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REVIEW ARTICLE

Management of Measurable Variable Cardiovascular Disease' Risk Factors

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Abstract: Aim: To summarize the main findings on variable cardiovascular risk factors and their management in everyday practice.

Methods: A narrative review of the relevant literature known to the authors and incorporation of healthy changes tips in defined variable cardiovascular risk factors.

Results: There are known variable cardiovascular risk factors to be claimed as those that should be changed in order to achieve a better prevention of cardiovascular disease development. But, most papers are informative and they didn't incorporate exact measures for each variable risk factor. Our paper shows exact measures for each variable cardiovascular risk factor that should be incorporate in everyday practice of family practitioners and cardiologists as well.

Conclusion: The best cardiovascular disease' prevention should include a multidisciplinary team of experts and the entire community with the support of governmental and non-governmental organizations that will contribute to improving the lifestyle of individuals and the entire community through their activities and legal provisions. The most important factors in cardiovascular disease management are: recognizing individual risk factors, monitoring them, and assisting in changes in life-style habits that directly affect the defined risk factors of a patient. The simplest and most practicable guidelines for CV prevention in accordance with the national, cultural and socioeconomic aspects of their country of work are needed.

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1. INTRODUCTION

Cardiovascular Diseases (CVD) are heart and circulatory system disorders. It is a set of heterogeneous diseases whose underlying cause of development is most often atherosclerosis [1, 2]. CVD are chronic diseases that are gradually evolving throughout life, and are asymptomatic for a long time. Usually only the advanced disease causes symptoms or the first symptom can be sudden death [3]. For years they have been the leading cause of premature mortality across the world. It is estimated that by the year 2030, 23.6 million people will die of CVD per year. There is a mild tendency to decrease mortality and incidence of CVD in north western and southern Europe [2].

CVD causes 49% of mortality in Europe, which is the most important cause of premature mortality and Disability Adjusted Life Years ("DALYS") in Europe, thus creating a great public health importance on this topic. Approximately € 192 billion is the cost of annual health care for CVD in the European Union [4].

CVD are caused by multiple factors. Some of them are invariable (age, gender, genetic heritage), others are variable, that is, they can be affected (smoking tobacco, physical inactivity, poor eating habits, elevated blood pressure, type 2 diabetes, dyslipidemia, obesity) [4].

For the reduction of the CVD mortality rate in highly developed countries, controlling risk factors (45-75%) and proper CVD treatment (25-55%) are responsible [5-7].

This review aims to summarize the available information on measurable variable CVD risk factors through existing literature and integrate them with healthy tips that can be managed in everyday practice.

2. PREVENTION OF CARDIOVASCULAR DISEASES

Prevention of CVD is defined as a coordinated pool of activity at the population level or individual level with the aim of eliminating or reducing to the lowest level of CVD incidence and their consequences [8].

The report of the Expert Committee for the Prevention of the CVD and WHO established in 1982 measures of prevention that need to have 3 components of the strategy [9]:

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1. Population strategy - Lifestyle habits and environmental factors, socioeconomic determinants that may cause CVD development, affect these activities at the level of the entire population [8, 10].
2. High-risk strategy - Identification of high risk individuals and measures that will reduce their risk factors.
3. Secondary prevention - Prevention of the occurrence or reoccurrence and progression of disease in patients with already proven CVD.

High-risk and secondary strategies are directed at individuals and must be an integral part of our clinical practice [9]. The population strategy is focused on the entire community, and is an integral part of food, transport, employment, education and health policies and other policies at the level of Europe, the state, the region and the local community. Population and clinical approach should be complementary, but the population strategy is the basis for reducing the incidence of CVD in Europe. It focuses on social and economic determinants of illness through political activities. It tends to change the lifestyle habits: reducing the number of smokers, increasing physical activity, promoting healthy living habits. Investment and political will are needed to achieve these goals [8-11].

According to the latest guidelines of the European Cardiology Society (ESC) CVD prevention, the focus is on the population approach to prevention, on disease-specific interventions, female population, younger individuals and ethnic minorities. The emphasis is on the whole life cycle of CVD prevention [12] (Figs. 1 and 2 and Table 1).

3. MONITORING MEASURABLE CHANGES OF FACTORS IMPORTANT FOR CARDIOVASCULAR DISEASES DEVELOPMENT

CVD prevention measures must be an integral part of everyday medical work to achieve optimal results. It is therefore important to define CVD prevention priorities. CVD prevention guidelines provide the procedures for defining the preventive measures to be taken, taking into account the health policies of individual countries and the incidence of CVD in individual countries in order to achieve unambiguous access to patients.

It is most important to have a consistent approach with defined monitoring parameters based on which an individual's risk assessment will be carried out. The risk assessment is one of the most important measures that define all future treatments of patients.

