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# The Use of Reynolds Risk Score in Cardiovascular Risk Assessment in Apparently Healthy Bosnian Men and Women: Cross-Sectional Study

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## 1. Introduction

Cardiovascular diseases (CVD) remain a major burden for public health worldwide. Pivotal concern of primary prevention is identification of individuals that are at risk for developing cardiovascular disease. The use of different algorithms for an assessment of cardiovascular risk allows physicians to identify and treat in a simple and cost-effective manner individuals that may be at high long-term cardiovascular risk.

A cardiovascular risk factor represents a condition that is related to increased risk for the development of cardiovascular disease. This relation is used in statistical terms. If certain individual has particular risk factor he/she has increased probability for the development of CVD. However, not all individual with cardiovascular risk will develop CVD and sometimes coronary events may occur in the absence of major risk factors (Ridker et al, JAMA 2007). Identification of individuals at cardiovascular risk results in a cost-effective prevention. Significant efforts are made to ensure most reliable tools in cardiovascular risk assessment. For a risk factor to be useful in routine clinical diagnostics, following criteria must be fulfilled: its analysis must be easy and available, there must be pathophysiological evidence that confirms causal link of risk factor with the disease, and also there must be certain knowledge on treatment options for patients with established high values of a certain risk factor (Thomas et al, 2009).

Cardiovascular risk factors are divided into three main categories: non-modifiable (age, gender, heredity); modifiable (increased blood pressure, dyslipidemia, fibrinogen, obesity, glucose intolerance, diabetes, left ventricular hypertrophy, cocaine, behavioral factors); and protective factors (HDL-cholesterol, exercise, estrogen, moderate alcohol intake). It is important to emphasize that treatment of certain modifiable cardiovascular risk factor will not result in total elimination of probability in CVD development, but the possibility of CVD development will be reduced.

As for non-modifiable cardiovascular risk factors, many epidemiological studies have reported age as one of the strongest predictors of CVD. Furthermore, investigations have

shown that men are more prone to CVD development than women for reasons yet not completely understood. In most societies, development of cardiovascular risk factors begins in younger age, and manifests itself in middle age. Almost 85% of all deaths due to CVD occur in people 65 years of age or older. It has been reported that mortality rate for men before the age of 50 with no pre-existing myocardial infarction or stroke was 20%, which increased up to 80% in those older than 70 years of age (Wannamethee et al, 1995).

Inherited likelihood for the development of CVD has been well documented. In some cases, such as familial hypercholesterolemia ways of inheritance are well defined. However, for other cardiovascular risk factors pattern of inheritance is still unknown. According to current assumptions, role of heredity in the development of CVD is multifactorial with genetic, environmental, and behavioral component (Phillips et al, 1988). Studies have shown that risk of developing premature CVD was increased more than threefold when any first-degree relative was affected and about sixfold when at least two first-degree relatives had a history of CVD (Eaton et al, 1996).

Of all the modifiable cardiovascular risk factors, hypertension is best investigated. Both systolic and diastolic blood pressures are important in the assessment of individual's risk. However, majority of complications of hypertension are attributed to systolic blood pressure. Studies have indicated that the risk of a cardiac event increases by 1.6 in men and 2.5 in women when blood pressure rises from an optimal (<120/80 mmHg) to high normal (130-139/85-89 mmHg) level (Vasan et al, 2000). Although hypertension is an independent cardiovascular risk factor, data have shown its strong relations with other risk factors, such as age, sex, race and hypercholesterolemia.

Increased levels of serum lipids are another common modifiable cardiovascular risk factor. According to current guidelines fasting lipoprotein profile (total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol) should be performed every five years in all adults age 20 years and older. Level of total cholesterol is strong predictor of CVD and to a lesser degree of stroke. Close linear relationship exists between cholesterol level and the mortality rate. Studies have shown that low-density cholesterol (LDL-C) and high-density cholesterol (HDL-C) and their relationship may have even more significant prognostic value in the prediction of CVD than total cholesterol. Men aged 45 to 65 years with total serum cholesterol level < 240 mg/dL and/or LDL-cholesterol > 160 mg/dL are considered to be at an increased risk for CVD (Wilson et al, 1998). Reduction of increased levels of total cholesterol and LDL-cholesterol is accompanied with the decline of cardiovascular risk. Earlier studies failed to demonstrate predictive value of triglycerides, but results of novel studies point to possible importance of triglycerides in the prediction of cardiovascular risk, especially in women and patients with diabetes. HDL-cholesterol attenuates atherogenicity of LDL-cholesterol. High levels of HDL-cholesterol have protective properties, while its low levels represent a major risk for CVD (P.W. Wilson, 1990; Schafer et al, 1994).

Recent data report on possible role of fibrinogen as cardiovascular risk factors. Even though mechanisms by which fibrinogen fulfills this role are still not completely known, it is believed that individuals with raised fibrinogen are more susceptible to the development of clots in arteries, and thereby have increased risk of heart attack or stroke. Evidences have shown that fibrinogen levels have tendency to rise with advancing age and in that sense fibrinogen does not represent modifiable cardiovascular risk factor. However, it has been

proven that smoking cessation reduces fibrinogen levels which make fibrinogen a cardiovascular risk factor that can be controlled. In a 13-year longitudinal CARDIA study (D. Green et al, 2010) higher levels of fibrinogen during young adulthood were positively associated with incidence of subclinical atherosclerosis and coronary artery calcification in middle-age. However, study has shown that this association declines with advancing age.

