BASELINE CHARACTERISTICS

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) Trial in Slovakia

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Abstract

Objectives: **We described the baseline characteristics of a cohort of patients who are a part of a large prospective study and compared with those characteristics of patients enrolled globally.**
Background: **The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) is a double-blind, randomized, multinational, multicenter, prospective, parallel group study. The primary objective of VALUE trial is to assess the effect of the angiotensin II (AT1 receptor) antagonist valsartan on the reduction of cardiac morbidity and mortality in patients 50 years of age or older with essential hypertension and a high risk of cardiovascular events.**
Methods: **A total of 15 314 patients from 31 countries were randomized. In Slovakia 103 patients were randomized. We compared baseline characteristics of patients enrolled in Slovakia with those of patients enrolled globally. Statistic analysis was made with F-test, t-test, chi-square test and binomial test.**
Results: **The Slovak group had of fewer men (40.8 %) and more patients of Caucasian race (99.0 %). A higher proportion of patients treated for hypertension for at least three months was found in the Slovak group (99.0 %), however the mean values of sitting systolic and sitting diastolic blood pressures remained similar in both groups. The value of serum creatinine >150 μmol/l did not occur in the Slovak group. The coronary heart disease was more prevalent in the Slovak group (77.7 %) and the mean value of hemoglobin was lower in the Slovak group (138.0 g/l).**
Conclusions: **The baseline characteristics of the 103 patients enrolled in VALUE trial in Slovakia indicate that the target population of patients with essential hypertension and a high risk of cardiovascular events was achieved.** ***(Tab. 1, Fig. 6, Ref. 21.)***
Key words: amlodipine, angiotensin II antagonist, calcium channel blockers, hypertension, valsartan.

Cardiovascular diseases are the main causes of death in adults and the elderly in the most countries in the world. Essential hypertension is the most prevalent cardiovascular disease and presents a major public health issue (1). Antihypertensive drugs have proven benefits, however cardiovascular morbidity and mortality rates remain relatively high with serious consequences for public health. The ultimate goal of treating patients with hypertension is to prevent or reduce the cardiovascular morbidity and mortality associated with this disease (2). The divergences of antihypertensive treatment effects lead to classification of the complications in hypertension into pressure-related (strokes and congestive heart failure) and atherosclerosis-related (coronary events). An extension of this concept is that other factors besides blood pressure elevation may be involved in coronary morbidity in hypertension. Among these other factors, the renin-angiotensin system has been suggested to play an important role (3). The visionary hypothesis has been formulated that a high activity of plasma renin in hypertension causes cardiovascular damage (4). The potent trophic effects of angiotensin II on blood

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vessels and on cardiac cells have been well demonstrated, especially in vascular hypertrophy, left ventricular hypertrophy, endothelial dysfunction and congestive heart failure. It is reason able to expect that an angiotensin II antagonist, besides blood pressure lowering, may have additional beneficial effects in hypertensive patients at a high risk of cardiovascular events.

The desired antihypertensive agent should normalize blood pressure levels along with a reduction of associated cardiovascular morbidity and mortality. Such effects were proved with calcium blockers (5–7) and angiotensin-converting enzyme inhibitors (8) compared to placebo. However, large hypertension trials (9–13) have not shown significant differences in treatment effects between various classes of antihypertensive agents (diuretics, beta-blockers, calcium blockers, angiotensin-converting enzyme inhibitors and alpha-blockers) on primary cardiovascular outcomes.