Reduction of CVD morbidity and mortality is the goal of clinical and population preventative strategies. Since CVD are multifactorial, it is necessary to monitor and act upon several different risk factors at the same time. Health professionals use the algorithm according to ESC guidelines in their work on CVD prevention. The first ESC prevention guidelines were published in 1994 and since then they have been revised several times. The last are published 2016.

At the same time, the existence of multiple risk factors multiplies the risk of CVD, and the risk of myocardial infarction progressively increases [13-17]. Therefore, the estimate of the CVD risk is of the most importance in the optimal management of prevention and treatment [18].

Stratification of CVD risk is important because there are people who do not yet have manifest atherosclerotic disease but can develop CVD [12]. Total CVD risk means that an individual is likely to develop a fatal cardiovascular event for a certain period of time. It is important for the physician to be able to assess the risk quickly and to make a quick decision on further treatment (evidence-based management). To help diagnose and monitor individuals who have increased risk for developing CVD, there are developed monitoring models that are being used today in Europe in the form of Systemic Coronary Risk Estimation (SCORE) tables (Figs. 1 and 2). SCORE tables are used only for people without known CVD. People with already manifest atherosclerotic vascular disease are in the group of high CVD risk and as such should be treated [19].

Recommendations for using the SCORE table [8, 13]:

- For apparently healthy adults (>40g.) without signs of CVD, Diabetes Mellitus (DM), chronic kidney disease, familial hypercholesterolemia, because these patients are already high risk and are therefore the priority for intensive counseling on risk factors.
- Evaluate for each individual the total ten-year risk of death by sex, smoking, age, systolic blood pressure and total cholesterol.
- Low risk individuals should be advised to maintain such status, and those with an estimated risk >5% should dedicate particular attention to reduce it.
- Define the relative risk for people under the age of 40.
- The effect of cholesterol, smoking status and systolic pressure can be estimated from the table.

The decision on treatment strategy depends on the initial risk level. Categorization into different groups of total CVD risks is agreed but is recommended for its simplicity [4]. The total CVD risk may be higher than that shown in the tables under the following circumstances:

- If an individual moves to an older age group.
- In asymptomatic patients with signs of atherosclerotic disease (computer tomography, ultrasound).
- In individuals with significant positive family history of early cardiovascular deaths.
- In individuals with low high density lipoproteins (HDL) cholesterol, high triglycerides, glucose intolerance, elevated C-Reactive Protein (CRP), elevated fibrinogen, elevated homocysteine, elevated apolipoprotein B (APOB), elevated lipoproteins, and obese people with the sedentary lifestyle [8].

Separate tables are compiled for the high and low risk countries of Europe of high and low risk, and in the future for each country will be able to define individualized risk tables.

SCORE - European High Risk Chart

10 year risk of fatal CVD in high risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status

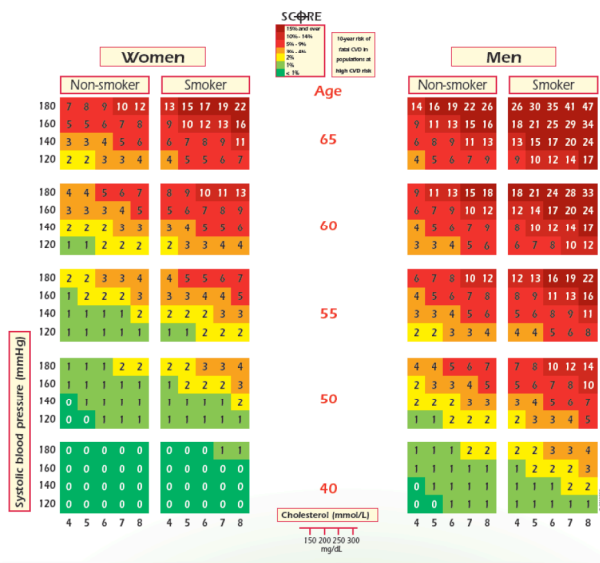


Fig. (1). SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries of high CVD risk. Source: 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Available at: <https://academic.oup.com/eurheartj/article/37/29/2315/1748952/2016-European-Guidelines-on-cardiovascular-disease>.

