Traditional Risk Factors of Acute Coronary Syndrome in Four Different Male Populations – Total Cholesterol Value Does Not Seem To Be Relevant Risk Factor

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Summary

Cardiovascular diseases are the most common cause of mortality and morbidity in most populations. As the traditional modifiable risk factors (smoking, hypertension, dyslipidemia, diabetes mellitus, and obesity) were defined decades ago, we decided to analyze recent data in patients who survived acute coronary syndrome (ACS). The Czech part of the study included data from 999 males, and compared them with the post-MONICA study (1,259 males, representing general population). The Lithuanian study included 479 male patients and 456 age-matched controls. The Kazakhstan part included 232 patients and 413 controls. In two countries, the most robust ACS risk factor was smoking (OR 3.85 in the Czech study and 5.76 in the Lithuanian study), followed by diabetes (OR 2.26 and 2.07) and hypertension (moderate risk elevation with OR 1.43 and 1.49). These factors did not influence the ACS risk in Kazakhstan. BMI had no significant effect on ACS and plasma cholesterol was surprisingly significantly lower ($P<0.001$) in patients than in controls in all countries (4.80±1.11 vs. 5.76±1.06 mmol/l in Czechs; 5.32±1.32 vs. 5.71±1.08 mmol/l in Lithuanians; 4.88±1.05 vs. 5.38±1.13 mmol/l in Kazakhs/Russians). Results from our study indicate substantial heterogeneity regarding major CVD risk factors in different populations with the exception of plasma total cholesterol which was inversely associated with ACS risk in all involved groups. These data reflect ethnical and geographical differences as well as changing pattern of cardiovascular risk profiles.

Key words

Acute coronary syndrome • Obesity • Hypertension • Cholesterol • Diabetes • Smoking • Prevalence

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Introduction

The etiology of atherosclerotic coronary disease is multifactorial. Aside from non-modifiable risk factors such as age, being male and genetic predisposition, many other risk factors could be managed by changes to individual life style and/or pharmacotherapy. More than

200 of these risk factors have been described (Hopkins and Williams 1981), of which the most important are considered to be high plasma cholesterol level, hypertension, diabetes mellitus, smoking and overweight/ obesity. The definition of these risk factors was assessed decades ago and is originally based on data obtained from the Framingham study (Dawber *et al.* 1962). Data are available on the prevalence and changes of these risk factors in European populations thanks to the MONICA and post-MONICA studies (Keil 2005, Cifkova *et al*. 2010, Lindroth *et al.* 2014, Vikhireva *et al.* 2014), but much less evidence is available regarding the real pattern of risk factors in patients suffering from cardiovascular diseases (CVD).

In order to estimate further development in mortality and morbidity on CVD, it is of substantial importance to be aware of the prevalence of the traditional risk factors both in healthy populations and in patients with CVD.

We analyzed traditional CVD risk factors in four populations of males with acute coronary syndrome (ACS) from Prague, Czech Republic, Kaunas, Lithuanian Republic and Astana, Kazakhstan and compared them with control populations.

Methods

Subject selection

We collected data in three completely independent centers.

In the Czech group, 999 male patients (younger than 65 years) hospitalized between 2006 and 2012 at the coronary care unit of the Institute for Clinical and Experimental Medicine for acute coronary syndrome (ACS) (Hubáček *et al*. 2015, Hubáček *et al*. 2016) were included. As a controls, we used a 1 % sample of the general population from the WHO MONICA study (MONItoring of CArdiovascular diseases (Tunstall-Pedoe *et al.* 2003) in 9 Czech regions) and a survey from 2000/2001 (1,259 males) was included.

In the Lithuanian group, 479 patients with ACS were enrolled in the study. The mean age of the patients was 59.9±11.0 years, all of whom were admitted to the Department of Cardiology of the Lithuanian University of Health Sciences Hospital between 2007 and 2011.

The control group consisted of 456 males free from symptoms of IHD and stroke, matching the study group design according to age. The control group consisted of subjects from a random sample of the Kaunas population screened within the international HAPPIE *(Health, Alcohol and Psychosocial factors In Eastern Europe)* project (Peasey *et al.* 2006), the CINDI *(Countrywide Integrated Non-communicable Disease Intervention)* project (Grabauskas *et al.* 2008) and the "Kaunas Healthy Ageing Study".

In the Kazakhstan group, 232 male patients (aged 50-74 years) hospitalized between 2013 and 2015 at the coronary care unit of the Astana City Hospital #2 for acute coronary syndrome were included in the analysis.

For the Kazakhstan control group, the study sample was randomly selected from registries of all inhabitants at local outpatient clinics. Persons in the age range 50-74 year were included. A total number of 416 male adults were used in the current analysis, excluding those who self-reported diagnosed CVD in the history (Supiyev *et al*. 2015, Supiyev *et al*. 2016). Excluded were also subjects with serious diseases (cancers, renal failure). In total, there were 63.7 % of Kazakhs, 24.9 % of Russians with 12.4 % declaring the others ethnicities.