Effects of a new class of antihypertensive agent, an angiotensin II (AT_1 receptor) antagonist, have been investigated on hypertensive patients in several large trials. LIFE (14) trial recruited patients with essential hypertension and electrocardiographic evidence of left ventricular hypertrophy, which were assigned to once-daily losartan-based or atenolol-based therapy. The results showed significant differences in the primary composite endpoint (cardiovascular mortality, MI, stroke) in favor of losartan, but this was driven solely by the reduction in stroke; the rates of MI and cardiovascular mortality did not differ between groups. Both losartan and atenolol provided similar blood pressure lowering effects. The SCOPE trial (15) investigated the effect of candesartan on cardiovascular morbidity and mortality in elderly hypertensive patients. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) (16) trial compared an angiotensin II (AT_1 receptor) antagonist (valsartan) with a third-generation calcium channel blocker, amlodipine (17). The inclusion criteria allowed recruitment of broad population of hypertensive patients with a high risk of a cardiovascular events.

The primary scientific hypothesis of the VALUE trial trial was that for the same level of blood pressure control valsartan would be more efficacious in reducing acute myocardial infarction, congestive heart failure and cardiac mortality than amlodipine. The objective is to execute a study capable of detecting a 15 % difference in cardiac morbidity and mortality between a group of hypertensive patients treated with valsartan 80 mg or 160 mg, with or without the addition of hydrochlorothiazide once daily compared to a group treated with amlodipine 5 mg or 10 mg once daily, with or without the addition of hydrochlorothiazide in a multinational, multicenter, prospective, double-blind, randomized, active-controlled design. The choice of a control was based on the belief that antagonizing the renin-angiotensin system by valsartan would offer clinical benefits against antagonizing the calcium channel by amlodipine.

Patients

The eligible patient population consisted of women and men 50 years of age or older with essential hypertension treated or untreated and a high risk of cardiovascular events. Previously untreated patients, had to have a mean sitting systolic blood pressure between 160 and 210 mmHg (inclusive), and a mean sitting diastolic blood pressure ≤115 mmHg, or a mean sitting systolic blood pressure ≤210 mmHg and a mean sitting diastolic blood pressure between 95 and 115 mmHg (inclusive) to be enrolled. Patients already under antihypertensive treatment had no lower limits of blood pressure, however, they had upper limits of ≤210/115 mmHg. The trial protocol introduced a new concept of the assessment of cardiovascular risk by risk factors or predisposing conditions and by diseases (16). The qualifying risk factors included diabetes mellitus, current smoking, high total cholesterol defined as >240 mg/dl (6.2 mmol/l), left ventricular hypertrophy (LVH), proteinuria and serum creatinine defined as >1.7 mg/dl (150 μmol/l). The qualifying diseases included coronary heart disease, history of peripheral arterial occlusive disease, history of stroke or transient ischemic attack (TIA) and LVH with strain pattern. The exclusion criteria included factors that may limit patients' long term follow-up and compliance (16). After a 2-week screening period, the patients meeting the inclusion/exclusion criteria were randomized to either valsartan 80 mg once daily or amlodipine 5 mg once daily. Depending on blood pressure response, patients were titrated up to either valsartan 160 mg once daily or amlodipine 10 mg once daily. Additional titration steps included an open label hydrochlorothiazide 12.5 to 25 mg once daily and, if needed, any an other antihypertensive agent except other angiotensin II (AT_1 receptor) antagonists, calcium channel blockers or angiotensin-converting enzyme inhibitors. The target blood pressure is <140/90 mmHg. The trial duration is variable (18). The population is being treated until at least 1450 patients experienced primary endpoint, unless interim analysis is statistically significant. The primary endpoint is defined as the time to first event of sudden cardiac death, fatal myocardial infarction, death during or following percutaneous transluminal coronary angioplasty (PTCA) or coronary artery graft bypass (CABG), death due to congestive heart failure (CHF), myocardial infarction on autopsy, new onset CHF or chronic CHF requiring hospital management, non-fatal myocardial infarction, emergency thrombolytic/fibrinolytic treatment and/or emergency PTCA/CABG to avoid myocardial infarction.

The study was approved by the Ethics Committees of the participating centers, and has been undertaken according to Good Clinical Practice guidelines and the Declaration of Helsinki (19). All patients enrolled in the study gave written informed consent.