A major contributor to CVD is cigarette smoking. It is estimated that out of approximately 500,000 deaths from coronary heart disease, 30-40% can be attributed to smoking. Studies have shown that risk of sudden death increases more than tenfold in men and almost fivefold in women who smoke. Smoking is associated with accelerated atherosclerosis and inflammatory processes. Smoking cessation and reduced tobacco exposure result in decrease of inflammatory component of CVD and this decrease is reversible (Bakhru & Erlinger, 2005; Tracy et al, 1997; Dobson et al, 1991).

Obese individuals (more than 30% over ideal body weight) are more likely to develop CVD, even in absence of other cardiovascular risk factors. A strong association has been found between overweight that begins in childhood and the development of other risk factors over time, such as hypertension and diabetes. The cause of overweight and obesity in majority of cases is excessive food intake and sedentary lifestyle. A study among middle-aged men has shown that risk of developing fatal and non-fatal CVD increased up to 72% if their body mass index (BMI) increased from less than 23 to the range of 25-29 (Rimm et al, 1995). For all of these reasons obese individuals tend to be at high risk for CVD, and weight management is extremely important lifestyle intervention that can lead to significant reduction of cardiovascular risk.

Individuals with glucose intolerance and diabetes mellitus have increased risk for CVD. These two conditions are often accompanied with raised levels of insulin that in this setting increases blood pressure and aids in plaque deposition. As a result of these insulin actions, atherosclerosis and its complications will develop. Data have reported that there is a linear association between glucose levels and CVD mortality (Balkaue et al, 1999). It is of note that influence of diabetes mellitus on the development of CVD differs among ethnic groups. A prospective study in individuals of African-American origin has shown that 27% of women and 8% of men had CVD that could be attributed to diabetes mellitus. In individuals of Caucasian origin, 15% of men and 12% of women had CVD that could also be attributed to diabetes mellitus (Folsom et al, 1997)

Even though certain authors disagree, many others find behavioral risk factors such as type A personality and stress as important risk factors for CVD. Type A or coronary-prone personality is an individual that is always in hurry, under pressure by time, becomes upset often with no objective reason, has chronic impatience and sometimes overwhelming hostility. Results from GAZEL French prospective study have demonstrated that neurotic hostility, coronary-prone personality and antisocial personality are all predictive of mortality outcomes (Nabi et al, 2008).

Left ventricular hypertrophy (LVHT) is a major independent risk factor for cardiovascular mortality. Studies have shown that individuals with LVHT are more susceptible to arrhythmias, heart failure and sudden death and this condition is often accompanied with hypertension. Appropriate treatment of these conditions reduces cardiovascular risk. Novel findings suggest that there are racial and ethnic differences in cardiovascular mortality related

to LVHT. It has been demonstrated that LVHT contributes more to the risk of cardiovascular mortality in African American than it does in White individuals (Havranek et al, 2008).

Cocaine is a sympathomimetic agent that can cause hypertension, arrhythmias, angina and sudden death. Cocaine is also a risk for congenital heart disease. Main mechanism of cocaine action is that it constricts coronary blood vessels and reduces oxygen supply to the heart. It has been reported that concomitant use of cigarettes exacerbates the deleterious effects of cocaine on myocardial oxygen supply and demand (Lange et al, 2004).

Alongside with non-modifiable and modifiable cardiovascular risk factors, there are also some proven protective factors that in fact protect from the development of CVD. Sedentary life-style is associated with the development of obesity, metabolic risk factors, insulin resistance, and early onset of diabetes mellitus type 2. Regular exercise is one of those protective factors that helps in weight management, increases HDL-cholesterol concentration, enhances utility of insulin in organism, reduces stress and decreases blood pressure. There are convincing data that it also reduces chances for having a myocardial infarction. Significant changes in classical cardiovascular risk factors are preceded by reductions of vascular functions. Important guidelines for primary and secondary prevention settings should be based on the encouragement of regular physical activity that has been shown to have many beneficial effects on the vascular wall (D.J. Green et al, 2008). Studies have found that increased physical activity leads to the decline of CVD mortality (Blair et al, 1995). Results of a meta-analysis reported that physical activity was inversely associated to the development of CVD, with a relative increased risk of 1.9 in people with sedentary lifestyle compared to physically active individuals (Berlin et al, 1990).

Another protective factor against CVD is estrogen. It reduces likelihood of heart attack by increase in HDL-cholesterol levels. However, once women reach an age of menopause this protective action of estrogen diminishes, and women are at same cardiovascular risk as men. According to recent findings, estrogen decreases production of reactive oxygen species in mitochondria. Studies have shown that estrogen promotes angiogenesis, enhances endothelial vasodilator function and modulates autonomic function (Miller et al, 2008).

Moderate alcohol consumption is proven to have protective effects against atherosclerosis and coronary heart disease. Mechanisms by which these effects are achieved are still not completely understood, but it seems that consumption of one or two drinks a day increases levels of HDL-cholesterol. A systematic review of literature and meta-analysis on association between alcohol consumption and overall mortality from CVD, incidence of and mortality from coronary heart disease, and incidence of and mortality from stroke has observed that light to moderate alcohol consumption is associated with reduced risk of multiple cardiovascular outcomes (Ronksley et al, 2011). However, consumption of alcohol in larger amounts increases blood pressure and risk of CVD.

