (accompanied by hypertension) is increasing. Paradoxically in developing communities, adverse changes first arise in people from the higher socio-economic strata (SES). Consequently, it is in this part of society that strokes and coronary events first tend to appear. As the development, process continues the exposure to risk factor reverses and the CVD are more prevalent in the lower SES.

Based on the large prospective observational data both systolic and diastolic BP show a strong direct relationship with all major adverse cardiovascular events, including coronary heart disease (CHD), stroke, cardiovascular mortality and heart failure.
Although the relationship varies by age and sex, a 20-mmHg rise in systolic BP or a 10-mmHg rise in diastolic BP doubles the cardiovascular (CV) risk. Support for this linear association between increased BP and risk of CV events arise from the results of hypertension treatment. Meta-analyses of these trial data consistently and clearly show that BP reduction is effective in reducing CV events. Highly significant and clinically important reductions of stroke and CHD events and vascular deaths were apparent using these agents. Interestingly the benefits in terms of CHD events reduction were less than those expected from prospective observational data. Nevertheless, 10-20 mmHg average reduction in BP achieved in the trials improves CHD prevention.

2.1.3 High blood pressure - hypertension
It is the one of most prevalent cardiovascular disorder, but is also a high-risk factor for the development of coronary heart disease. Compared with normal blood pressure in healthy subjects, hypertension increases the risk of developing CVD fivefold. In people over the age of 45, high blood pressure is the main risk factor for the development of myocardial infarction. However, the risk for development of myocardial infarction increases with blood pressure in all age groups. Treatment of hypertension results in clear reduction of associated disorders such a myocardial insufficiency, renal disorders and stroke. Those who are 65 years or more benefit most from a reduction of raised blood pressure in terms of prevention of myocardial infarction. Borderline hypertension in the young is an indicator of increased risk for cardiovascular disease in older age, therefore early prevention and prophylactic treatment is advised.

2.2 Lipids
Lipids are not water-soluble and their transport in blood is only possible in complexes with protein-apoprotein. Lipoprotein particles have spherical shape. Their main goal is the transfer of lipids and fat-soluble vitamins. They consist of hydrophobic core containing nonpolar lipids (triglycerides and esterified cholesterol) and hydrophilic surface layer of polar lipids (phospholipids and nonesterified cholesterol). Apoproteins are located on the surface but their nonpolar part reaches the core particles. The main metabolic role of apoprotein is to act as a cofactor of some enzymes involved in the metabolism of lipoprotein particles and to bind to specific receptors on the surface of various cells and thus facilitate the entry of lipoproteins into them and catabolism of these particles in the cells. Lipoproteins are divided as follows:
1. Chylomicrons
2. Very low density lipoprotein - VLDL
3. Low density lipoprotein - LDL
4. High density lipoproteins - HDL
5. Intermediate density lipoproteins - IDL
The largest particles - chylomicrons transport triglycerides and cholesterol ingested in meals from the small intestine to the liver. Bloodstream is abundant with chylomicrons after meal, especially the one rich and fat. VLDL particles are synthesized in the liver and transport triglycerides and cholesterol to the heart muscle and adipose tissue. Since VLDL particles hydrolyze triglyceride and release smaller particles IDL particles during their travel through bloodstream, they are believed to promote atherosclerosis. LDL particles are the product of VLDL catabolism and mainly consist of cholesterol. LDL carries cholesterol from the liver...
and blood cells. Excess of cholesterol not used by cells is deposited in artery walls. Gradually, deposited cholesterol and other substances create plaque, which can eventually cause a blockage of blood vessel. HDL particles contain more protein than any other lipoprotein. HDL circulates through the blood and removes excess cholesterol from the blood and tissues, returning it to the liver from where one can again be incorporated into LDL. High HDL cholesterol levels are associated with low levels of chylomicrons, VLDL remnants, LDL and consequently a lower risk of atherosclerosis.

HDL-cholesterol particles are rich in cholesterol, but it is descended from the atherosclerotic fatty deposits on artery walls where it is in surplus. Therefore, the particles are protective, preventing the development of atherosclerosis.

Unlike HDL-cholesterol, LDL-cholesterol particles, which also has the highest cholesterol content are highly atherogenic and play a key role in various stages of atherosclerosis. Increased amount of LDL-cholesterol in the blood is the most important etiological factor for the occurrence of coronary heart disease and myocardial infarction. Low HDL-cholesterol is also an important risk factor. Clinical importance of diagnosing and treating dyslipidemia is prevention of emergence and development of atherosclerosis and its major clinical forms - coronary heart disease and myocardial infarction.

Relation between level of cholesterol (especially LDL-cholesterol) and CVD risk is supported by data from studies of patients with a family hypercholesterolemia. Heterozygous for this disease usually die in the fifties of myocardial infarction, while homozygous have even higher cholesterol levels and die from CVD before age 20. Epidemiological studies in different countries in the world, which include socio-economic conditions and diet, show a direct correlation between the concentration cholesterol in blood and mortality from CVD. There is no population with high CVD and overall low cholesterol level in the blood. In case of exceptions, there are other risk factors for CVD.

It is interesting to notice that the Japanese, who live in Japan on local diet with low concentration of cholesterol, after migrating to USA, acquire dietary habits of the host country and their level of blood cholesterol is much greater than in Japan. Consequently, the incidence of coronary disease is increased.

High triglycerides blood level is also a risk factor for cardiovascular disease, but less important than hypercholesterolemia.

In contrast to hypercholesterolemia, where CVD risk rises with concentration of cholesterol in the blood, the biggest risk arises with moderate increase in triglyceride level. Hypertriglyceridemia is regularly accompanied by a decreased HDL-cholesterol and low HDL-cholesterol is an important atherosclerotic risk factor, independent of other factors. VLDL and IDL particles, both rich in triglycerides have atherogenic effect and hypertriglyceridemia promotes thrombogenesis and inhibits fibrinolysis. Only extremely severe hypertriglyceridemia (greater than 10 mmol/L) increases risk of acute pancreatitis. Increase in levels of special types of lipoprotein particles Lipoprotein (a) (Lp (a)) which are similar in composition to LDL particles, but also containing Apo (a), (intervenes in the process of thrombogenesis), is an independent risk factor for atherosclerosis.

2.2.1 Dyslipidemia

Dyslipidemia is defined as an abnormal plasma lipid status. Common lipid abnormalities include elevated levels of total cholesterol, LDL-cholesterol, lipoprotein (a), triglyceride, HDL-cholesterol and a preponderance of small dense LDL particles. These abnormalities
can be found alone or in combination. Most patients with atherosclerotic vascular disease have some form of dyslipidemia, even though their total cholesterol may not differ significantly from normal values. 35-40% of all CVD cases occur in patients with normal total cholesterol levels (< 5 mmol/L < 190 mg/dl).

Total plasma cholesterol level should be below 5 mmol/L (190 mg/dl) and LDL-cholesterol should be below 3 mmol/L (115 mg/dl). For patients with clinically established CVD, patients with diabetes and asymptomatic people at high risk of developing CVD, treatment goals should be total cholesterol < 4.5 mmol/L (175 mg/dl) and LDL-cholesterol < 2.5 mmol/L (100 mg/dl).