Methods

Demographic parameters

Gender, race and date of birth were taken as a part of patients' history and/or medical records. Height was recorded in cm rounded to the nearest whole digit. Weight was recorded in kg rounded to the nearest whole digit. Body mass index (BMI) was calculated from weight in kg divided by height squared in meters.

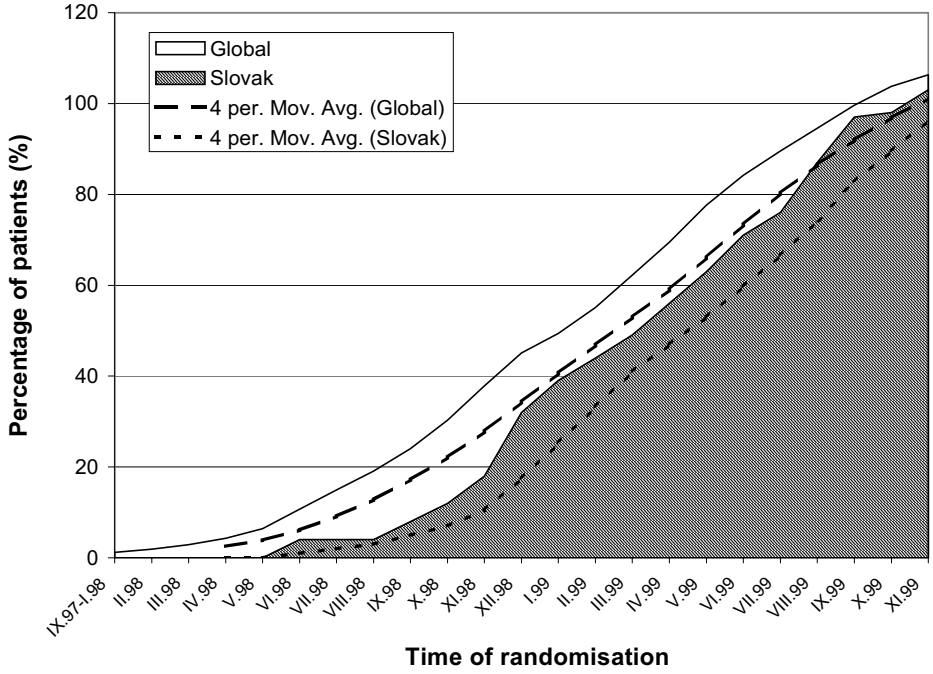

Fig. 1. Enrollment progress.

Cardiovascular parameters

The parameter „previously treated for hypertension" was classified „yes" if the patient had been pharmacologically treated for hypertension for at least 3 months before randomization, even if not continuously. Blood pressure was measured using the arm in which the highest sitting diastolic blood pressure was found. The cuff was deflated at a rate not greater than 2 mmHg/second. After having a patient sitting for five minutes, measurements were taken at one- to two- minute intervals. The mean of three readings was calculated and used as an average value of blood pressure.

Cardiovascular related risk factors and diseases

All conditions related to diabetes mellitus, current smoking, coronary heart disease, stroke or TIA, and peripheral arterial disease were taken as a part of the medical anamnesis and/or medical records. Diabetes mellitus was defined as overnight fasting plasma glucose concentration >140 mg/dl (7.8 mmol/l) on at least two separate occasions or chronic treatment with oral hypoglycemic agents and/or insulin. Current smoking was defined as smoking at least 10 cigarettes per day on a regular basis for at least 5 years before randomization. High total cholesterol was defined as >240 mg/dl (6.2 mmol/l). The electrocardiograph (ECG) was recorded in 12 leads and sent to a central ECG analysis. The sensitivity selection was set to 10 mm/mV. The LVH was classified using Sokolow Lyon (20) or Cornell (21) criteria. The LVH with strain pattern was classified by the central ECG cardiologist interpretation. The urinalysis for proteinuria was performed locally. The proteinuria was defined as 1+ or more on morning dipstick on two subsequent days. Risk factor serum creatinine was defined as >1.7 mg/dl (150 μmol/l).