Prevalence of cardiovascular risk factors differs around the globe. Data from USA indicate that nearly 70% of adult Americans are overweight or obese. Less than 15% of adults or children exercise sufficiently, and over 60% do not engage in vigorous activity. Among adult population, 11%-13% have diabetes, 34% have hypertension, 36% have prehypertension, 36% have prediabetes, and 12% have both prediabetes and prehypertension. At least one cardiovascular risk factor is present in 50% of adults. Furthermore, almost 65% of patients do not have their traditional cardiovascular risk biomarkers under control (Kones, 2011).



Another study in US population (Danaei et al, 2009) aimed to assess the number of disease-specific deaths attributable to all non-optimal levels of risk factors exposure, by age and sex. Results have shown that in year 2005, cigarette smoking was responsible for an estimated 467.000 deaths and high blood pressure for 395.000 deaths in US adults. Overweight-obesity, physical inactivity, and high blood glucose caused 8%-9% of all deaths in same population. Other dietary risk factors also caused significant number of deaths in the US.

A comprehensive, population-based study compared cardiovascular risk profiles among individuals of white, South Asian, Chinese and black ethnic groups living in Canada (Chiu et al, 2010). Results have shown that there is a considerable variation in the prevalence of smoking, hypertension, obesity, and diabetes mellitus among four ethnic groups included in the study. Authors concluded that these results may lead to the development of CVD prevention programs for specific ethnic groups.

Prediction of risk for future cardiovascular events or stratification of healthy individuals into risk categories by different algorithms has been widely used in clinical practice. Important issue is critical appraisal of implemented prediction models. Even though validity of models can be evaluated by different means, calibration and discrimination represent two most important measures of accurate models assessment. Calibration is a measure of how well predicted probabilities agree with actual observed risk, whereas discrimination is a measure of how well the model can separate those who do and do not have the disease of interest. A measure of discrimination that is broadly used is *c* statistics, also known as the area under the Receiver Operating Characteristic (ROC) curve, or *c* index. Results of a Women Health Study have shown that use of *c* statistics can be advocated because of its specificity and sensitivity in differentiating between those who do and those who do not have a certain disease. Also, its use may contribute to more exact reclassification of large proportion of patients into higher- risk or lower-risk categories. However, it seems unlikely that it can be used in the evaluation of algorithms that predicts future risk or stratify individuals into risk categories. Another conclusion of this study was that use of *c* statistics as the only measure of the possible usefulness of traditional or novel risk factors could not be advised (Cook N, 2007). Finally, decision on inclusion of novel risk marker in prediction algorithms should be based on the knowledge whether measurement of potential risk marker will result in different treatment options, and whether it has perspectives in disease prevention.

Etiology of CVD is multifactorial. In order to better assess cardiovascular risk, new biomarkers have been introduced as part of global cardiovascular risk assessment. Novel findings suggest that important role in atherosclerosis has inflammation. These conclusions led to the measurement of numerous markers of inflammatory processes to better identify individuals that are at the increased risk. C-reactive protein (CRP) is currently most studied and best validated biomarker of inflammatory processes. It is an acute phase protein, which is primarily synthesized in the liver and it represents a marker of systemic, non-specific, inflammation. CRP production is stimulated by cytokines (in particular interleukin-6, interleukin-1, and tumor necrosis factor- $\alpha$ ) in response to systemic or local infection or inflammation by variety of cells, including adipocytes (Pepys & Hirschfield, 2003).

The Centers for Disease Control and Prevention and the American Heart Association published a statement in 2003 in which measurement of CRP is given at the discretion of

physicians to be used in clinical practice as part of global risk assessment in adults (Pearson et al, 2003). According to existing guidelines, individuals with CRP values  $< 1$  mg/L are considered to be in low, those with CRP values 1-3 mg/L in moderate and those with CRP values  $> 3$  mg/L in high cardiovascular risk (Packard et al, 2008).

Current main goal in CRP testing is to identify individuals that can benefit from lipid-lowering treatment in order to prevent first cardiovascular event, especially for those individuals that have CRP  $> 3$ mg/L, and are in intermediate risk (10-20% 10-year predicted risk). However, it is of critical importance in any interpretation of CRP values to differentiate modest increase of CRP baseline values from its major rise that occurs in conditions such as tissue necrosis, sepsis and acute trauma. Furthermore, because of its completely unspecific nature, it is not possible or clinically appropriate to interpret CRP values without full medical information of individual, including history, physical examination, and results of all investigations (Casas et al, 2008). Although more sophisticated inflammatory biomarkers (such as interleukin-6, intercellular adhesion molecule-1, macrophage inhibitory cytokine-1, and CD40 ligand) have been shown to be predictive of cardiovascular disease, their use in routine clinical evaluation is highly unlikely because of short half-lives of these proteins (Katrinchak &Fritz, 2007 ).

Findings of many clinical, experimental, prospective epidemiological and cohort studies have demonstrated that CRP may play role in atherogenesis, since it was found in endothelial atherosclerotic lesions, and raise in CRP concentrations is linked with the increased prevalence of myocardial infarction, peripheral vascular disease, and stroke. Furthermore, CRP provides additional information for the prevention of cardiovascular disease, has a prognostic value of incident cardiovascular events in those with and without preexisting CVD, the increased risk associated with high CRP is independent of other established risk factors, and CRP is biologically stable over time and assays for its measurements are standardized (de Ferranti et al, 2007). For all of the stated properties, certain authors believe that CRP represents not only a marker but as well a mediator of cardiovascular disease (Ridker et al, 2004). Conversely, there are studies that reported that CRP is only a relatively modest predictor of coronary heart disease, and suggest that its use in the prediction of coronary heart disease development should be revised (Danesh et al, 2004).