Treatment for HDL-cholesterol and triglycerides disorders are indicated if HDL-cholesterol values are < 1.0 mmol/L (< 40 mg/dl) in men and < 1.2 mmol/L (46 mg/dl) in women and fasting triglycerides > 1.7 mmol/L (150 mg/dl).

Target cholesterol values according to European Guidelines for CVD prevention in clinical practice:

1. Target cholesterol levels for the general population:
   - Total cholesterol < 5 mmol/L (190 mg/dl)
   - LDL-cholesterol < 3 mmol/L (115 mg/dl)
   - HDL-cholesterol > 1.2 mmol/L (46 mg/dl) in women and > 1.0 mmol/L (40 mg/dl) in men
   - Triglycerides 1.7 mmol/L (150 mg/dl) or < 1.7 mmol/L (150 mg/dl)

2. Target cholesterol levels for patients at high risk:
   - Total cholesterol < 4.5 mmol/L (175 mg/dl)
   - LDL-cholesterol < 2.5 mmol/L (100 mg/dl)
   - HDL-cholesterol in women > 1.2 mmol/L (46 mg/dl) and in men > 1.0 mmol/L (40 mg/dl)
   - Triglycerides < 1.7 mmol/L (150 mg/dl)

Studies demonstrate an association between increased concentrations of cholesterol, especially LDL-cholesterol and advanced atherosclerosis. Association of HDL-cholesterol levels with atherosclerosis is often underestimated, partly because most studies address the need for statin therapy.

However noted that the increased concentration of lipoprotein (a), Lp (a), a special kind of particles that have no metabolic close ties with other lipoproteins, a risk factor for coronary heart disease as well as increased LDL-cholesterol. To explains the structural similarity glycoprotein (a) which is a major apoprotein of these particles with plasminogen and content of cholesterol and apoprotein B in these particles. These particles can inhibit fibrinolysis and promote competitive thrombogenesis by inhibiting binding of plasminogen for its binding sites on endothelium. The importance of risk factors is similar to smoking.

Dyslipidemia is a disorder of lipoprotein metabolism, caused by their excessive or otherwise, insufficient production. Disturbances characteristic of dyslipidemia include elevated levels of triglycerides (hypertriglyceridemia), decreased levels of HDL-cholesterol, elevated levels of LDL-cholesterol, lower LDL/HDL ratio and elevated levels of free fatty acids. Dyslipidemia is a heterogeneous disorder of complex etiology. The causes of dyslipidemia may be a primary and secondary. Primary causes include hereditary factors such as the deficit for the LDL receptor or apoprotein B involved in binding LDL particles to LDL receptor. In practice, the primary causes account for only a small part of cases, with predominance of secondary causes such as obesity, high fat intake, physical inactivity, smoking, diabetes and hypothyroidism.
Dyslipidemia, especially elevated concentration of LDL-cholesterol and decreased HDL-cholesterol, along with high blood pressure significantly contribute to wear-accelerated development of atherosclerosis, a condition in which fat, calcium and cellular degradation products accumulate along the walls of arteries forming atherosclerotic plaque. Over time, the plaque increases by reducing the diameter of blood vessels, its elasticity and therefore blood flow. Result of decreased elasticity can be ruptured blood vessels leading to cardiovascular diseases such as coronary heart disease or cerebrovascular disease.

A fasting lipoprotein profile, consisting of total cholesterol, LDL-cholesterol and triglycerides should be obtained in all adults over 20 and repeated at least once every 5 years. Blood samples should be drawn after 9-12 hour fast while the person is in a steady-absence of active weight loss, acute illness, recent trauma or surgery, pregnancy or recent change in diet. To ensure reliable measurements, blood samples should send to a laboratory recognized by an established standard program.

Once a dyslipidemia is diagnosed, a history, physical examination, and basic laboratory tests should be performed to screen for secondary cause of dyslipidemia, including diet, medications, alcohol abuse, diabetes, hypothyroidism, nephritic syndrome, chronic renal failure and obstructive liver disease. Raised cholesterol and free fatty acid levels in the blood represent a further risk factor for development of atherosclerosis and CHD. The strong relationship between LDL-cholesterol and CVD mandates intensive lowering of LDL-cholesterol thus reducing cardiovascular morbidity and mortality. Elevated levels of total cholesterol and LDL-cholesterol and low levels of HDL-cholesterol are major modifiable lipid risk factors for CVD and other forms of atherosclerotic vascular disease. It is estimated that for each 1% decrease in LDL-cholesterol and for each 1% increases HDL-cholesterol, the risk for cardiovascular events is reduced by 2% and 3%, respectively. Other important modifiable risk factors for CVD include elevated levels of triglyceride, lipoprotein(a), small dense LDL particles, homocysteine, C-reactive protein (CRP), fibrinogen and lipoprotein-associated phospholipase A2 (Lp-PLA2).

The frequent occurrence of raised blood lipid values in the western industrials and countries is attributable to a diet, which is high in fats, calories and carbohydrates and low in dietary fiber in combination with relatively little exercise. Blood lipids are bound to transport proteins in blood. Of particular interest in this respect is what known as the VLDL (very low-density lipoprotein) lipoprotein transport molecule, the LDL (low-density lipoprotein) lipoprotein transport molecule and the HDL (high-density lipoprotein) lipoprotein transport molecule. These terms describe the physical-chemical properties of the molecules and serve to distinguish between them when analyzing lipids in laboratory. The LDL molecules carry more than 60-70% of the cholesterol bound in the blood and are therefore the „risk molecule” for atherosclerosis. The HDL molecule carries about 35% of the cholesterol and above all captures the cholesterol, which passes from the tissues into the blood. Ultimately, the VLDL molecules carry only 10-15% of total cholesterol and most of the free fatty acids.

The frequent development of general atherosclerotic condition increases with the proportion of LDL and VLDL molecules in the blood and decreases with the level of the HDL content. In general, a reduction in total cholesterol, or LDL fraction, leads to a reduction of 2 to 3% of the risk of developing CHD. Assessment of the risk of each individual patient requires individual assessment of each component of blood lipids, and the determination of total cholesterol and of the free fatty acids. The HDL values are about 10-20% higher in women than men of all ages. They increase with regular participation in
sports, but are lower in smokers, overweight and diabetics. The other known risk factors are also reflected by the individual blood lipid values.

2.2.2 Identification of genetic dyslipidemia
If severe hypercholesterolemia is present (total cholesterol > 7.7mmol/L or > 300mg/dl) or a genetic disorder is discovered, a family history and measurement of cholesterol in other family members is indicated.

2.2.3 Hyperlipidemia
Hyperlipidemia is a type of lipid disorder consisting of hypercholesterolemia and hypertriglyceridemia and is marked by increased lipids concentration in the blood. It is classified in six classes (according to Fredericksen). For clinical purpose, it is divided into primary, or familial hyperlipidemia caused by genetic factors and secondary (acquired) hyperlipidemia, which arise because of liver disease, diabetes or thyroid gland disorder. Other important risk factors for the occurrence of secondary hyperlipidemia are the use of some medications and birth control pills. Although part of hyperlipidemia is due to genetic reasons, the majority of secondary hyperlipidemias occurs as the effects of lifestyle, inadequate physical activity and improper and diet. One should borne in mind that, despite all the pathology caused by hyperlipidaemia, fats are essential for normal functioning of the organism.