A history of myocardial infarction was verified by Q-wave ECG and/or hospital records, and/or cardiovascular revascularization. Coronary heart disease was verified by angiography and/or hospital records. History of stroke or TIA was verified by angiography, Doppler measurement, positron emission tomography or computerized axial tomography scan, or persistent hemiparesis (stroke) or hospital record. History of peripheral arterial occlusive disease was verified by angiography or Doppler measurement or hospital records or statement of angiologist. LVH with strain pattern was verified by the central ECG reading.

Blood factors assessment

After an overnight fast, blood samples were drawn from a vein. The assessment for serum GOT, GPT, creatinine, potassium, sodium, uric acid, total cholesterol, glucose and hemoglobin was performed by a central laboratory.

Statistical methods

The aim of the statistical analysis of data was to compare the baseline characteristics of patients enrolled in Slovakia with those of patients enrolled globally.

Connecting and column graphs and synoptical tables of fundamental statistic parameters (mean, standard deviation, percentile values) as graphic tools were used.

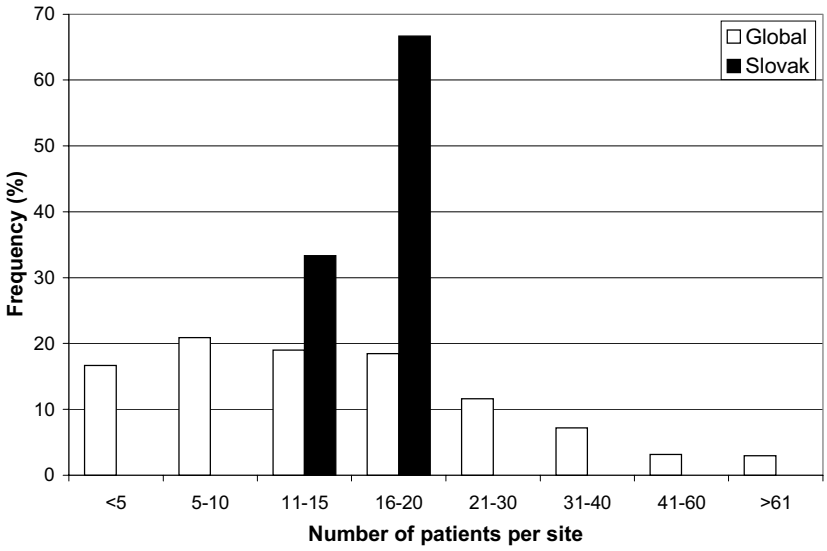

Fig. 2. Distribution of sites by number of patients.

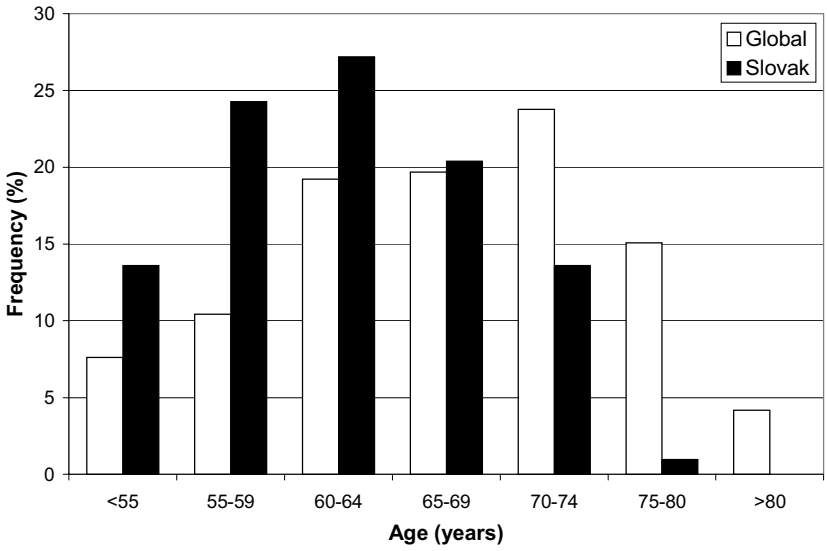

Fig. 3. Distribution of age at baseline.