Data have shown that conventional cardiovascular risk factors fail to predict development of coronary heart disease in 25-50% of cases. Certain authors believe that possible explanation of observed discrepancy may be endothelial dysfunction that may be a missing link between atherosclerotic disease and cardiac risk factors (Reriani et al, 2010). According to relatively recent hypothesis endothelial dysfunction has significant impact on the development and progression of atherosclerosis and atherothrombosis. One of the currently mostly used markers of endothelial dysfunction is asymmetric dimethylarginine (ADMA). ADMA is a endogenous inhibitor of all three isoforms of the enzyme nitric oxide synthase (NOS) and causes endothelial dysfunction by inhibiting production of nitric oxide (one of the major endothelium-derived vasoactive mediators). Prospective clinical studies have shown that elevated levels of ADMA are related to increased incidence of cardiovascular events, as well as with overall mortality (Anderssohn et al, 2010). Large multicentric CARDIAC study has found that elevated ADMA concentration significantly increases the risk of coronary heart disease (Landim et al, 2009). These findings point to the important role of functional vascular status in cardiovascular prognosis. However, it remains unclear

whether increased values of ADMA represent only a marker of endothelial dysfunction that may be used in cardiovascular risk assessment or elevated ADMA concentration itself predispose the development of CVD.

Alongside with conventional biomarkers for the prediction of incident cardiovascular events, there are also some other novel biomarkers that are tested for their possible usefulness in cardiovascular risk assessment. Recent Swedish study assessed a panel of contemporary biomarkers, such as mid-regional-pro-atrial natriuretic peptide, N-terminal pro-B-type natriuretic peptide (N-BNP), mid-regional-pro-adrenomedullin (MRproADM), lipoprotein-associated phospholipase-2, and cystatin C in prediction of future cardiovascular events. Results have shown that 10-year incidence of coronary events was 4.4%. Another important finding of the study was that selected biomarkers may be used in the prediction of future cardiovascular events, but benefits over traditional risk factors are minimal. Furthermore, their use did not reclassify a substantial proportion of individuals to higher or lower risk categories (Melander et al, 2009).

A study in Hispanic population used standard risk assessment tools and the B-type natriuretic peptide biomarker to assess coronary heart disease risk (Macabasco-O'Connell et al, 2011). Based on their findings, authors concluded that the inclusion of B-type natriuretic peptide to the traditional risk scores may be helpful in cardiovascular risk prediction.

One of the most frequently used cardiac risk prediction model in clinical practice is Framingham Risk Score. Its use started in the 1980s and based on its implementation in cardiovascular risk assessment, individuals can be divided in those at low (less than 5%), intermediated (6-20%) and high (>20%) cardiovascular risk (Ridker et al, 2004). However, over time, Framingham Risk Score showed certain limitations. Evidences have shown that cardiovascular events occur in every fifth individual in whom classical risk factors have not been recognized. Furthermore, there is a limitation in specificity of conventional risk factors and it has been shown that overall cardiovascular risk differs across populations. It has also been concluded that intermediate risk category is broad and that there is a necessity for better risk stratification of that risk category. For all of the above reasons, there was a need for new and more comprehensive cardiovascular risk prediction tools.

So far, several other risk prediction models have been proposed to be used in every-day clinical practice for cardiovascular risk assessment, such as: Adult Treatment Panel III, ASSIGN (Assessing Cardiovascular Risk to Scottish Intercollegiate Guidelines Network), QRISK (QRESEARCH Cardiovascular Risk Algorithm), and SCORE (Systematic Coronary Risk Evaluation) project (Berger et al, 2010).

Majority of the studies so far evaluated risk of CVD in a 10-year or shorter time period. Contrary to these studies, there is a study in which individuals, free of conditions at baseline, were followed-up for 30-years and in that period incidence of CVD and death was ascertained. Results of this study demonstrated that standard risk factors remain highly predictive of cardiovascular risk over 30-years follow-up period and their impact is significant even if levels are not updated (Pencina et al, 2009).

A global vascular risk score was recently designed and validated that combines conventional risk factors with behavioral (alcohol consumption and physical activity) and



anthropometric risk factors in African-American and Hispanic individuals at risk for vascular disease (Sacco et al, 2009). The use of this risk prediction model demonstrated an improvement in the prediction of global vascular risk.

Reynolds Risk Score (RRS) represents risk prediction algorithm that was designed, validated and used in the prediction of 10-year cardiovascular risk in initially healthy men and women. It is based on two separate large prospective studies that included more than 20,000 women, 45 years of age and older, with median follow-up period of 10.2 years and more than 10,000 men, 50 years of age and older, that were followed up over a median period of 10.8 years for incident myocardial infarction, stroke, coronary revascularization, or cardiovascular death (Ridker 2007, 2008). The main aim of these two studies was to compare predictive value of traditional risk prediction model based on age, blood pressure, smoking status, total cholesterol and high-density lipoprotein cholesterol and RRS in which alongside with traditional risk markers, hsCRP and parental history of cardiovascular diseases are included. Results have confirmed significant predictive value of traditional risk factors as well as of hsCRP and parental history. Furthermore, both of the studies have shown that RRS had better predictive value in the prediction of incident cardiovascular events in women and in men compared to traditional cardiovascular risk prediction model. Study in initially healthy female subjects have also demonstrated that use of RRS improved risk stratification in a sense that 40-50% of women that were previously categorized to be at intermediate risk could be reclassified into higher or lower risk categories. Study in initially healthy male subjects showed that up to 20% of men previously categorized to be at intermediate risk could be reclassified into higher or lower risk categories. Conclusion derived from both of the studies was that use of RRS can serve in primary prevention settings to better targeting of treatments in order to increase benefits and reduce toxicity. RRS comprises of four 10-year risk categories: 0% to less than 5% - low risk category, 5% to less than 10% - low to medium risk category, 10% to less than 20% - medium to high risk category, and > 20% - high risk category (Ridker et al, 2004; Cook et al, 2006).