2.2.3.1 Hypercholesterolemia
Hypercholesterolemia or increased blood cholesterol level found in diseases such as hepatitis, renal disease, hypothyroidism and diabetes. Hypercholesterolemia is often a consequence of inadequate nutrition, rich in saturated fatty acids. Therefore, dietary changes, increased physical activity and finally pharmacological therapy are advised for people with elevated cholesterol levels in blood. Unfortunately, most of the blood cholesterol is produced in liver so lifestyle changes can lower cholesterol level no more than 15%. Therefore, therapy in indicated in cases of insufficient results from diet. Studies show that high levels of total cholesterol and LDL-cholesterol are one of the major causes of cardiovascular diseases and maintaining proper LDL/HDL ratio reduces the risk of CVD.

2.2.3.2 Hypertrygliceridemia
Hypertriglyceridemia is elevated level of triglycerides, with normal LDL-cholesterol level. Hypertriglyceridemia usually occurs as results of poor eating habits and inadequate physical activity and is common in obese people. Basic recommendation in the triglyceride lowering diets are reducing fat intake up to 15% of total calories (fatty meat, fried foods, replacing animal fat with vegetable), reducing the amount of carbohydrates up to 55% of total daily caloric intake, selection of complex carbohydrates (cereals, pasta, potatoes) and intake of foods rich in omega-3 fatty acids (fish, fish oil).

2.2.3.3 Combined hyperlipidemia
There are often combined hyperlipidemias with the elevated blood levels of both cholesterol and triglycerides. It can be result of bad habits and obesity, genetic predisposition or as a result of certain diseases and condition. It also represents major risk for coronary heart disease.
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2.2.4 Lipoproteins and lipoproteins components

Lp (a)-Lp little is low-density lipoprotein that binds an additional protein called lipoprotein a. High concentration Lp (a) increases the risk of atherosclerosis.

Apolipoprotein A is the main components of HDL-cholesterol. Lower values of Apo A and low HDL-cholesterol is associated with increased risk of atherosclerosis.

Apolipoprotein B is a major component of LDL, IDL, and VLDL apoB chylomicrons. Therefore, it is located in atherogenic lipoproteins. The concentration of apoB is a direct of concentration of atherogenic lipoproteins in plasma. This parameter is a useful indicator of atherosclerosis in patients with hypertriglyceridemia and with normal LDL-cholesterol.

2.2.5 Severe familial hyperlipidemias

Familial hypercholesterolemia (FH) is characterized by hypercholesterolemia and associated with elevated levels LDL-cholesterol, xanthomata, premature coronary heart disease with positive family history. CVD occur in men between 30-50 years, in women 50-70 years. It is present in 5-10 % of individuals with CVD at age below 55 years.

Familial Combined hyperlipidemia (FCH) is this most common among severe hyperlipidemia, with the prevalence of 1/100 (the most common clinically relevant genetic disorder).

2.3 Diabetes mellitus, insulin resistance and metabolic syndrome

2.3.1 Diabetes mellitus

Diabetes mellitus, both type 1 and type 2, is also a major risk factor for cardiovascular disease. Hyperlipoproteinemia, hypertriglyceridemia in particular, i.e. elevated levels of very-low density lipoprotein (VLDL) particles and atherogenic LDL deriving from VLDL, with concurrent decrease in the level of protective HDL particles are quite common in diabetic patients. LDL particles that undergo no enzymatic glucosylation due to elevated blood glucose undergo prompt phagocytosis by macrophages, thus stimulating atherogenesis. In addition, hyperinsulinemia causes damage to vascular endothelium.

Since diabetes is one of the major modifiable risk factor for CVD, its’ prevention in one of the main goals of modern cardiovascular medicine. Inadequate physical activity decreases the concentration of HDL, whereas obesity is associated with hyperglycaemia and hyperinsulinemia. CHD is the major threat to modern society and, according to estimations; it will remain so at least by 2020. Therefore, all efforts invested in the study of cardiovascular disease are fully justified. In line with this, recording and analysis of the prevalence of risk factors for cardiovascular disease as the most common cause of CVD. Progression to diabetes can be prevented or delayed by lifestyle intervention in individuals with impaired glucose tolerance. In patient with type 1 and type 2 diabetes, good metabolic control prevents microvascular complications and can prevent cardiovascular events. In type 1 diabetes, glucose control requires appropriate insulin therapy and concomitant professional dietary therapy. In type 2 diabetes, professional dietary advice, reduction of overweight and increased physical activity should be the first treatment aiming at good glucose control. Treatment goals for blood pressure and lipids are generally more ambitions in patient with diabetes (see previous sections).

Diabetes is also a very important CVD risk factor. It is known that the frequency and intensity of artery atherosclerosis is higher in diabetes, especially type 2. Three quarters of diabetic patients die from diseases caused by atherosclerosis, especially coronary artery
disease and ischemic stroke. Only long-term reduction of glucose level decreases a risk of atherosclerosis. The men with proven glucose intolerance have even 50% higher risk of coronary heart disease than men with normal test submission glucose. Risk is even twice higher in women. Mortality from CVD in diabetic’s disease is ten times higher than in people who have no diabetes. In diabetic’s hyperlipoproteinemia, particularly hypertriglyceridemia, is more common, the amount VLDL-particles is higher, more atherogenic LDL-particles are generated by VLDL-particles degradation and the amount of protective HDL-particles is reduced. Macrophages phagocytes LDL- particles faster, due to increased amounts of glucose in the blood promoting non-enzymatic glycosylation, thus stimulating atherogenesis. Altered metabolisms of glycosaminoglycans in diabetic patients are also important for the increased incidence of hyperglycaemia-related atherosclerotic changes. Hyperglycemia, similar to LDL-cholesterol and VLDL-cholesterol in plasma, slows down the regeneration of endothelial cells, encouraging atherogenesis. Hyperglycemia acts as oxidant, accelerating oxidation of LDL-cholesterol particles, partially by reducing concentrations of vitamin C. No enzymatic glycosylation of collagen, accelerated by hyperglycemia also stimulates platelet aggregation and thus atherogenesis. Altered collagen strongly binds LDL-particles. Diabetic platelets synthesize more thromboxane and endothelial cells synthesizes less prostacyclin, also contributing to thrombocyte aggregation. Elevated concentrations of insulin promote atherogenesis, because insulin stimulates migration of smooth muscle cells from media into the intimae, their proliferation at the site of endothelial injury and activity of their receptors for LDL-cholesterol. It is widely known that many diabetics, particularly those with type 2 are overweight, with hyperinsulinemia due to peripheral vascular tissue resistance to insulin. Many of them have hypertension, which also contributes to the rapid atherosclerosis. Glucose intolerance or insulin resistance and consequent hyperinsulinemia is associated with central obesity type, hypertension, elevated triglycerides and decreased HDL-cholesterol, making up metabolic syndrome, which further increases the risk of atherosclerosis. Since diabetics have a much greater, risk than others patients, diabetic patient with another risk factor, particularly hyperlipidemia, demands more aggressive approach.