Statistic tests in respect to the data character and distribution were applied to evaluate the differences between the observed patient groups. The F-test and t-test were used for continuous data (comparison of mean values). In case of statistically significant F-test (calculated from value variance, $p<0.05$), the t-test could not be used to compare two mean values of global and Slovak groups. The chi-square test and binomial test were used to compare the discrete data and percentile values. The data were evaluated at the significance level of $\alpha=0.05$.

Results

Enrollment progress

The enrollment started in September 1997 and finished in December 1999. The original target study population was 14 400 patients. There are 947 participating centers, which have screened 18 119 patients and randomized 15 314 patients in 31 countries. The original target population for Slovakia was 100 randomized patients. Six centers participated in Slovakia (acknowledgement).

Tab. 1. Demographic and clinical characteristics.

Values are (mean, SD) or % of total	Unit	Global						Slovak					
		Men	SD	Women	SD	Total	SD	Men	SD	Women	SD	Total	SD
Demographic characteristics													
gender	%	57.6		42.4		100		40.8		59.2		100	
race													
caucasian	%	89.3		88.9		89.1		100.0		98.4		99.0	
black	%	3.7		5.2		4.3		0.0		0.0		0.0	
oriental	%	4.0		2.8		3.5		0.0		0.0		0.0	
other	%	3.0		3.1		3.1		0.0		1.6		1.0	
age	years	65.7	8.1	69.4	7.6	67.2	8.1	61.1	6.5	62.5	6.2	61.9	6.3
weight	kg	84.9	15.0	73.4	14.8	80.0	15.9	83.5	9.2	79.9	12.3	81.3	11.2
body mass index	kg/m2	28.5	4.5	28.8	5.6	28.6	5.0	27.9	3.0	30.9	4.4	29.7	4.2
Cardiovascular characteristics													
previously treated for hypertension	%	92.2		92.6		92.3		100.0		98.4		99.0	
systolic blood pressure sitting	mmHg	153.0	18.9	156.9	18.9	154.7	19.0	150.6	17.6	154.6	14.9	153.0	16.1
diastolic blood pressure sitting	mmHg	87.8	10.7	87.1	10.9	87.5	10.8	88.4	8.4	88.8	7.8	88.7	8.0
heart rate	beats/min	71.4	10.9	73.7	10.3	72.4	10.7	70.4	9.5	69.4	7.1	69.8	8.2
Risk factors													
Total cholesterol >6,2 mmol/l	%	23.9		45.2		33.0		38.1		39.3		38.8	
Diabetes mellitus	%	29.8		34.2		31.7		26.2		26.2		26.2	
Current smoking	%	26.7		20.3		24.0		23.8		27.9		26.2	
Proteinuria	%	22.1		23.2		22.5		16.7		36.1		28.2	
LVH incl. LBBB	%	9.2		16.3		12.2		11.9		18.0		15.5	
Serum creatinine >150 umol/l	%	4.7		2.1		3.6		0.0		0.0		0.0	
Disease factors													
Coronary heart disease	%	53.5		35.4		45.8		69.0		83.6		77.7	
Stroke or TIA	%	21.1		17.9		19.8		19.0		14.8		16.5	
Peripheal arterial disease	%	15.5		11.6		13.9		16.7		3.3		8.7	
LVH with strain pattern	%	6.2		6.0		6.1		7.1		4.9		5.8	
Blood examinations													
serum GOT	U/l	22.9	8.0	21.6	8.1	22.3	8.1	22.7	6.9	22.3	6.8	22.5	6.9
serum GPT	U/l	25.0	12.4	21.0	11.1	23.3	12.0	27.4	15.6	21.1	7.5	23.7	11.9
serum creatinine	umol/l	108.1	23.2	91.5	21.2	101.1	23.8	111.4	16.0	87.5	12.2	97.3	18.2
serum potassium	mmol/l	4.4	0.4	4.4	0.5	4.4	0.5	4.6	0.4	4.5	0.4	4.5	0.4
serum sodium	mmol/l	140.6	2.6	140.7	2.7	140.7	2.7	142.1	2.4	141.9	2.2	142.0	2.3
serum uric acid	umol/l	393.0	93.0	347.0	92.0	373.0	95.0	398.3	76.3	334.0	84.6	360.5	86.9
serum total cholesterol	mmol/l	5.4	1.1	6.0	1.2	5.7	1.2	5.7	1.0	6.0	1.2	5.9	1.1
serum glucose	mmol/l	6.8	2.7	6.9	2.9	6.9	2.8	6.7	2.4	6.7	2.3	6.7	2.4
hemoglobin	g/l	145.7	12.0	134.0	11.0	140.8	13.0	147.2	11.0	131.6	11.0	138.0	13.0