At all centre's, the patients completed a questionnaire and their lipoprotein parameters were measured in the local laboratory within 24 h of the onset of symptoms. ACS was defined according to the standard criteria based on clinical symptoms, ECG findings and cardiac-enzyme abnormalities.

The studies were performed in agreement with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All patients signed informed consent before they were included in the study.

Definition of risk factors

Basic/traditional risk factors were defined as follows: 1) current or past smokers; 2) body mass index (BMI) $\geq$25 kg/m^2; 3) hypertension (self-reported and/or antihypertensive treatment and/or blood pressure over 139/89; and 4) diabetes as self-reported diabetes and/or antidiabetic (also dietary) treatment. Both in controls and in patients, data were obtained from personal questionnaires completed under the supervision of a trained nurse prior to discharge. Diagnoses were determined by coronary care unit physicians, during which time anthropometric and biochemical parameters were reviewed.

Cholesterol and triglycerides (in fasting plasma, day after admission) were assessed using conventional

enzymatic methods (reagents from Boehringer Mannheim Diagnostics and Hoffmann-La Roche).

Statistical analyses

Data from questionnaires and biochemical parameters were entered into the database. Statistical analysis was performed using standard statistical tests as follows: chi square test for categorical variables and ANOVA for continuous variables. As the study is focused on confirmation of the traditional CVD risk factors, no multivariate analysis has been performed. For adjustment purposes, we used ANCOVA for continuous variables and logistic regression for discrete variables. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated using http://www.hutchon.net/ConfidOR.htm.

Results

Czech branch

We collected complete data from 999 males (93.2 % out of 1,072 hospitalized patients fulfilled the basal criteria; 55 refused to participate; and in the case of 18 patients, data were incomplete) with ACS. Controls were slightly but significantly (P<0.001) younger than patients (Table 1).

The largest difference between patients and controls was observed with regard to prevalence of smoking. Among the patients, only 14.9 % were never smokers, in comparison to 40.3 % in the general population (P<0.0001; OR (95 % CI) 3.85 (3.12-4.73)).

The second major risk was associated with the prevalence of diabetes – there were twice as many diabetics (P<0.0001; 2.26 (1.76-2.91)) in patients (17.8 %) than in controls (8.9 %).

With regard to hypertension, a significant difference was observed only in the unadjusted model, but not after adjustment for age. Prevalence of overweight was almost identical between patients and controls.

Plasma cholesterol levels were significantly lower (P<0.001) in patients (4.80±1.11 mmol/l) than in controls (5.76±1.06 mmol/l). This difference remained significant even after the exclusion of patients (13.4 % were treated by statin or fibrate) and controls (8 %) on hypolipidemic treatment.

Lithuanian branch

This part of the study included 479 patients and 456 age matched controls (Table 2) and observations revealed similar results to those obtained in the Czech patient/control branch.

This part further underlines the importance of smoking as a major risk factor of ACS. Among the patients, 28.4 % were never smokers, in comparison to 64.1 % in the general population (P<0.0001), which means that the OR (95 % CI) associated with smoking was 5.76 (3.78-6.75).

Diabetes (OR 2.13, 95 % CI 1.22-3.73) was the second most important risk factor, more than doubling the increase of risk.

Similar to the Czech data, hypertension (OR 1.49, 95 % CI 1.03-2.16) had only a minor effect (but still significant at P=0.04) and body weight had no effect (P=0.76).

Finally, total plasma cholesterol was also here significantly lower (P<0.001) in patients (5.32±1.32 mmol/l) than in controls (5.71±1.08 mmol/l).

Kazakhstan branch

Within the Kazakhstan subjects, the risk of myocardial infarction was not associated with any traditional risk factor (Table 3). The proportion of diabetes and obesity were even slightly higher among controls in the Kazakhstan group, and the hypertension and smoking were more prevalent in patients, but there were not statistically significant differences between the groups.

The difference between total cholesterol levels was in the similar direction (P<0.001) like in other two countries (Table 3). Surprisingly, the differences remain significant (P<0.05) even after dividing the group according the ethnicity – among Kazakhs, controls (N=267) had cholesterol 5.34±1.19 mmol/l and cases (N=138) 4.77±1.03 mmol/l, and among Russians the values were 5.43±1.04 mmol/l for controls (N=89) vs. 4.99±1.04 mmol/l for cases (N=72).

Discussion

Our study analyzed the prevalence of the five most commonly examined risk factors of cardiovascular disease among males suffering from ACS. Some of our results are surprising, especially the (absence of) association of the total cholesterol and acute forms of ischemic heart disease.

Table 1. Prevalence of traditional risk factors among Czech males with acute coronary syndrome and controls.