Diabetes mellitus is metabolic disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or a combination of both. The etiological classification has proposed by the WHO in 1999. There are 4 specific categories:

1. Type I diabetes characterized by an absolute insulin deficiency of autoimmune or idiopathic nature. Typically, in the vast majority of cases it occurs at younger age.
2. Type 2 diabetes characterized by a relative insulin deficiency coupled with an insulin resistance state. It includes over 90% the diabetic states developing after middle age. This diabetic state is often seen in people with visceral obesity and metabolic syndrome.
3. Gestational diabetes developing during pregnancy and in most cases disappearing after delivery. 60-70% of these patients will progress to diabetes during their life.
4. Other particular forms of diabetes include the clinical conditions secondary to diseases of exocrine pancreas (inflammation, trauma, neoplasm, and pancreatectomy) and endocrine system (Syndrome Cushing, phaeochromocytoma, acromegalia). It also includes genetic defects of beta cells and drug-induced diabetic states, such as those triggered by cortisone, antidepressants, beta-blockers and thiazide diuretics.

The clinical classification is based on criteria proposed by the WHO in 1999. In addition, The American Society of Diabetology (ADA, 2003.). The WHO recommendations for
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Glucometabolic classification based on measuring both fasting and two hour post-load glucose concentrations and recommend that a standardized 75g glucose tolerance test (OGTT) should be performed in the absence of overt hyperglycaemia. Glycated haemoglobin (HBA1c) is useful measure of metabolic control and the efficacy of glucose lowering treatment in people with diabetes. It presents a mean value of blood glucose during the preceding six to eight weeks (life span of erythrocytes). HBA1c not recommended as a diagnostic test for diabetes. Because normal values do not exclude diabetes or impaired glucose tolerance. The approach for early detection of diabetes and people in risk of acquiring diabetes is measuring of blood glucose in people who are at risk due to their demographic and clinical characteristics. Collecting questionnaire-based information on etiological factors for type 2 diabetes is necessary. Glycaemia testing (OGTT) is always necessary as a secondary step to accurately defined impaired glucose homeostasis. Glucometabolic abnormalities are common in patients with CVD and an OGTT should carry out in them. In the general population the appropriate strategy is to start with risk assessment as the primary screening tool combined with subsequent glucose testing (OGTT) of individuals identified to be at high risk. The relationship between hyperglycaemia and CVD should be seen as continuum. For each 1% increase of HBA1c there is defined increased risk for CVD. The risk of CVD for people with overt diabetes increased by two to three times for men and three to five times for women compared with people without diabetes. In type 1 diabetic patients prevalence of CVD amounts to 10% with a pronounced increase when diabetic nephropathy is detected. In type 2 diabetic patients prevalence of CVD is higher and almost similar to that displayed by patients with history of a previous myocardial infarction. Cardiovascular complications have a higher adverse impact on mortality in type 2 than type 1 diabetes (55% vs. 44%). It is still debated whether asymptomatic hyperglycaemia is associated with an increased risk of coronary events. Information on post-prandial (post-load) glucose also predicts increased cardiovascular risk in subjects with normal fasting glucose levels. The most common cause of death in adults with diabetes is CVD. Their risk is two to three times higher than that among people without diabetes. The combination of type 2 diabetes and previous CAD identifies patients with particularly high risk for coronary deaths. The relative effect of diabetes is lager in women than men (Table 3).

Elevated 2-hour post-load plasma glucose has much bigger impact on cardiovascular risk than fasting glucose. For major cardiovascular risk factors, mortality and cardiovascular morbidity are predicted by hyperglycaemia itself. Elevated blood glucose levels have an adverse impact on cardiovascular risk profile by decreasing vascular function (in particular endothelial function) and reducing nitric oxide bioavailability.

2.3.2 Insulin resistance
Insulin resistance contributes to the development and progression of several of the above-mentioned abnormalities. This is because the insulin-resistance state (and the related hyperinsulinemic condition) impairs the endothelium-dependent vasodilatation and promotes, through the activation of specific protein-kinase subfamilies, the development and progression of the vascular inflammatory and atherogenic process.

2.3.3 The metabolic syndrome
Dyslipidemia of diabetic patient is characterized by moderate hypertriglyceridermia, low HDL-cholesterol and impaired post-prandial lipid response. The prevalence of dyslipidemia

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is two/three times greater in patients with glucose intolerance and diabetes, compared to metabolically healthy subjects. LDL-cholesterol values participate in determining the cardiovascular risk. The evidence that a raise in LDL-cholesterol amounting to 1.0mmol/L (38.7mg/dl) is associated with a 57% elevation in cardiovascular events rate confirms this. Similar data have reported for low HDL-cholesterol. It is still uncertain whether the relationship between plasma triglycerides and vascular risk is independent from other metabolic factors (so called hyperinsulinemic cluster).

There has been an interest in clustering factors, each one associated with increased risk for CVD, together in the metabolic syndrome. It was debated whether such clustering represents a disease entity in its own, but it helps identifying individuals at high risk for cardiovascular disease and type 2 diabetes. Currently there are several definitions. The International Federation of Diabetes has issued the most recent. The pathogenesis of the metabolic syndrome and its components is complex and not yet well understood. However, central obesity and insulin resistance are important causative factors. Abdominal circumference and waist to hip ratio (W/H) is very useful screening factors for the metabolic syndrome, much more associated with metabolic risk then commonly used body mass index.

International Diabetes Federation-Metabolic Syndrome Definition
- Central Obesity (defined as waist circumference > 94 cm for European men and >80 cm for European women, with ethnicity specific values for other groups).

In addition, any two of the following four factors:
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- Raised TG level: > 1.7 mmol/L (150 mg/dl), or specific treatment for this lipid abnormality.
- Reduced HDL cholesterol: < 1.0 mmol/L (40 mg/dl) in males and < 1.2 mmol/L (50 mg/dl) in females, or specific treatment for this lipid abnormality.
- Raised blood pressure: systolic BP > 130 or diastolic BP > 85 mmHg, or treatment of previously diagnosed hypertension.
- Raised fasting plasma glucose (FPG): > 5.6 mmol/L (100 mg/dl) or previously diagnosed type 2 diabetes.

If glucose level is above 5.6 mmol/L or 100mg/dl, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Compared to the opinions expressed by other Guidelines and Scientific Societies, the European Guidelines seem to take a conservative position on the clinical impact of cardiovascular risk profile in patients with metabolic syndrome. This is partially because the two Societies are still waiting for further evidence.

The diabetogenic risk of patients with CVD is superimposable to the one characterizing subjects with obesity or metabolic syndrome. Patient with a high cardiovascular risk a glucose intolerance state may be responsible for the elevated prevalence of sudden death. Adequate control of postprandial hyperglycaemia has a favourable impact on cardiovascular and all-cause mortality. The elevated cardiovascular risk profile displayed by the diabetic patient depends not only on the glycaemia (and insulin) abnormality but also, and largely, on the development and progression of the atherogenic vascular process. The mechanisms include oxidative stress, the dyslipidemic state and the pro-atherogenic process.