SCORE - European Low Risk Chart

10 year risk of fatal CVD in low risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status

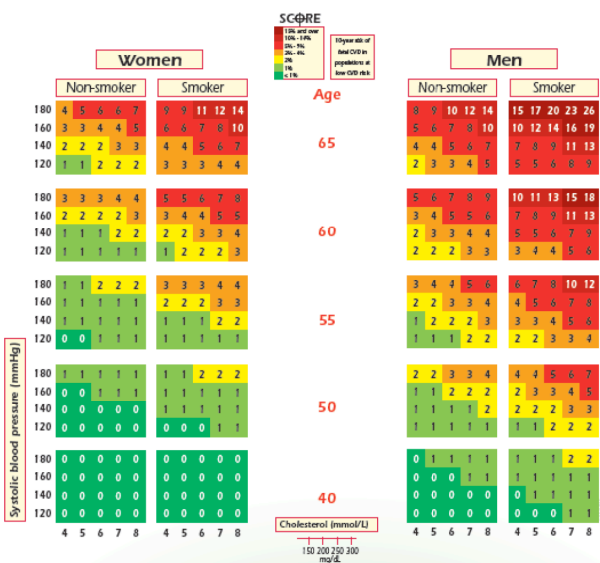


Fig. (2). SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries of low CVD risk. Source: 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Available at: <https://academic.oup.com/eurheartj/article/37/29/2315/1748952/2016-European-Guidelines-on-cardiovascular-disease>.

The benefits of estimating total CVD risk and treating accordingly are 2-fold [20]. The first is the direction of preventive efforts toward those who will be most likely to benefit. The second is the reassurance and avoidance of side effects in lower-risk persons who will derive less benefit [20]. In the most people, CVD is the product of more than 1 risk factors. A combination of several factors result in much higher total risk [20]. Therefore, SCORE system help to estimate total risk. For young person, we use relative risk estimation (they can be at low absolute but high relative risk) [20]. We must encourage risk evaluation and management because it improves the primary prevention of CVD.

4. VARIABLE RISK FACTORS OF CARDIOVASCULAR DISEASES

Factors contributing to the development of atherosclerosis and CVD are called CVD risk factors. Their action is multiplied thus presenting a big public health problem. CVD risk factors may be variable and invariable.

Invariable risk factors are those we cannot influence (age and gender, men over age 45 and women over 55 years respectively in menopause, inheritance-positive family history).

Variable risk factors are those we can influence by changing bad habits. Variable risk factors include: smoking, inadequate physical activity, elevated blood pressure, increased body weight (obesity), increased levels of fat in the blood (cholesterol, triglyceride), DM.

The goal of managing the variable risk factors is to reduce CVD morbidity and mortality. Clinical studies: Framingham, Multiple Risk Factor Intervention Trial (MRFIT) [21], Asia Pacific Cohort Studies Collaboration (APSCS) [22], INTERHEART [23] has shown that multiple risk factors multiply CVD risk and the risk of myocardial infarction progressively increases. Thus, CVD are multifactorial diseases, and these have to be monitored at several levels and in particular, an important estimate of variable risk factors is in diagnosis, monitoring and treatment [24].

The influence of variable risk factors at the risk of myocardial infarction has been demonstrated in the major international clinical study INTERHEART, which included 52 countries and the results of which were published in 2004. It has proven the importance of preventive measures to reduce the incidence of myocardial infarction [25]. According to the European Society of Cardiology (ESC) Guidelines, recommendations are given for managing variable CVD risk factors in the way presented below.

4.1. Smoking

Smoking cigarettes is a dominant risk factor for cardiovascular and non-cardiovascular mortality and morbidity. It is estimated that by the year 2025, there will be 1.6 billion smokers in the world, and that 10 million people a year will die for smoking [10]. Unfortunately, there is still a rise in smokers among women and adolescents in Europe [12, 26]. The ten-year risk of fatal cardiovascular events is doubled in smokers [12]. Passive smoking increases the risk of CVD [8, 12, 27].

Smoking is one of the preventable risk factors with the greatest contribution in the development of CVD and as such must be the most important factor that the physician tends to reduce.

There are a number of measures we can use to help the patient and our recommendations range from individual approaches through group therapies to medication approaches:

1. Self-help technique.
2. Individual advisory.
3. Group therapy.
4. Substitution therapy with nicotine.
5. Antidepressants (smoking cessation and nicotine up-set can provoke depression).
6. Family support and spouse.

Promoting non-smoking includes social programs as part of health promotion activities. Many European countries have declared a "smoke-free" zone (ban on smoking at the workplace, in public institutions, restaurants ...), which is very important in stimulating individual efforts to stop smoking [9]. The goal is to reach Europe as a smoking-free Europe by 2030 [8]. Public health measures and legislation are also important: smoking ban, tobacco tax, media campaigns ... High taxes on all tobacco products have been shown to be an effective measure to reduce youth smoking [8]. Children in schools should be taught with healthy lifestyle habits, including noxiousness smoking lectures, encouraging young people not to start smoking or to stop smoking [8].

4.2. Physical (in) Activity

Physical inactivity is a risk factor of CVD development, but also the development of a number of other chronic diseases. Even 60% of the world's population does not meet the minimum recommended 30 minutes daily of moderate physical activity. The CVD risk is increased by 1.5 times in people living a sedentary lifestyle. Physical inactivity causes 2 million deaths per year and 22% of all ischemic heart disease [28]. Due to the increased physical inactivity of young people, a higher increase in CVD is expected.