To date, no data exist on use of RRS in cardiovascular risk assessment among apparently healthy Bosnian men and women. To address this issue, we used Reynolds Risk Score calculator (<http://www.reynoldsriskscore.org>) to ascertain 10-year cardiovascular risk with the use of traditional factors such as age, smoking status, systolic blood pressure, blood levels of total cholesterol, HDL-cholesterol, as well as hcCRP and parental history of myocardial infarction and stroke before the age 60 in our study sample.

## **2. Methods**

### **2.1 Subjects**

Between February and March 2011, 230 of men and 270 women visited Family Medicine Out-Patient Clinic "Visnjik", Sarajevo, Bosnia and Herzegovina, for general health screening. Among them, 200 of men and 250 women signed informed consent. Excluding subjects with history of cardiovascular disease, malignancy, liver disease, alcohol abuse, use of antidiabetic, antihypertensive, or lipid-lowering drugs, or CRP values > 10 mg/L, and those aged < 45 years, the resulting 76 men and 120 women comprised the subjects in the present study. The study was approved by the Ethics Committee of the Medical Faculty University of Sarajevo. Written informed consent was obtained from all subjects included in the study. Participants

underwent a medical history, physical examination and laboratory assessment. Investigations were carried out in accordance with the Declaration of Helsinki as revised in 2000.

## 2.2 Blood sampling

Blood was collected in the morning after an overnight fast and after a 30-minutes rest in a semi-recumbent position. Sampling was done without stasis, using the vacutainer technique.

## 2.3 Blood chemistry analysis

High sensitivity CRP was determined by means of particle enhanced immunonephelometry (BN Systems, Dade Behring, Marburg, Germany). The lower limit of detection of this assay was 0.18 mg/L. Levels of hs-CRP >10mg/L were excluded from the analysis, as they are likely related to infections or other acute inflammatory processes. Total cholesterol, HDL - cholesterol, triglycerides were measured by direct colorimetric reflectance spectrophotometry using Dimension clinical chemistry system (Dade Behring, Marburg, Germany). LDL - cholesterol was calculated by means of Friedwald formula.

## 2.4 Blood pressure measurements

Three supine blood pressure recordings were made after a 5-minutes rest using an Omron 705c oscillometric device. The mean of the second and third readings was used. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, diastolic pressure  $\geq 90$  mmHg, or self-reported high blood pressure with use of anti-hypertensive medications. Prehypertension was defined as systolic blood pressure of 120–140 mmHg or diastolic blood pressure of 80–90 mmHg.

None of the included subjects was pregnant or had a history of intercurrent diseases. Parental history of myocardial infarction or stroke before the age 60 (genetic factor) was defined as family history of heart disease or stroke. Smoking status and genetic factor were assessed by self-administrated questioner.

*Statistical analysis.* The Kolmogorov-Smirnov test of normality was used to test the distribution of variables. Normally distributed data are presented as mean  $\pm$  SEM and skewed variables as median and interquartile ranges. An unpaired Student t-test or Mann-Whitney U-test was used to compare the difference between two groups, as appropriate. Frequencies were tested by Chi-square test. In order to determine the factors associated with absolute 10-year Reynolds Risk Score, multiple regression analysis was performed. A p value of less then 0.05 was considered statistically significant. The software used was SPSS for Windows (version 17.0; SPSS, Chicago, IL, USA).

## 3. Results

Variables	Men (n=76)	Women (n=120)	p<
Age (yrs)	58.64 $\pm$ 2.12	57.06 $\pm$ 1.67	NS
Smoking (yes/no)	(29/47)	(36/84)	NS
SBP (mmHg)	136.43 $\pm$ 2.13	130.92 $\pm$ 1.71	0.05

Variables	Men (n=76)	Women (n=120)	p<
TC (mmol/L)	5.48±0.13	6.01±0.12	0.001
HDL (mmol/L)	1.22±0.04	1.39±0.03	0.001
hsCRP (mg/L)	1.33(0.78-3.92)	1.71(0.80-3.92)	NS
GF (yes/no)	(17/59)	(11/109)	0.05
Absolute RRS (%)	19.37±1.67	9.76±1.03	0.0001

Data are presented as mean ± SEM, median and inter-quartile range, or in total count. SBP: systolic blood pressure; TC: total cholesterol; HDL-cholesterol: high density lipoprotein - cholesterol; hsCRP: high sensitivity C-reactive protein; GF: genetic factor; Absolute RRS: absolute Reynolds Risk Score, n: number of subject.

Table 1. The values of Reynolds Risk Score factors in apparently healthy male and female subjects. Subjects did not differ in age, smoking status and CRP values. Statistically significant difference was observed in systolic blood pressure, total cholesterol, HDL-cholesterol, genetic factor presence and in absolute Reynolds risk score values between men and women.