1. Oxidative stress represents one of the cornerstones of the endothelial dysfunction as well as of the atherogenic process, but clinical studies are still inconclusive on this issue and do not to clarify whether and to what extent anti-oxidative drugs have a favourable therapeutic impact on the atherosclerotic process.

2. Dyslipidaemic state - lipid disorders classically described in diabetes include an elevated triglycerides and LDL and decreased HDL levels. Recent evidences support the role of free fatty acids (whose plasma concentrations increased in diabetes) in favouring the atherogenic process. Along with free fatty acids, another proatherogenic factor is the accumulation of triglyceride-rich lipoproteins, due to a reduced clearance by lipoprotein lipases.

3. Pro-atherogenic process and thrombosis - hyperglycaemia and insulin resistance exert adverse effects on thrombosis and coagulation by altering platelet function. Key features of the altered thrombosis process are the increased expression of glycoproteins, overproduction of fibrinogen, thrombin and von Willebrand factor as well as the reduction in endogenous anticoagulants (thrombomodulin and protein C).

4. The pathophysiological alterations responsible for the increased atherogenic risk, typical of the diabetic state are multifaceted. Several of these alterations are shared by the metabolic syndrome, which also includes glycaemia abnormalities as a key pathophysiological feature.

Diabetes doubles the probability of developing CHD or a cardiovascular disease in general. Death from the consequences of CHD increases by a factor of four to six. Next to occlusive diseases of the vessels of the lower extremities, (peripheral arterial occlusive vascular disease) coronary heart disease is the most frequent complication in diabetes. The presence of additional risk factors, such as obesity, lipometabolic disorders, high blood pressure or smoking, endangers diabetics more than any other patient group.
Unfortunately, a great deal is still unclear regarding the effects of diabetes on the development and course of CHD.

2.4 Obesity and overweight

Many people believe that central or abdominal type of obesity is not an independent risk factor, but is associated with hypertension, diabetes and dyslipidemia. In extremely obese persons, low level of protective HDL-cholesterol is an independent risk factor for the hyperinsulinemia combined with hyperglycaemia. Insufficient physical activity is another major risk factors. Regular physical activity significantly reduces the incidence of coronary artery disease and myocardial infarction. Current recommends daily exercise, swimming, walking, cycling and other physical activity. Regular physical activity slightly lower blood pressure, affects weight loss, improves glucose tolerance and exerts a positive effect on the blood clotting system. Physical activity stimulates rise in HDL-cholesterol concentration, and reduces triglycerides level in the blood. The most common reason for the accumulation of excessive weight is a sedentary lifestyle and unhealthy diet. Obesity is often perceived as a necessary companion of the thirties and forties. Proper nutrition, education and moderate physical activity can solve most of these problems so that education and prevention offers a solution for obesity and overweight. Adipose tissue on the hips and abdomen is deleterious only to our appearance and confidence, because it causes hormonal imbalance. Adipose tissue in obese people is the biggest endocrine organ in the body. Secretion of various hormones (the most important leptin), leads to insulin resistance and the occurrence of type 2 diabetes. Weight gain increases proportionately with blood pressure and all its harmful effects on the walls of blood vessels. Excessive calories intakes, which are, not spend but stored in our body as fat. It is believed that cholesterol and fatty acids in the blood have a crucial effect on the development of atherosclerotic plaques in blood vessels. Obesity burdens the entire organism, making obese people jumpy and easily fatigued. Large deposits of fat in the abdomen decrease lung capacity because the chest cannot expand of the lungs normally. This causes shortness of breath, especially at night due to a horizontal body position. Often awakening because of shortness of breath disturbs the normal structure of sleep and causes sleep deprivation and chronic fatigue. Consequently, obese people are less efficient at work and have much more incidence of bad mood and depression.

Today, definition of overweight and obesity is made according to by Body Mass Index (BMI), representing the ratio of body weight and body height squared. Values of BMI range from 18.5 to more of 30. BMI less than 18.5 indicates malnutrition, optimal values ranging from 18.5 to 24.9, overweight point value of 25 to 30 and a value greater than 30 indicate obesity and represent a serious health risk. Being overweight has a negative effect on other risk factors such as high blood pressure, immobility, lipometabolic disorders and a tendency to diabetes. However, being overweight by approximately 10% above the ideal weight, when taken into consideration as an independent risk factor, has great significance for the development of cardiovascular diseases, particularly in people below the age of 50. People who throughout their lives remain approximately 20% overweight have about a 50% greater risk of developing CVD than those who are of normal waist 88 cm in women. Avoiding overweight or reducing existing overweight is important. Weight reduction is strongly recommended for obese people (BMI > 30 kg/m2) or overweight individuals (BMI > 25 and > 30 kg/m2) and for those with increased abdominal fat as indicated by waist circumference >102 cm in men and > 88 cm in women. Restriction of total caloric intake and regular practice of physical exercise should advise in overweight and obese patients.
2.5 Mental stress
Nowadays it is believed that lack of social support and social isolation, unemployment, stress at work with an indefinite time, night work, family conflicts and depression also present an important risk factors. Such people are more likely to smoke, consume large quantities of alcohol and unhealthy food. The people with lower socio-economic status, lower education, who hold lower-paying jobs are three times more likely to suffer from coronary disease. Permanent alertness of the autonomic nervous system and hypothalamus-pituitary-adrenal axis, leads to increased blood pressure, changes in endothelial function and blood coagulation system and proinflammatory stimulus, which encourages atherogenesis.

Mental stress and depression both predispose to increased vascular risk and from a clinician’s perspective should be considered as modifiable risk factors. The adrenergic stimulation during mental stress can augment myocardial oxygen requirements and aggravate myocardial ischemia. Mental stress can cause coronary vasoconstriction, particularly in atherosclerotic coronary arteries and hence can influence myocardial oxygen supply as well. Recent studies have further linked mental stress to platelet and endothelial dysfunction, the metabolic syndrome and the induction of ventricular arrhythmias.

Acute stress such (studied in cases of great natural disasters) has long been recognized as a risk factor for coronary events. More recently, work-related stress has gained recognition as a source of vascular risk. Work stress has two components: job strain (which combines high work demands and low job control) and effort-reward imbalance (which more closely reflects economic factors in the workplace). Both components are associated with an approximate doubling of risk for myocardial infarction and stroke in European and Japanese populations. Other psychological metrics, including anger and hostility scales, have also been associated with elevated vascular risk.

Clinical depression strongly predicts coronary heart disease. In meta-analysis of studies involving initially healthy individuals, those with depression had a significantly higher risk of developing coronary disease during follow-up, with clinical depression being more important than depressive mood. While depression is also associated with an increased prevalence of hypertension, smoking and lack of physical activity, the effects of depression on overall risk remain after adjusting for these and other traditional risk factors. Thus, findings that depressed individuals also have increased platelet activation, elevated levels of high sensitive C-reactive protein (hsCRP), and decreased heart rate variability support depression as an independent predictor of cardiovascular events. Onset of depression after myocardial infarction is common and predicts cardiovascular mortality independent of cardiac disease severity. Whether therapy for post infarction depression reduces recurrent event rates remains controversial and open to research.