Regular physical activity is protective and has many benefits: it directly affects the reduction of already existing vascular lesions and reduces other risk factors (reduces body weight, reduces lipid levels, blood sugar, reduces arterial pressure) and thus decreases the incidence of coronary disease [8, 9].

It reduces the progression of atherosclerosis, protects the patient from oxidative stress, increases insulin sensitivity, decreases the incidence of malignant arrhythmias, balances the vegetative system [9, 29-31]. Consequently reduces total and CV mortality.

Promoting physical activity should start already in childhood. In all age groups, physical activity is an important part of preventative CVD measures.

Cardiovascular patients, especially after acute coronary syndrome, intervention on the coronary arteries or heart surgery, should undergo a CVD rehabilitation program during

which they will be monitored, and tested using treadmill bicycle exercise with Electrocardiography (ECG) and blood pressure monitoring. The patient should monitor his frequency on the pulse monitor while exercising at home. Coronary patients with low clinical risk should moderately or intensively exercise 30 minutes 3 to 5 times a week. Coronary patients with moderate to high clinical risk should strictly individually adjust the exercise program. Even the heaviest patients have benefit from low intensity exercise, but under the supervision of experts. Exercising encourages their self-reliance and reduces depression [8].

Regular exercise is important in primary and secondary CVD prevention. Before starting the exercise, to determine the intensity of the exercise, it is important to stratify the CV risk to prevent possible unwanted cardiovascular events. According to the ESC Guidelines, the following recommendations are [8]:

1. Healthy adults all ages of 2.5 to 5h a week of moderate physical activity or 1 to 2.5h per week of intense physical activity.
2. Healthy adults who lead a sedentary lifestyle should be encouraged to start with a light exercise intensity.
3. Patients with coronary heart disease (myocardial infarction, after aortic coronary bypass or coronary intervention with stable angina pectoris, with stable heart failure) need 3 or more times a week moderate to intense aerobic exercise for 30 minutes.
4. Patients with coronary heart disease conducting a sedentary lifestyle should begin with light exercise after CVD risk assessing.

4.3. Blood Pressure

Blood pressure (BP) is commonly defined as persistent blood pressure 140/90 mmHg and above, and affects one quarter of the adult population [9].

Arterial hypertension (AH) is one of the most important preventable factors of premature mortality in the world. AH is also the most important independent risk factor of CVD. In most developed countries more than 30% of adults suffer from AH. Primary prevention should start at the earliest age [32].

Arterial hypertension is a risk factor of CVD, but also mortality from coronary illness or stroke [8, 33]. CVD risk doubled in every increase in BP: diastolic for 10 mmHg and systolic for 20 mmHg [33].

Classification of BP and AH according to ESC guidelines [14]:

	Systolic BP (mmHg)		Diastolic BP (mmHg)
Optimal BP	<120	and	<80
Normal BP	120-129	and / or	80-84
Highly Normal BP	130-139	and / or	85-89
1st degree AH	140-159	and / or	90-99
2nd degree AH	160-179	and / or	100-109

3rd degree AH	≥180	and / or	≥110
Isolated systolic AH	≥140	and	<90

According to the new 2017 American Heart Association (AHA) Guidelines for high blood pressure in adults AH and BP are classified [34]:

	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal BP	<120	and	<80
Elevated BP	120-129	and	<80
AH Stage 1	130-139	or	80-89
AH Stage 2	≥140		≥90

In order to prevent AH, it is important to encourage the following measures in childhood: reducing salt intake, regular physical activity and prevent obesity. BP can be reduced by changing life habits and pharmacotherapy.

Life habits in BP reduction include:

- Reduced intake of salt in food (<5g/day).
- Decrease in intake of alcoholic beverages (10-30g/day).
- Mediterranean diet type (increased omega 3 fatty acid intake).
- Increased physical activity.
- Smoking cessation.
- Body weight regulation.

According to the ESC guidelines, the goal is to lower BP to 140/90 mmHg or to lower than 140/85 mmHg in diabetics. The beginning of pharmacotherapy will depend on the estimated total CVD risk and the degree of AH. In the case of CVD already present or the target organs are damaged, pharmacotherapy starts immediately and the choice of anti-

hypertensive will depend on the already present disease [8, 33].

AHA guidelines recommend healthy lifestyle for all. They recommend one BP lowering medication for the patients with AH stage 1 if the 10-year risk for heart disease and stroke assessment is >10% or they have CVD, diabetes mellitus or chronic kidney disease. For the patients with AH stage 2 they recommend immediately two medications of different class [34].

4.4. Eating Habits

There is a well-known association between eating habits and CVD risk. One of the first clinical studies to prove this connection is the study of "Seven Countries Study" [35]. It has shown a correlation between poor eating habits (food rich in saturated fats) and the onset of ischemic heart disease [8].