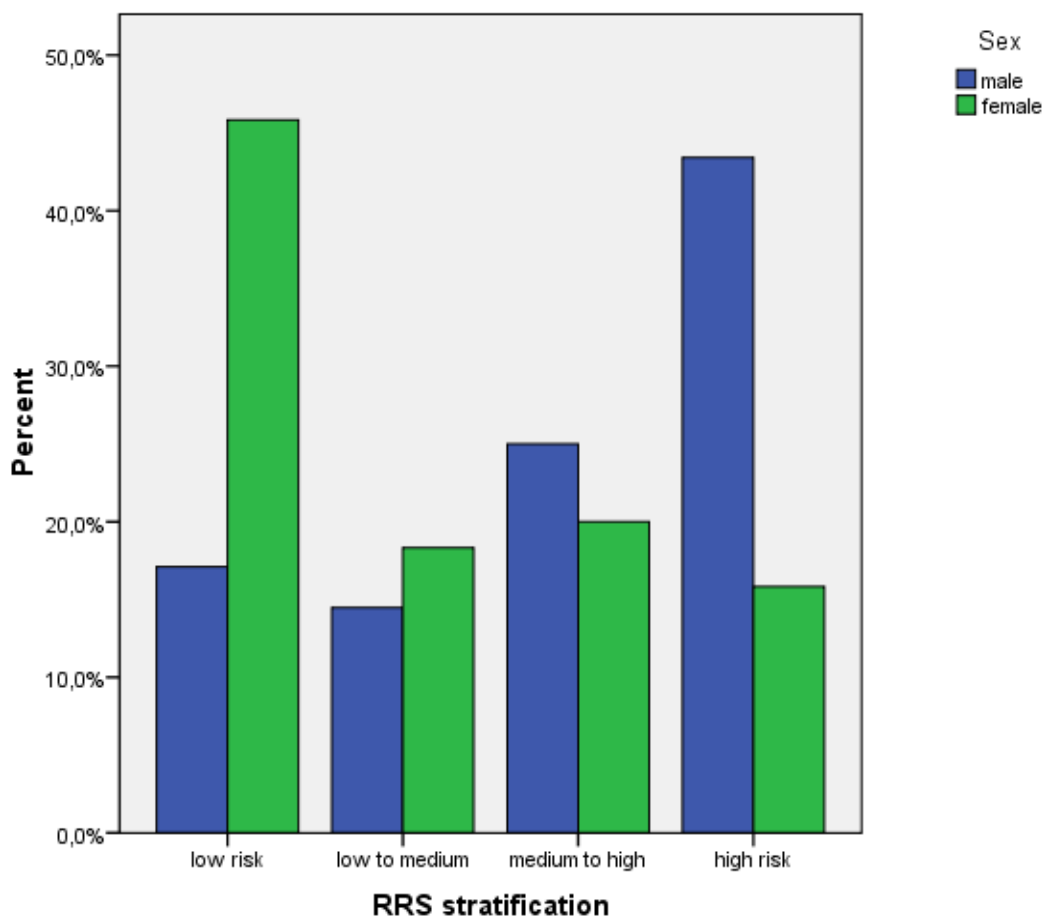


Fig. 1. Frequency of Reynolds Risk Score categories by gender. Results have shown that 6.63% of men and 28.6% of women were in low risk category, 5.6% of men and 11.2% of women in low to medium risk category, 9.7% of men and 12.2% of women in medium to high risk category, and 16.8% of men and 9.7% of women in high risk category.

Independent Variables	$\beta$ coefficient	t value	p<
Age (yrs)	0.553	7.753	0.0001
Smoking (yes/no)	0.023	0.359	NS
SBP (mmHg)	0.420	5.905	0.0001
TC (mmol/L)	0.095	1.422	NS
HDL (mmol/L)	-0.016	-0.244	NS
hsCRP (mg/L)	-0.005	-0.073	NS
GF (yes/no)	-0.143	-2.244	0.05

Table 2. Results of multiple regression analysis for absolute 10-year Reynolds Risk Score as dependent variable in men. Multiple regression analysis revealed that in male subjects most predictive value in cardiovascular risk assessment had age followed by systolic blood pressure and genetic factor, respectively.

Independent Variables	$\beta$ coefficient	t value	p<
Age (yrs)	0.287	4.394	0.0001
Smoking (yes/no)	-0.230	-4.265	0.0001
SBP (mmHg)	0.561	8.647	0.0001
TC (mmol/L)	0.093	1.701	0.092
HDL (mmol/L)	0.012	0.222	0.825
hsCRP (mg/L)	0.075	1.367	0.174
GF (yes/no)	-0.044	-0.804	0.423

Table 3. Results of multiple regression analysis for absolute 10-year Reynolds Risk Score as dependent variable in women. In female subjects most predictive value in cardiovascular risk assessment had systolic blood pressure, followed by age and smoking, respectively.

#### 4. Discussion

CVD is one of the leading causes of death worldwide. It is estimated that for individuals at age of 50 years, the lifetime risk of CVD is, on average, for men 52% and 39% for women (Berger et al, 2010).

To the best of our knowledge, we are the first to report high prevalence of cardiovascular risk factors in apparently healthy Bosnian men and women with the use of Reynolds Risk Score calculator. Results have shown that in a total study sample, 34.7% of subjects were in low, 16.8% in low to medium, 21.9% in medium to high, and 26.5% of subjects were in high cardiovascular risk category. Our results are consistent with previous report (Cushman et al, 2009). Majority of women in both studies belonged to low and low to medium risk category group, and majority of men belonged to medium to high and high risk category group. The mean absolute 10-year cardiovascular risk determined with RRS calculator in men included in our study was 19.37%, and 9.97% in women. Our observations are not in accordance with the study among commercial pilots in UK that revealed that 9.7% of all male pilots were at high cardiovascular risk and that the mean 10-year cardiovascular risk for the entire pilot population was 8.41% (Houston et al, 2010).