2.5.1 Stress and the heart
When organism is under stress, secretion of stress hormones adrenaline and noradrenalin strains the heart. This can gradually lead to cardiac arrhythmias, angina pectoris on exertion and eventually myocardial infarction. Additional risk factors for such persons are unhealthy diet, excessive smoking and alcohol consumption.

2.6 Lack of physical activity
Regular physical activity protects against the onset of cardiovascular disorders. Inactive people have about twice the risk of developing a vascular disease than people who are
active. Regular physical activity, whether pursuing a sport or just in the form of working in the garden, improves the heart muscle oxygenation its function, delays ageing of the vessels and protects against cardiac arrhythmias. The duration, intensity and frequency of the activity must be sufficient to achieve a training effect. Physical exercise also has a beneficial effect on other risk factors: reduced weight, improved glucose tolerance in diabetes and normalized blood lipid and lowering of blood pressure. People with risk factors for CHD who have previously not undertaken any sports should only do so after advice from a physician because unaccustomed exertion in the presence of underlying CHD can lead to sudden cardiac death.

2.7 Personality structure and social environment

The attempt of psychologists to establish a personality structure, which is particularly at risk of developing coronary heart disease, has led to definition of the „type A“ behavior pattern. „Type A“ personalities are characterized by latent aggression, impatience, competitive thoughts, time pressure in everyday life and brusqueness in the way they speak and behave. Chronically suppressed hostile behavior towards others and feelings of fury appear to be linked to particular disadvantage. One reason for this could be that an unbalanced mental state leads to a permanent state of stress. This reflected in particularly by increased production of catecholamine, the stress hormones of the body.

2.8 Smoking cigarettes and nicotine

Nicotine is a powerful poison that causes dependency. In the cardiovascular system, heart rate and blood pressure raise with narrowing of blood vessels. Nicotine exerts additional adverse effect on the nervous system, heart, blood vessels, kidney, gastrointestinal tract and genital organs.

2.8.1 Cigarette smoking

Cigarette smoking increases LDL and decreases HDL, also increasing carbon monoxide in serum, thus leading to endothelial hypoxia and potentially to vasoconstriction of the already narrowed atherosclerotic arteries. Cigarette smoking can also enhance platelet activity, which in turn may lead to the formation of thrombus and an increase in plasma fibrin and hematocrit, thus contributing to blood viscosity. Beyond acute unfavourable effects on blood pressure, sympathetic tone and a reduction in myocardial oxygen supply, smoking affects atherotrombosis by several other mechanisms. In addition to accelerating atherosclerotic progression, long-term smoking may enhance oxidation of LDL-cholesterol and impairs endothelium-dependent coronary artery vasodilatation. This latter effect has been directly linked to dysfunctional endothelial nitric oxide biosynthesis following chronic as well as acute cigarette consumption. In addition, smoking has adverse haemostatic and inflammatory effects, including increased levels of hsCRP (high-sensitivity C-reactive protein) soluble intercellular adhesion molecule-1 (ICAM-1), fibrinogen and homocysteine. Smoking is associated with spontaneous platelet aggregation, increased monocyte adhesion to endothelial cells and adverse alterations in endothelial derived fibrinolytic and antithrombotic factors, including tissue-type plasminogen activator and tissue pathway factor inhibitor. Compared with non-smokers, smokers have increased prevalence of coronary spasm and may have reduced thresholds for ventricular arrhythmia. Accumulating evidence suggest that insulin resistance represents an
additional mechanistic link between smoking and premature atherosclerosis. Smoking is a strong risk factor for the development of arteriosclerosis and CHD. There is a dose-related connection between the number of cigarettes smoked, the number of years of smoking and the risk of the development of cardiovascular disease. Habitual smokers have twice the risk of developing a cardiovascular disorder and three times the risk of sudden cardiac death. Cigar and pipe smokers also exposed to an increased risk. Various factors contribute to the negative effects of smoking on health: the damaging effect on the endothelium, the negative change in blood lipid values, increased propensity to thrombosis (particularly in women also on oral hormonal contraception), increased propensity to heart rhythm disturbances and the associated pulmonary diseases, which involve the heart consequently. Usage of oral hormonal contraception containing estrogen compounds is not recommended in smokers. If there is already underlying CHD, smoking has particularly negative consequences, because the red blood pigment (haemoglobin) of smokers cannot supply sufficient oxygen to the heart muscle cells when the coronary vessels are constricted. Symptoms of angina pectoris are particularly likely to occur during exertion in smokers with CHD. With regard to prevention, it is important that the risk of becoming ill from a cardiovascular disorder is reduced to that of a non-smoker after just one year of abstaining from nicotine. Unfortunately, this does not apply to the same extent for risk of a former smoker from developing cancer or a chronic pulmonary disease.

2.8.2 Second hand smoke exposure
Second hand smoke exposure is the risk factor when person experiences more than 1 hour of passive smoke exposure per week.

2.9 C-reactive protein (CRP)
Inflammation characterizes all phases of atherotrombosis and provides a critical physiological link between plaque formation and acute rupture, leading to occlusion and infarction.
CRP is a circulating member of the pentraxin family and plays a major role in the human innate immune response. It is primarily produced in the liver; recent data indicate that cells within human coronary arteries, particularly in the atherosclerotic intimae, can synthesise CRP. More than being a marker of inflammation, CRP may influence directly vascular vulnerability through several mechanisms, including enhanced expression of local adhesion molecules, increased expression of endothelial PAI-1 (plasminogen activator inhibitor), reduced endothelial nitric oxide bioactivity, altered LDL uptake by macrophages and co localization with complement within atherosclerotic lesions. The expression of human CRP in CRP transgenic mice directly enhances intravascular thrombosis and accelerates atherogenesis. In primary prevention, CRP, when measured with hsCRP, strongly and independently predicts risk of myocardial infarction, stroke, peripheral arterial disease and sudden cardiac death even among apparently healthy individuals. These data apply to women as well as to men across all age levels and consistently to diverse populations. Hs-CRP is an independent marker of risk and, in those judged at intermediate risk by global risk assessment, measurement of hs-CRP may help direct further evaluation and therapy in the primary prevention of cardiovascular disease. The benefits of such therapy based on this strategy remain uncertain. In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker of prognosis for
recurrent events, including death, myocardial infarction, and restenosis after percutaneous coronary intervention (PCI). The benefits of therapy based on this strategy remain uncertain. Hs-CRP levels, using standardized assays, should categorize patients into one of three relative risk categories: low risk < 1.0mg/L; average risk 1.0-3.0 mg/L; high risk > 3.0mg/L. Measurement of hs-CRP should be done twice (averaging results), optimally two weeks apart, fasting or no fasting in metabolically stable patients. If hs-CRP level is > 10mg/L, the test should repeat and the patient examined for sources of infection or inflammation. The entire adult population should not screen for hs-CRP for cardiovascular risk assessment, nor should hs-CRP levels used to determine preventive measures for secondary prevention or for patients with acute coronary syndromes. CRP was relatively moderate predictor of CVD risk and added only marginally to the prediction of CVD risk based on established risk factors.