	Patients	Controls	P	P#
N	999	1,259		
Age (years)	54.7 ± 8.0	49.0 ± 10.8	0.001	-
Total cholesterol (mmol/l)	4.80 ± 1.11	5.76 ± 1.06	0.001	0.001
Total cholesterol (mmol/l)*	4.89 ± 1.13	5.75 ± 1.06	0.001	0.001
Triglycerides (mmol/l)	2.06 ± 1.49	1.97 ± 1.28	n.s.	0.02
Triglycerides (mmol/l)*	2.03 ± 1.47	1.94 ± 1.24	n.s.	0.02
Ever smokers (%)	85.1	59.7	0.00001	0.0001
Diabetes (%)	17.8	8.9	0.0005	0.01
Hypertension (%)	50.6	41.6	0.001	n.s.
Overweight (%)	80.1	79.9	n.s.	n.s.
Statin treatment (%)	13.4	8.0	0.005	-

* Patients (N=134) and controls (N=101) treated by statin or fibrate are excluded. # P adjusted for age.

Table 2. Prevalence of traditional risk factors among Lithuanian males with acute coronary syndrome and controls.

	Patients	Control group	P value
N	479	456	
Age (years)	59.9 ± 11.0	59.1 ± 10.6	0.27
Total cholesterol (mmol/l)	5.32 ± 1.32	5.71 ± 1.08	0.0001
Triglycerides (mmol/l)	1.74 ± 1.60	1.34 ± 0.77	0.0001
Ever smokers (%)	71.6	35.9	0.0001
Diabetes (%)	10.6	6.8	0.005
Hypertension (%)	82.3	74.6	0.05
Overweight (%)	77.7	76.8	0.76
Statin treatment (%)	6.3	5.6	0.61

Table 3. Prevalence of traditional risk factors among Kazakhstan males (63.7 % Kazakhs and 24.9 % Russians included) with acute coronary syndrome and controls.

	Patients	Control group	P value
N	232	416	
Age (years)	59.9 ± 6.9	60.6 ± 7.3	0.27
Total cholesterol (mmol/l)	4.88 ± 1.05	5.38 ± 1.13	0.001
Triglycerides (mmol/l)	1.65 ± 0.83	1.65 ± 1.32	0.995
Ever smokers (%)	74.2	69.7	0.224
Diabetes (%)	12.6	14.2	0.555
Hypertension (%)	59.4	53.1	0.127
Overweight (%)	74.9	78.9	0.250
Statin treatment (%)	7.1	9.0	0.63

It seems that only two risk factors for acute forms of ischemic heart disease are now considered important. These are: smoking and diabetes mellitus. Our study showed that smoking status was the most extreme factor, as only about 20 % of all patients consisted of never smokers and, based on our results, smokers are about five times more likely to experience ACS than never smokers. Surprisingly, in Kazakhstan, these factors have not been associated with CVD risk.

The two other risk factors, namely hypertension and overweight/obesity, seemed to be of less importance. This is underlined by the fact that both factors were not significantly associated with ACS after adjustment for age in Czech Republic or Kazakhstan and that only a borderline significance was observed in the Lithuanian population. From the MONICA study, it is clear that the prevalence of hypertension in the general population is now lower than it was (Dawber *et al.* 1962, Cifkova *et al*. 2010, Lindroth *et al.* 2014, Vikhireva *et al.* 2014). As a consequence of the success of primary prevention, we detected relatively low differences in hypertension prevalence between patients and controls. However, this finding needs to be further interpreted very carefully. There was a higher prevalence of individuals treated with antihypertensive drugs in patients than in controls. Furthermore, as our blood pressure values were obtained on the second day of hospitalization, it is possible that they do not exactly reflect the values before the onset of ACS.

Also, based on the analysis of the prevalence of overweight, controls were not leaner than patients.

The most interesting finding was that ACS patients had lower plasma total cholesterol than controls, independently in all three different countries. This was valid even after exclusion of patients and controls on hypolipidemic treatment, and after adjustment for age. One of explanations is that plasma total cholesterol is going down as a consequence of acute myocardial infarction. Studies have detected a decrease of about 7 % of total cholesterol after the onset of ACS (Wattanasuwan *et al.* 2001, Fresco *et al.* 2002). In a Czech branch, where we have for the majority of subjects both cholesterol values at admission and from fasting blood sampling, the identical decrease was obtained (Staněk *et al.* 2016). In this study, the total cholesterol values at admission were nonsignificantly lower than in age matched controls (Staněk *et al.* 2016). If we assume that the effect in all our populations is identical, then total plasma cholesterol would still not be a risk factor for cardiovascular disease, as expected.