Data on prevalence of cardiovascular risk factors in less developed countries are not abundant. In urban Tanzania, prevalence of cardiovascular risk factors was high, especially in women. The age-adjusted prevalence of obesity in men was 13%, and 35% in women. In men, BMI and waist circumference (WC) were significantly correlated with blood pressure, triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol (BMI only), and fasting glucose. Conversely, in women only blood pressure was positively associated with BMI and WC (Njelekela et al, 2009).

Study in urban Asian Indian subjects observed low prevalence of smoking, hypertension, dyslipidemia, metabolic syndrome and diabetes in adolescents, with rapid escalation of these risk factors by age of 30-39 years (Gupta et al, 2009).

Results of a first nationwide survey on cardiovascular risk factors in Grand-Duchy of Luxembourg have shown the most predominant cardiovascular risk factors was dyslipidemia (69.9%), followed with hypertension (34.5%), smoking (22.3%), and obesity (20.9%), while diabetes was present in 4.4% of study population. Furthermore, only 14.7% of men and 23.1% of women were free of any cardiovascular risk factor (Alkerwi et al, 2010).

Studies have demonstrated that incidence and prevalence of CVD increase with advancing age. However, the predictive value of classic risk factors diminishes with age. The mean value of age of male participants in our study was 58.64 years, and of female participants 57.06 years. There was no significant difference in age between these two groups. Population based observational cohort study in very old people (aged 85 years) with no history of CVD aimed to assess classic risk factors and some new biomarkers (homocysteine, folic acid, CRP, interleukin-6) as predictors of cardiovascular mortality in this age group. Their results have shown that homocysteine alone accurately identified individuals at high cardiovascular risk, whereas classic risk factors included in the Framingham risk score did not (de Ruijter et al, 2008).

A study that investigated age relations of blood pressure, anthropometric indexes, serum lipids, and hemostatic variables in a population of Papua New Guinea (Lindberg et al., 1997) has found that diastolic blood pressure was not associated with age, while systolic blood pressure linearly increased after 50 years of age in both sexes. BMI decreased with age in both sexes. Serum total cholesterol, triglycerides, LDL-cholesterol increased in males between 20 and 50 years of age, whereas HDL-cholesterol decreased. Authors concluded that some of the relations of age with other cardiovascular risk factors represent effects of biological aging.

Results from EURIKA study (Guallar et al, 2011), which involved participants from 12 European countries with at least one cardiovascular risk, but without CVD reported that the average 10-year risk of CVD death in study participants was 8.2%. Hypertension was responsible for 32.7%, hyperlipidemia for 15.1%, smoking for 10.4%, and diabetes for 16.4% of CVD risk. The four risk factors accounted for 57.7% of CVD risk, representing a 10-year excess risk of CVD death of 5.66%. Study also demonstrated that lack of control of these cardiovascular risk factors was responsible for almost 30% of the risk of CVD death.

Besides age, hypertension, smoking, diabetes, and hyperlipidemia, risk factors for CVD also include obesity, physical inactivity and insulin resistance. A study conducted among adults seeking primary care in Germany reported high prevalence of overweight and obese individuals. Furthermore, a high waist to hip ratio (WHR) was associated with an increased prevalence of high triglycerides, a high blood pressure, an increased fasting glucose, and the



presence of diabetes mellitus. On the other hand, a family history of myocardial infarction was not more frequent in patients with high WC compared to patients with normal WC. The prevalence of smoking was significantly lower in overweight men with an elevated and high WC, but not in women (Haurer et al, 2008).

According to Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, systolic blood pressures of 120–139 mmHg and/or diastolic blood pressures of 80–89 mmHg are classified as prehypertension. Individuals with this condition are thought to be at increased risk of CVD. Results from a cross-sectional study in Jamaica have shown that the prevalence of prehypertension among Jamaicans was 30%. Prehypertension was found in 35% of male subjects, and 25 % of female subjects. Almost 46% of study participants were overweight; 19.7% were obese; 14.6% had hypercholesterolemia; 7.2% had diabetes mellitus, and 17.8% smoked cigarettes. With the exception of cigarette smoking and low physical activity, all the CVD risk factors had significantly higher prevalence in the prehypertensive and hypertensive groups compared to the normotensive group (Ferguson et al, 2008). Results of our study have shown that mean value of systolic blood pressure both in men and in women was below 140 mm/Hg. Men had significantly higher values of systolic blood pressure compared to women. Another observation of our study was that there was no significant difference in smoking status between men and women.

Diets high in fat, especially saturated fat, are frequently associated with hypercholesterolemia, hypertension and obesity. Recent findings have reported significant increase in the prevalence of obesity in all age groups, including children, adolescents and adults. A study conducted among physically active college students reported that 45% of participants were overweight or obese. Furthermore, positive association between grain consumption, alcohol intake and BMI was observed. Another finding of this study was that high percentage of subjects had high WHR, elevated systolic and diastolic blood pressure, blood glucose and total cholesterol levels (Sharma et al, 2008). The average value of total cholesterol level both in men and women in our study was above referent limits. On the contrary, average values of HDL-cholesterol in both groups were within normal range. However, since we did not conduct a survey on dietary habits of our participants, we are in no position to draw any conclusions whether there is an association between total cholesterol and HDL-cholesterol values and dietary habits of our study sample. Future studies should address this issue, among population of Bosnia and Herzegovina, since it has been well documented that caloric intake differs between ethnicities, age and socioeconomic groups.