Healthy nutrition is the basis of CV prevention. Food habits affect the level of fat and blood sugar, BP, body weight. Healthy nutrition reduces the risk of other chronic diseases. It is considered that the Mediterranean type of nutrition satisfies all the healthy nutritional recommendations [9]. Healthy food must contain [12, 36-40]:

1. Saturated fatty acids <10% of total daily energy intake; replace them with polyunsaturated fatty acids.
2. Transfat acids should be avoided (they are found in the factory processed food) and should be <1% of the total energy input.
3. Salt <5g per day.
4. 30 to 45 grams of fiber per day (whole grains, fruits, vegetables).
5. 200g of fruit a day (2 to 3 meals per day).
6. 200g vegetables a day (2-3 servings per day).
7. Fish at least 2x per week (1 meal a week blue fish).
8. Alcoholic beverages: 2 glasses a day (20g/day) for men and 1 glass per day (10g/day) for women.

Table 1. Stratification of CVD risk.

Other risk Factors, Asymptomatic Organ Damage or Disease	Blood Pressure (mmHg)			
	High normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3HT SBP ≥ 180 or DBP ≥ 110
No other RF		Low risk	Moderate risk	High risk
1-2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP = Blood Pressure; CKD = Chronic Kidney Disease; CV = Cardiovascular; CVD = Cardiovascular Disease; DBP = Diastolic Blood Pressure; HT = Hypertension; OD = Organ Damage; RF = Risk Factor; SBP = Systolic Blood Pressure.

Source: <http://eurheartj.oxfordjournals.org/content/ehj/34/28/2159.full.pdf>

According to the new ESC Guidelines on CVD prevention, a population approach has been introduced according to dietary measures, physical activity and smoking. Structural measures such as limiting marketing and taxing unhealthy food, reducing the price of healthy food and making them better labelled to make it easier for consumers to view and choose (“consumer-friendly”) are important [9]. Healthy lifestyles should be stimulated in the community, schools and workplaces [8].

The general recommendations of a healthy diet according to ESC recommendations are [9]:

1. A varied well-balanced diet.
2. Proper energy intake with regular physical activity contributes to good body weight control.
3. Regularly consume fish.
4. Eat fruits, vegetables, cereals and whole grain products.
5. Consume non-fat milk products.
6. Eat unleavened meat, avoid fried.
7. Use vegetable oils rich in mono and polyunsaturated fats.
8. Avoid salty and factory processed foods.

Legislative regulations (except, of course, existing) are needed to limit trans fat acid and salt in food products. The food industry can significantly contribute to salt reduction in processed food [8].

4.5. Obesity

The prevalence of obesity in the world is rising, especially in industrialized countries. It contributes to a significant increase in CVD morbidity. The sedentary lifestyle and bad nutrition habits are the cause of obesity. Obesity is associated with CVD mortality. There is a linear association of body mass index (BMI), obesity and especially abdominal thickness with total mortality. The lowest mortality rate in BMI ranges from 20 to 25 kg/m² [12].

The effects of obesity are the following [12]:

1. Increased insulin resistance.
2. Increased systemic inflammation and prothrombotic effect.
3. Dyslipidemia.
4. Albuminuria.
5. Disorder of the cardiovascular system (endothelial dysfunction, coronary heart disease, heart failure, atrial fibrillation, stroke, systolic and diastolic left heart failure, increased sympathetic activity).

The most important is obesity prevention at the earliest age. Education and media influence are important in the prevention of child obesity. Each kindergarten, school, and working environment should provide a healthy environment and healthy meals. Already in childhood, physical activity should be promoted. In schools should be provided minimum 30 minutes and an optimum 60 minutes physical activ-

ity per day. Each person should be moderately physically active at least 150 minutes a week or more intense physically active 75 minutes a week [8].

The basis of obesity treatment is diet, physical activity, lifestyle changes. Often, these measures are unsuccessful in long-term treatment. In cases of BMI >40 kg/m² or BMI >35 kg/m² with the presence of comorbidities leading the patients into a high risk group, including pharmacotherapy (orlistat) or bariatric surgery is recommended, along with changes of bad lifestyle habits [8].

4.6. Lipids

In blood plasma lipids (cholesterol and triglycerides) circulate as lipoproteins associated with proteins (apolipoproteins). Most of the circulating cholesterol is in the form of LDL cholesterol (atherogenic) that is directly associated with CVD risk. Hypercholesterolemia is an indicator of increased risk. There is a positive association between total LDL cholesterol and CVD [8, 12, 13, 41]. The role of triglyceride-rich lipoprotein is actively studied. These are chylomicrons and very low density lipoproteins (VLDL) that can lead to pancreatitis at high concentrations [8, 12, 13].