2.10 Fibrinogen
Increased plasma fibrinogen is a risk factor because it increases blood viscosity and platelet aggregation and promotes thrombogenesis. More over fibrinogen is the acute phase reactant, and serves as a marker of inflammation, an important component of atherogenesis. Plasma fibrinogen influences platelet aggregations and blood viscosity, interacts with plasminogen binding and in combination with thrombin, mediates the final step in clot formation and the response to vascular injury. In addition, fibrinogen associates positively with age, obesity, smoking cigarettes, diabetes and LDL-cholesterol level and inversely with HDL-cholesterol level, alcohol use physical activity and exercise level. Fibrinogen level, like CRP, an acute phase reactant, increases during inflammatory responses. Studies found no significant positive associations between fibrinogen levels and future risk of cardiovascular events.

2.11 Immunoreactivity
Immunoreactivity could also be an important factor in the development of endothelial damage and thus atherosclerosis development. It is supported by the finding of the accumulated lipids in the affected arterioles of patients with dermatomyositis, systemic lupus erythematosus, scleroderma and rheumatoid arthritis. Atherosclerosis is more common after the transplantation of organs; it also explains the deposition of immune complexes in the walls of arteries and their damage.

2.12 Homocysteine
Increased homocysteine level is also a risk factor for atherosclerosis. People with levels of homocysteine higher than 12 mmol/L have twice the risk of myocardial infarction regardless of sex. Homocysteine acts proatherogenically because it changes the function of the endothelium and promotes the oxidation of LDL.
Homocysteine is a sulfhydryl-containing amino acid derived from the demethylastion of dietary methionine. Patient with rare inherited defects of methionine metabolism can develop severe hyperhomocysteinemia (plasma level >100μmol/L) and have markedly elevated risk of premature atherothrombosis as well as venous thromboembolism. The mechanisms that account for these effects remain uncertain but include endothelial dysfunction, accelerated oxidation of LDL-cholesterol, impairment of flow-mediated endothelial-derived relaxing factor with subsequent reduction in arterial vasodilatation,
platelet activation, increased expression of monocyte chemoattractant protein (MCP-1) and interleukin-8 leading to a proinflammatory response and oxidative stress. Measurement of homocysteine levels should reserve for individuals with atherosclerosis at a young age or out of proportion to established risk factors. Clinical trials have not shown that intervention to lower homocysteine levels reduces CVD events.

2.13 Albuminuria
Albuminuria is a result of kidney glomerular damage; increased albuminuria indicates a higher risk of progression of kidney disease. Hypertension and albuminuria are independent factors affecting long-term reduction of kidney function. Renal disease is both a cause and consequence of hypertension. Treating arterial hypertension reduces cardiovascular risk and risk of kidney damage. Reducing albuminuria also reduces total cardiovascular risk and kidney damage.

2.14 Hyperuricemia
Hyperuricemia is a high value of serum uric acid in blood: higher of 360 μmol/L (6 mg/dl) for women and 400 μmol/L (6.8 mg/dl) for men. It has double effect: damages the endothelium and smooth muscle cells of blood vessels and acts as an oxidant. Epidemiologic study found an association between hyperuricemia and hypertension, renal disease and CVD.

3. Non-modifiable risk factors

3.1 Sex and age
3.1.1 Sex
It is well known that blood vessels age more rapidly in men than in women. As a result, women in their 50-es demonstrate significantly less advanced atherosclerotic changes than men of the same age. Only one of seven women aged between 45 and 64 have signs of coronary heart disease. After the age of 65, however, the frequency increases to one in three. Two thirds of women affected by CHD die because of the it. An increase in free fatty acids and blood cholesterol, high blood pressure, diabetes, nicotine and alcohol consumption promote the vessel ageing process in women as well. The epidemiological observation that before the menopause women are affected by CHD much less than men has led to the conclusion that the female sex hormone, estrogen, has a protective effect on the cardiovascular system. Data from clinical trials indicates a 35-50% reduction in the risk of developing CHD if estrogen supplemental treatment is undertaken.

This effect of estrogen is partially attributed to a hormone-induced increase in HDL-cholesterol blood lipid carrier protein and on the other to a reduction in the potentially vessel-damaging LDL-cholesterol blood lipid carrier protein, which is loaded predominantly with cholesterol. One should emphasize, however, that observed men and women should be exposed to the same risk factors. Before the start of the menopause women benefit from a relative protection from development of CHD due to the presence of the female sex hormone, estrogen. After the onset of the menopause, the relative risk for men and women equals. The administration of synthetic estrogens can, irrespective of the reasons why gynaecologists prescribe hormone treatment, also have the positive side effect of protecting against CVD.
Male sex is a risk factor that has been proven in numerous epidemiological studies, regardless of the higher incidence of other risk factors in men than in women. It is known that the atherosclerotic changes, especially coronary arteries and blood vessels, come about 10 years later in women than in men. This is partly explained by the beneficial effects of estrogen on lipoproteins, because they increase HDL-cholesterol and reduce LDL-cholesterol and Lp(a), oxidation LDL-cholesterol, fibrinogen and homocysteine. Sex hormones may have direct effects on blood vessels because existence of receptors for androgens and estrogens on smooth muscle cells of the blood vessels has been proven. Even after menopause, cardiovascular risk is still significantly lower in women than in men of the same age. Nevertheless, in most developed countries cardiovascular diseases are the major causes of mortality in women, not only in men.

3.1.2 Menopause and hormonal therapy

Women who enter menopause early (before age 50) are three times more likely to have coronary disease. Although some earlier studies suggested that there is an association between taking oral hormonal contraception (OHC) and the occurrence of coronary disease, today we know that (OHC) usage presents cardiovascular risk only in women with additional risk factors, especially smoking cigarettes. Estrogen containing oral contraceptives stimulate liver production of VLDL-cholesterol and therefore LDL-cholesterol level in women who have previously known family hyperlipidemia. On the other hand, taking oral contraceptive with higher dose of estrogen causes an increase in HDL-cholesterol concentration and might be antiatherogenic, but it not scientifically proven. Although hormone replacement therapy in postmenopausal women have numerous benefits (control of vasomotor symptoms, prevention of osteoporosis, etc.), previous opinions about its positive effect on the prevention coronary disease, are no longer uniformly endorsed.

3.1.3 Age

The risk of developing coronary heart disease and suffering myocardial infarction increases with age for both sexes. However, atherosclerosis does not however begin abruptly. The signs of incipient coronary atherosclerosis can be apparent from a very early stage. Studies have shown that atherosclerotic transformation processes of aorta can become apparent even in three years old children. Thus, the coronary vessels are involved in this process from in patient’s youth (20 or 30 years). Although age is an important factor, the probability of developing coronary heart disease varies according to the presence of the additional risk factors. The best estimate of the individual’s risk is therefore provided by consideration of age in relation to other risk factors present. The observation that significant atherosclerotic changes in the coronary vessels can start very early in life emphasizes the need for prevention at an early stage.

3.2 Genetic factors

Genetic information can be divided into categories: data from family history, data on genotypes and phenotypes.