The growing evidence supports the hypothesis that there is ethnic variation in CRP levels. Results of a large population-based study in Black and White men and women in the United States have shown that increased CRP values were more common among women than men, blacks than whites, and in the stroke belt compared to the rest of the U.S. Results of a same study also demonstrated that the use of RRS reclassified population to a different 10-year vascular risk level than the new Framingham Vascular Score (Cushman et al, 2009)). Our results did not show significant difference in CRP values between men and women included in our study. Thus, we were not able to confirm previous findings that gender influences CRP levels. However, this could be due to a limited size of our study sample.

Earlier results have demonstrated that inclusion of CRP in global risk prediction model improves risk classification in women (Cook et al, 2006). On the contrary, critical appraisal of literature on CRP measurement for the prediction of coronary heart disease event (Shah et al, 2009) have revealed that benefits of addition of CRP to models based on traditional risk factors are small and are only slightly resulting in better improvement in risk classification and reclassification.

It is of interest to note that in the present study CRP did not show significant predictive value in cardiovascular risk assessment both in men and in women. Thus, data on possible use of CRP in cardiovascular risk assessment remain conflicting and inconsistent. Possible explanation for the observed inconsistency may be a fact that normal functions of CRP as well as its possible roles in diseases are yet incompletely defined (Casas et al, 2008). The reason for this is that so far no deficiency or structural polymorphism of human CRP have been reported nor is any therapeutic intervention available which specifically inhibits CRP in vivo. Consequently, until today the effects of absence, lack of function or inhibition of human CRP have not been tested.

A large prospective study in Chinese male adults has demonstrated that hypertension and cigarette smoking were the leading predictive parameter for CVD (Ji et al, 2011). Our study had similar observations. We established that in male subjects most predictive value in cardiovascular risk assessment had age followed by systolic blood pressure and genetic factor, respectively. In female subjects, most predictive value in cardiovascular risk assessment had systolic blood pressure followed by age and smoking, respectively.

Limitations of our study merit careful considerations. Importantly, present study was cross-sectional and we did not include prediction of cardiovascular events. Subjects were not a general population but visitors to a Family Medicine Out-patient Clinic in capital city of an urban region in Bosnia and Herzegovina. Longitudinal studies and in larger populations are warranted to test present findings. Another limitation is that this study relied on self-reported smoking history and parental history of myocardial infarction which could bias the validity of findings. However, this potential limitation is extremely unlikely, because self-reported risk factors are commonly used in studies with reasonable accuracy (Sesso et al, 2001).

## 5. Conclusion

In conclusion, results of this cross-sectional study showed that significant proportion of our study sample belong to medium to high and high cardiovascular risk category. Significant reduction in cardiovascular risk can be achieved by scheduled cardiovascular risk assessment accompanied with appropriate interventions. One of the purposes of the present study was to inform physicians, especially in Bosnia and Herzegovina, about advantages of possible use of web-based RRS calculator in cardiovascular risk assessment of patients they treat in their everyday practice.

The advantage of RRS is that it includes traditional cardiovascular risks accompanied with blood-based biomarkers and parental history of cardiovascular disease that results in better risk assessment and is easily accessible and cost-effective in primary prevention. With the use of RRS, we were able to identify individuals who may require more comprehensive risk stratification. Moreover, findings of the present study suggest that use of RRS may serve in better targeting of treatments in primary prevention settings.

RRS calculator provides information not only on total cardiovascular risk but also how control of certain cardiovascular risk can lead to the reduction of absolute cardiovascular risk in percentages. The use of RRS in cardiovascular risk assessment may result in a better compliance of patients and physicians in their joint efforts to achieve better control of cardiovascular risks.

Based on the results of present study, physicians are strongly encouraged to promote and to intensify well established interventions such as blood pressure control, lipid reduction, smoking cessation, heart-healthy diet, physical activity and weight reduction. One can not foresee that CVD will be eliminated in a near future, but education, screening, monitoring, and appropriate treatment will certainly lead to the decrease of the morbidity and mortality of these diseases.

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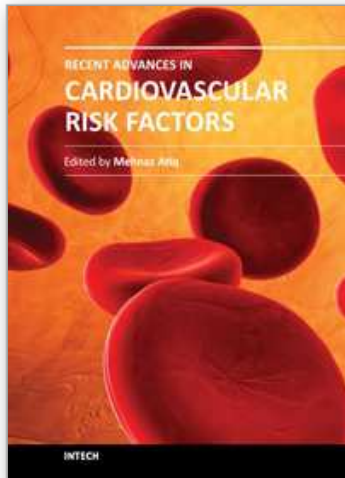
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## **Recent Advances in Cardiovascular Risk Factors**

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Among the non-communicable diseases, cardiovascular disorders are the leading cause of morbidity and mortality in both the developed and the developing countries. The spectrum of risk factors is wide and their understanding is imperative to prevent the first and recurrent episodes of myocardial infarction, stroke or peripheral vascular disease which may prove fatal or disabling. This book has tried to present an update on risk factors incorporating new research which has thrown more light on the existing knowledge. It has also tried to highlight regional diversity addressing such issues. It will hopefully be resourceful to the cardiologists, general practitioners, family physicians, researchers, graduate students committed to cardiovascular risk prevention.

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