Disturbed lipid metabolism leads to dyslipidemia, which alone or in interaction with other CVD risk factors, leads to atherosclerosis and consequently CVD. Dyslipidemia can also have genetic predisposition (hereditary dyslipidemia), can be an integral part of other diseases (secondary dyslipidemia), but are mostly the result of external factors (diet rich in saturated fats and carbohydrates, reduced body activity, smoking, stress) [4].

There are a number of clinical studies that have proven that cholesterol reduction leads to a reduction in coronary events [12, 42]. The most significant are the following studies [12]:

- 1) Scandinavian Simvastatin Survival Study (4S) [43].
- 2) Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) [44].
- 3) Cholesterol and Recurrent Events (CARE) [45].
- 4) Heart Protection Study (HPS) [46].
- 5) West of Scotland Coronary Prevention Study (WOSCOPS) [47].
- 6) Heart AIR Force Texas Coronary Atherosclerosis Protection Study (AFCAPS/TexCAPS) [48].

These studies evaluated cardiac patients with hypercholesterolemia. They have demonstrated a positive effect of hypolipemic therapy in the prevention of myocardial infarction and/or cardiac death [27].

For asymptomatic individuals, the first step is an estimate of total CVD risk. Within the scope of CVD risk protocols, lipid analysis is recommended [4, 13]:

- Total Cholesterol (TC).
- Low Density Lipoprotein (LDL)-Cholesterol (LDL-C).
- Triglycerides (TG).
- HDL Cholesterol (HDL-C).

- Non HDL cholesterol - alternative risk factors (mixed dyslipidemia, diabetes, metabolic syndrome, chronic kidney disease).
- Lipoprotein (A) - high CVD risk and positive family history of early CVD.
- APO B - alternative marker (mixed dyslipidemia, diabetes, metabolic syndrome, chronic kidney disease).
- The ratio APO B/APO A (alternative to the probing).
- The ratio of non HDL C / HDL C (alternative in probing).

LDL C and TC are closely related to CVD risk. LDL C is an indicator to therapy response and its values are monitored during treatment. It is recommended that appropriate LDL C target values be achieved for each patient category [12, 13]:

1. Very high CVD risk (CVD, diabetes mellitus type 2 over 40 years and 1 or more risk factors or target organ damage, diabetes mellitus type 1 with target organ damage, moderate to severe chronic kidney disease, SCORE >10%) - target LDL C <1.8mmol/l and/or >50% LDL C if the target LDL C values cannot be achieved.
2. High CVD risk (diabetes mellitus type 2 without other risk factors or target organ damage, significantly high individual risk factors, SCORE >5% and less than 10%) - target LDL K <2.5mmol/l.
3. Moderate CVD risk (SCORE >1% and less than 5%) - target LDL C <3.0mmol/l.

Hypertriglyceridemia is also a risk factor for the development of CVD. It is a significant independent CVD risk factor, but in relation to hypercholesterolemia, it is less associated with CVD [12, 48]. Possible causes of hypertriglyceridemia include obesity, non-insulin-dependent diabetes mellitus (NIDDM), alcohol consumption, simple carbohydrate-rich diets, chronic kidney disease, hypothyroidism, pregnancy, autoimmune diseases, drugs (corticosteroids, estrogens, tamoxifen, beta blockers, thiazides, isotretinoin, cyclosporine, antiretroviral drugs, psychotropic drugs), but also genetic predisposition [4].

5. THERAPY OF DYSLIPIDEMIA

5.1. Hypercholesterolemia

General strategies for treatment [4]:

- Assess the total CVD risk.
- Involve patients in deciding on risk management.
- Assess the target value of LDL C for the risk level.
- Calculate the percentage reduction of the LDL C needed to achieve this goal.
- Select a statin that can achieve this reduction.
- The dose titration of the drug is required to reach the target values of LDL C because the response to the treatment of statins is different.
- Consider introducing a combination of drugs if the statins do not reach the LDL target value.

- Take into account the clinical condition of the patient, possible drug interactions that the patient is taking, statin intolerance.

Recommendations for pharmacological treatment of hypercholesterolemia [4]:

- To give statin at the highest dose the patient tolerates to achieve the target values of LDL C.
- In the case of non toleration, administer ionic exchangers or nicotinic acid.
- In the case of non toleration also consider cholesterol absorption inhibitors, alone or in combination with ion exchangers or nicotinic acid.
- If the target values of LDL C are not reached, consider statin in combination with a cholesterol or nicotinic acid absorption inhibitor.

Reduction of 1 mmol/l LDL cholesterol leads to 20-25% reduction in CV mortality and nonfatal myocardial infarction [12, 42].

5.2. Hypertriglyceridemia

In the case of patients with high total CV risk and TG >2.3 mmol/l which cannot be reduced by changing lifestyle, the following medications should be given [5]: fibrates, niacin, niacin + laropirant, omega 3 fatty acid, statin + nicotinic acid, statin + fibrates, omega-3 fatty acids combinations. Low HDL cholesterol is a factor associated with CVD risk [8, 12, 13, 49]. Physical activities and other healthy habits increase HDL cholesterol [8].