3.2.1 Family history (hereditary risk)

Heritage is considered a risk factor because it was observed that familial predisposition for atherosclerosis, especially history of coronary artery disease in family members before age
55 (men) and 65 (women) leads to increased cardiovascular risk. It is difficult to separate legacy as an independent factor, especially because other risk factor such as hyperlipoproteinemia, hypertension, coagulation disorders and diabetes have hereditary component. Besides that family can help develop various healthy an unhealthy habits, such as smoking, physical activity, excessive food consumption and obesity, all of which increases the risk of atherosclerosis. It is known that some hereditary lipid disorders of (family hypercholesterolemia, family combined hyperlipidemia), directly cause premature atherosclerosis. Patients with homocystinuria, which is inherited autosomal recessive, usually die from the consequences of atherosclerosis before the age of thirty. If person has a close relative (father, mother or sibling) who has developed CVD before the age of 55, the risk of suffering from a cardiovascular disease is increased two to five fold. The presence of additional risk factors such as high blood pressure, lipid metabolic disorders or diabetes further increases this risk. Families with this particular risk profile require special medical care and preventive measures.

3.2.2 Genotypes and phenotypes
The availability of a wide array of genetic data should also change coronary risk prediction in the future, and many large-scale evaluations of polymorphism and haplotype patterns designed to understand better the atherotrombotic process are well underway. Progress in human genetics holds considerable promise for risk prediction and for individualization of cardiovascular therapy. There are many reports about genes that candidate as predictors of cardiovascular risk. To date, the validation of such genetic markers of risk and drug-responsiveness in multiple populations has often proved disappointing. The advent of technology that permits relatively rapid and inexpensive genome-wide screens and of powerful bioinformatics tools, should spur haplotype analyses and unbiased identification of risk and therapy-response genotypes in the future.

4. Conclusion
There is no doubt that patients with CVD and those with multiple risks factors deserve attention to the term you have particular risk factors extensively and persistently treated. All previous population studies indicate, despite a large palette of new drugs with proven usefulness, many patients who have survived a CVD incident continue smoking, remain overweight, and are treated unsatisfactory. Failure to treat high blood pressure and other risk factors is partly explained by the fact that these patients often simultaneously take several medications with potential side effects. One solution is fixed combination of drugs for treating hypertension, dislipidaemia and diabetes.

CVD prevention refers to all measures taken to prevent their occurrence. It must be carried out in patients who already have documented CVD (coronary disease, previous AMI, stroke, transient ischemic attack, peripheral arteries atherosclerotic disease), hence called the secondary prevention. Primary prevention refers to preventing and treating risk factors in people who have one or more risk factors, but no clinical signs of CVD. Evaluation of the total risk burden is always needed in primary and secondary prevention, and cannot be limited to only one risk factor. Epidemiological studies have proven that many people with an increased risk of CVD, have several risk factors simultaneously, which poses significant challenge to physician.
When it comes to treating dyslipidemia, particularly hypercholesterolemia, all professional societies issued a joint recommendation by which the value of total blood cholesterol should be less than 5.0 mmol/L, and LDL-cholesterol less than 3.0 mmol/L. Secondary prevention mandates total cholesterol less than 4.5 mmol/L, LDL-cholesterol less than 2.5 mmol/L and blood pressure less than 130/80 mmHg, particularly in patients with established CVD, diabetes and renal disease.

Specific focus in prevention is changing of lifestyle habits, solving major cardiovascular risk factors and use of other prophylactic drug therapy for prevention of clinical CVD. All risk factors such as hypertension, adiposity, hypercholesterolemia, diabetes, nicotine use and stress are equally important and present in the development of CVD.

Today, we have a new model to estimate total patients cardiovascular risk - SCORE (Systematic Coronary Risk Evaluation), which is derived from large databases and predicts the total 10-year risk of fatal CVD.

This interactive system of risk assessment aims to provide the physician and patient information on the overall risk and help control interventions. Risk factors, with a completely individual approach to each patient require continuous training complex of the total population in the prevention of risk factors and therefore coronary heart disease.

4.1 Relative risk chart

This chart may used to show younger people at low total risk that, relative to others in their age group, their risk may be many times higher than necessary. This may help to motivate decisions about avoidance of smoking, healthy nutrition and exercise, as well as flagging those who may become candidates for medication (Table 4).

4.2 Stratification of total CV risk

Total CV risk is stratified in four categories. Low, moderate, high and very high risks refer to 10-year risk of fatal or non-fatal CV event. The term „added” indicates that category risk is greater than average. The dashed line indicates how the definition of hypertension (and thus the decision about the initiation of treatment) is flexible, i.e. may be variable depending on the level of total CV risk (Table 4).
Table 5. Stratification of CV Risk in four categories. SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: cardiovascular; HT: hypertension. Low, moderate, high and very high risk refer to 10 year risk of a CV fatal or non-fatal event. OD: subclinical organ damage; MS: metabolic syndrome. (Reproduced from 2007.European Guidelines for the management of arterial hypertension, Croatian Society of Hypertension).

Using the SCORE charts, we can assess CVD risk in asymptomatic persons as follows (Table 5, Table 6):

1. use the low risk chart in Belgium, France, Italy, Greece, Luxemburg, Spain, Switzerland and Portugal; use the high risk chart in other countries in Europe
2. Find the cell nearest to the person’s age, cholesterol and blood pressure (PB) values, bearing in mind that risk will be higher as the person approaches the next age, cholesterol or BP category
3. Check the qualifiers
4. Establish the total 10-year risk for fatal CVD

Note that a low total cardiovascular risk in a young person may conceal a high relative risk; this may explain to the person by using the relative risk chart. As the person’s ages, a high relative risk will translate into a high total risk. More intensive lifestyle advice will need in such persons.

People who stay healthy tend to have certain characteristics:

0. no tobacco
3. walk 3 kilometres daily or 30 minutes any moderate activity
5. portions of fruit and vegetables a day
140. Blood pressure less than 140 systolic
5. total blood cholesterol < 5mmol/L
3. LDL-cholesterol < 3mmol/L
0. avoidance of overweight and diabetes

Continuous training program of the total population in the prevention of risk factors and therefore coronary heart disease, one of the most common causes of morbidity and mortality in developed countries of Europe is mandatory.
Education should start in the younger age groups to prevent the emergence of risk factors, encourage proper diet and lifestyle changes, primarily in the populations who have high total cardiovascular risk. Considering increasing incidence of CVD in rapidly ageing population, prevention is the only way to overcome CVD in the future.

Table 5. 10-year risk of fatal CVD in low risk regions of Europe (reproduced from 2004. European guidelines on cardiovascular disease prevention in clinical practice, Croatian Society of Cardiology)
Table 6. 10-year risk of fatal CVD in high-risk regions of Europe (reproduced with permission from 2007. European guidelines on cardiovascular disease prevention in clinical practice, Croatian Society of Cardiology)

5. References

McGorrian, C. (2011). Estimating modifiable coronary heart disease risk multiple regions of the world: the INTERHEART Modifiable Risk Score, European Heart Journal, The Zurich Heart House, ISSN 0195-668X; Zurich, Switzerland

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Atherosclerotic Cardiovascular Disease


Cardiovascular diseases (CVD) are still one of the leading causes of death in the world. The book Atherosclerotic Cardiovascular Disease is a contribution to the application of new knowledge in the area of cardiovascular diseases. The book comprises six chapters divided in three subsections, starting with the General Considerations of Cardiovascular Disease, through Diagnostic Techniques, and Specific Therapy.

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