Second explanation is unique role of LDL cholesterol and not total cholesterol. Unfortunately, calculating (using the Friedewald formula) precise values of LDL cholesterol in ACS patients through the hospitalization are not reliable. One of reasons is possibility that heparinization (as a standard approach in pre-hospital ACS patients care) results in a decrease of plasma triglyceride levels (Mulder *et al.* 1993) due to hydrolysis of TG-rich lipoprotein particles. This could also modify LDL levels in not well predictable manner.

In the literature, the fact that total plasma cholesterol levels are lower in patients with ACS/MI is often "hidden" and not clearly presented. Other publications (for example see Pérez-Hernández *et al.* 2012) have confirmed the risk associated with dyslipidemia, but not with plasma total cholesterol. Dyslipidemia is defined as abnormal values of total plasma/LDL cholesterol, HDL cholesterol and triglycerides. In most subjects, in fact, elevated plasma TG values are the reason of dyslipidemia. As prevalence of obesity and diabetes mellitus is increasing, elevated plasma triglycerides and associated lipid disorders (small atherogenic LDL particles, remnant lipoprotein particles) are becoming the essence of atherogenic dyslipidemia. Similarly, in our two populations, TG values were significantly higher in patients than in controls. In agreement with this finding, plasma TG values, rather than plasma TC values are predictors of total mortality (Hubáček 2015, Liu *et al.* 2013, Pikhart *et al.* 2015, Piťha *et al.* 2015).

Even the global INTERHEART study recognize as risk factor of myocardial infarction the high ApoB/ApoA1 ratio, which was considered to be superior to commonly used cholesterol derived values and ratios (Mc Queen *et al.* 2008), one of reasons was that not all samples have been available after fasting status, reflecting to certain extent also settings of our study.

It should be noted that our results are not unique (Morales-Suarez-Varela *et al.* 2011, Nikolajević-Starčević and Petrovič 2013). In fact, some other recent studies have recorded similar results, questioning the health risks associated with elevated plasma cholesterol levels, especially in the case, if they have been focused on the mortality data. For example, a study by Tamosiunas *et al.* (2014) presented the results from the Lithuanian MONICA and HAPIEE studies and concluded that CVD mortality was not associated with plasma cholesterol in males or in females and that plasma

cholesterol below 5.2 mmol/l was associated with enhanced risk of CVD. Also, values of adjusted hazard ratios obtained from the NHANES III study point to the insignificance of plasma cholesterol levels in cases where cardiovascular or total mortality was analyzed (Yang *et al.* 2012). Based on their results, researchers from the HUNT2 study (Petursson *et al.* 2012) even concluded that plasma cholesterol levels should be omitted from cardiovascular risk calculation. Similarly, the Seoul Male Cohort Study (Kim *et al.* 2013) found that cholesterol was not associated with CVD mortality and, finally, a study of almost 100 000 Chinese subjects found no effect of plasma cholesterol on cardiovascular or total mortality (Liu *et al.* 2014). It should be noted that these studies also did not confirm the risks associated with higher BMI values.

Thus, we can conclude that the importance of total plasma cholesterol as a discriminating risk factor of CVD is becoming less and less important at least at the population level and other lipid parameters – mainly triglycerides and possibly LDL and/or non-HDL cholesterol are of importance. This may also be further supported by the fact that, first, plasma levels of lipids have significantly declined over recent decades for about 20 % of the general population (Cífková *et al.* 2010); therefore, a much higher proportion of the population now corresponds to recommended values. A further explanation could be linked to the role played by higher levels of remnant lipoprotein particles and their cholesterol content, which are not detected in the fasting state (Varbo *et al.* 2013, Varbo *et al.* 2015), but which are reflected in higher plasma triglycerides.

Despite the continuous decline in cardiovascular mortality since 2000 in all EU countries, CVD is still responsible for almost 40 % of deaths in these countries (OECD 2016). Despite the refinement of the ACS criteria (Thygesen *et al.* 2012), no significant development has been observed over the last forty years in relation to the definition of CVD risk factors. For example, the selection of risk factors is based on the Framingham offspring study (Dawber *et al.* 1962). But the population's prevalence for most of these CVD risk factors (as defined more than a half of the century) has significantly changed (Keil 2005, Cifkova *et al.* 2010, Lindroth *et al.* 2014, Vikhireva *et al.* 2014). We strictly keep to the "big five", while failing to acknowledge the prevalence and importance for these factors to rise in some cases (smoking and diabetes) and decline in others (BMI and plasma cholesterol).

As a consequence, estimating CVD risk might be misleading when based on total plasma cholesterol levels as the main risk factor. Even though we are aware of the limitations of this cross-sectional study, similar findings from our three independent centers, along with further published studies, allow us to propose a more cautious approach to the development of algorithms based on cardiovascular risk factors established decades ago. New prospective studies are definitely needed to confirm this important change in traditional cardiovascular risk factors.

Conflict of Interest

There is no conflict of interest.

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