In mixed dyslipidemia (increased cholesterol and triglycerides) is important to combine therapy.

Special groups of dyslipidemia patients who need to receive statin [40]:

1. Familial hypercholesterolemia (should receive high doses of statin, often in combination with ezetimibe).
2. Elderly people if they have a proven CVD.
3. Diabetics (type 1 and microalbuminuria and/or kidney disease, type 2 and CVD or chronic renal disease or older than 40g with 1 or more CVD risk factors or target organ damage, type 2 without additional risk factors LDL C should have < 2.6 mmol/l).
4. Patients with acute coronary syndrome and those preparing for percutaneous coronary intervention.
5. Severe renal disease.
6. Peripheral arterial disease.
7. Primary stroke prevention if a patient with high or very high risk and secondary stroke prevention.

6. DIABETES MELLITUS

In 2011, 52 million Europeans aged 20-79 were suffering from type 2 diabetes mellitus (T2DM). Until 2030, 64 million people in Europe will suffer from T2DM. This is a worrying fact because most diabetics die for CVD [6].

Diabetes is classified according to the World Health Organization and the American Diabetes Society on: diabetes mellitus type 1 (T1DM), diabetes mellitus type 2 (T2DM), "other specific types" DM and gestational DM [6].

According to the ESC guidelines [12] there are diagnostic criteria set by the World Health Organization (WHO) and those designated by the American Diabetes Association (ADA) in diagnosing diabetes, glucose intolerance and glucose maturation disorder:

Diabetes mellitus: HbA1c $\geq 6.5\%$ (WHO, ADA), GUK starving ≥ 7.0 mmol/l (WHO, ADA), glucose after 2h of a meal ≥ 11 mmol/l (WHO, ADA);

Glucose intolerance (GI): GUK starving < 7 mmol/l (WHO, ADA), glucose after 2h of the meal ≥ 7.8 - < 11.1 mmol/l (WHO) and 7.8-11 mmol/l (ADA);

Glucose maturation disorder: GUK starving 6.1-6.9 mmol/l (WHO) and 5.6 -6.9 mmol/l (ADA), glucose after 2h of the meal < 7.8 mmol/l (WHO), and ADA no states the criterion.

In GI cases, it is important to modify lifestyle habits (regulating body weight, increasing body activity and adopting healthy eating habits) to prevent DM and CVD from developing or its progression [6].

People with DM are at high risk and do not evaluate their risk with the SCORE table.

According to the last European Guidelines for Diabetes (ESC/EASD), it is recommended to establish patient centres [6]. These centres would support patients in achieving healthy living habits and advice on improving their own disease management and treatment. Such centres would have a multidisciplinary approach [6].

The ESC/European Association for the Study of Diabetes (EASD) guidelines on diabetes in order to prevent CVD give the following recommendations [6, 8]:

- Target HbA1c should be $< 7\%$.
- Statins therapy.
- Avoid hypoglycemia, as well as increase body weight.
- In the first line of DM treatment give metformin.
- Further reduction of HbA1c $< 6.5\%$ can reduce the risk of microvascular events.
- Target BP $< 140/85$ mmHg.
- Target LDL < 2.5 mmol/l (in case of very high risk of LDL < 1.8 mmol/l), target cholesterol < 4.5 mmol/l.
- Key recommendations in diabetic treatment [6, 8]:
- Intensive treatment of hypertriglyceridemia reduces the CVD risk.
- Intensive AH treatment reduces the CVD risk.
- It is often necessary to include more antihypertensive drugs in the therapy to achieve the target BP.

Each risky CVD factor in diabetes should be treated according to the existing recommendations [6, 8].

7. PSYCHOSOCIAL FACTORS

Low socioeconomic status, lack of social support, stress, depression, anxiety, and type D personality increase the risk of high risk for the disease [12, 50-53]. These factors also make difficult the treatment of cardiovascular patients, as well as the impact on the change of bad habits [8].

The risk factors are the following [8, 52, 53]:

- 1) Low socioeconomic status - includes low level of education, low financial income, low level of business status, poor living environment. It leads to an increase in CVD mortality.
- 2) Social isolation and low social support - people who live isolated from society have an increased risk of premature deaths, as well as a weaker prognosis of CVD.
- 3) Work or family stress - increases the risk of CVD.
- 4) Depression - increases the incidence of CVD and exacerbates the prognosis of the disease.
- 5) Anxiety - increases the risk of CVD.
- 6) D type of distress - those with negative affectivity, social inhibition - has a poorer prognosis of CVD.

The biggest problem in evaluating psychosocial factors is the fact that they are more difficult to measure, so it is more difficult to define the relationship.

Poor psychosocial factors are often associated with higher incidence of smoking, poor eating habits, decreased physical activity, and consequently greater risk of CVD. Such patients are more difficult to accept medical advice and treatment. The exact pathophysiological effect of psychosocial factors is still being investigated [8].

Interviews or questionnaires should assess psychosocial risk factors [1]. The interview should be done by a doctor. In order to remove stress, depression, anxiety, and adopt healthy living habits, psychosocial interventions are needed. According to the ESC guidelines, the following recommendations are on the management of psychosocial factors [9]:

- Multimodal behavioural interventions, health education, physical activity, psychological therapy when needed.
- In the case of clinical symptoms of depression, anxiety should be applied to psychotherapy and pharmacotherapy.
- Interventions include individual and group counseling on psychosocial risk factors and how to cope with the disease; Cognitive-behavioural therapy, stress management programs, meditation, autogenic training, yoga, breathing exercises, muscular relaxation. Psychological interventions reduce stress, promote healthy habits, and affect CVD prevention and treatment.

CONCLUSION

In our day-to-day cardiology practice, we are concerned about the high mortality and morbidity of CVD in the world. Nearly 50% of Europe's mortality is waste at CVD. Cardi-

ologists and public health need information about patients and their lifestyle in order to improve the activities of CVD prevention and to make prevention more effective. All health care professionals should be involved in CVD prevention, and all preventive activities should be started by family physicians. A family medicine practitioner is the one who needs to start, coordinate and permanently monitor his/her patient's CVD prevention. Thus regrettably, many patients remain undiagnosed, and therefore without adequate therapy. Unfortunately, the first manifestation of CVD is sudden death at those patients. Also, among patients with already established CVD, many have not achieved the target values of their risk factors. In primary prevention, just because of the omitted estimates of the CVD risk and the lack of recognition of those patients with high and very high risk, no adequate preventive measures or therapies are implemented. These patients are endangered by the development of complications of illness or fatal CVD outcomes.

In Europe, from 1995 to 2014, 4 clinical studies of EUROSPIRE I-IV (Including the Republic of Croatia) investigated the implementation of the ESC guidelines for CVD prevention in practice. They have shown that at the level of Europe they do not achieve the target values of risk factors in primary and secondary prevention. According to the EUROSPIRE III study, only 36-57% of GPs in Europe comply with the CVD prevention guidelines and less than 50% of them assess the overall risk of their patients.

Today, an insufficient number of doctors in their daily practice use the SCORE table to estimate CVD risk (62% do not use it, but rely on a subjective assessment). There are several reasons: government policies and local community policies, lack of time in work with a patient (over-burdening physicians, insufficient number of cardiologists), SCORE table not implemented through information technology, etc.

Individual approach to CVD prevention begins with a CVD risk assessment: the higher the risk, the prevention measures need to be more intense. Clinicians are important to make a quick CVD assessment. It is especially important in this assessment to identify patients with an unrecognized CVD. It would be ideal for all adults to have an estimated risk of CVD. A risk assessment of CVD should be repeated every 5 years for persons without proven CVD. In that sense, cardiologists in outpatient practice have an important role in CVD prevention, and need to be consultants of family medicine practitioners and general internists.

Cardiologists should do medical evaluation of cardiovascular patients. In this evaluation, the cardiologist will evaluate the risk of CVD, estimate CVD capacity (non-invasive, invasive), echocardiographic and Doppler artery estimation. This cardiac treatment provides a detailed evaluation and assessment of the risk and disease risk. Although identifying CVD risk factors, basic treatment and counseling about healthy lifestyle habits should be in the domain of GPs and general internists, the cardiologist is a counselor in cases where doubts remain about the need for introducing therapy with preventative measures or there are various contraindications and/or complications. The cardiologist is always involved in secondary and tertiary CVD prevention.

Successful management of measurable variable risk factors for cardiovascular disease development will include: recognizing individual risk factors, monitoring them, and assisting in changes in life-style habits that directly affect the defined risk factors of a patient. In addition, those risk factors that can be expected to be the most successful in preventing cardiovascular disease development, if corrected, include: smoking habit, increased body mass, physical (in)activity, arterial hypertension, dyslipidemia and diabetes. In addition to all the above-mentioned risk factors, it is indispensable to include adequate psychosocial support as future stress, misunderstanding and patient inadequacy greatly reduce the results of preventive actions.

The best will be the prevention of the CVD, which includes a multidisciplinary team of experts and the entire community with the support of governmental and non-governmental organizations that will contribute to improving the lifestyle of individuals and the entire community through their activities and legal provisions.

All health care professionals, including cardiologists, need the simplest and most practicable guidelines for CVD prevention in accordance with the national, cultural and socioeconomic aspects of their country of work.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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