111 patients were screened and 103 patients were randomized between June 1998 and December 1999. The recruitment rate in Slovakia was initially slower, however gradually increased over the global rate (Fig. 1). Generally, study sites were enrolling from 1 to 100 patients per site. In Slovakia, there were sites including patients in higher numbers: 66 % of sites included 16 to 20 patients and 33 % of sites included 11 to 15 patients (Fig. 2).

Demographic characteristics of patients at baseline

The demographic and clinical characteristics are presented in Table 1.

The difference was quoted in gender proportion: The Slovak group had fewer men (40.8 %) than the global group (57.6 %). The difference was statistically significant (p=0.001). The global ethnic distribution included 89.1 % patients of Caucasian race and 4.3 % patients of Black race. The Slovak group includes more patients of Caucasian race (99.0 %, p=0.001) and none of Black race (0 %, p=0.038).

The values of minimum, maximum, mean, median, standard deviation (SD) and frequency tables were available for the analysis of age. The global mean age was 67.2 years while in the Slovak group it was 61.9 years. The statistically significant difference was quoted in age class distribution between the global group and Slovak group (p<0.001) (Fig. 3). The global group had a mean body mass index 28.6 kg/m^2 and the Slovak group has 29.7 kg/m^2.

The values of minimum, maximum, mean, median and SD were available for the analysis of weight and BMI. The F-test was statistically significant, therefore we could not analyze these values for the moment.

Cardiovascular characteristics

Statistically significantly more Slovak patients (99.0 %) were treated for hypertension for at least 3 months at the time of study entry, than in the global group (92.3 %, p=0.009). The sitting systolic and sitting diastolic blood pressures were similar at the time of randomization in both groups (p=0.211 for sitting systolic blood pressure difference and p=0.125 for sitting diastolic blood pressure difference (Fig. 4, 5). Even if groups were subdivided by boundary values 140/90 mmHg, no differences were found. (The variables of systolic blood pressure and diastolic blood pressure were similar in both groups.)

There was no difference between groups in heart rate (p=0.068) (Fig. 6). With cutt-off according to a heart rate 70 beats/min, a greater part of patients below this value were found in Slovak group (58.2 %) than in global group (44.2 %, p=0.004).

Characteristics of cardiovascular related risk factors and diseases

The prevalence of coronary heart disease was 45.8 %, high cholesterol 33.0 %, type two diabetes mellitus 31.7 % and smokers 24.0 % in global group. The prevalence of high total cholesterol, diabetes mellitus, current smoking, proteinuria and LVH were similar in both groups. We noted a statistically significant difference in the prevalence of serum creatinine >150 μmol/l: the glo-

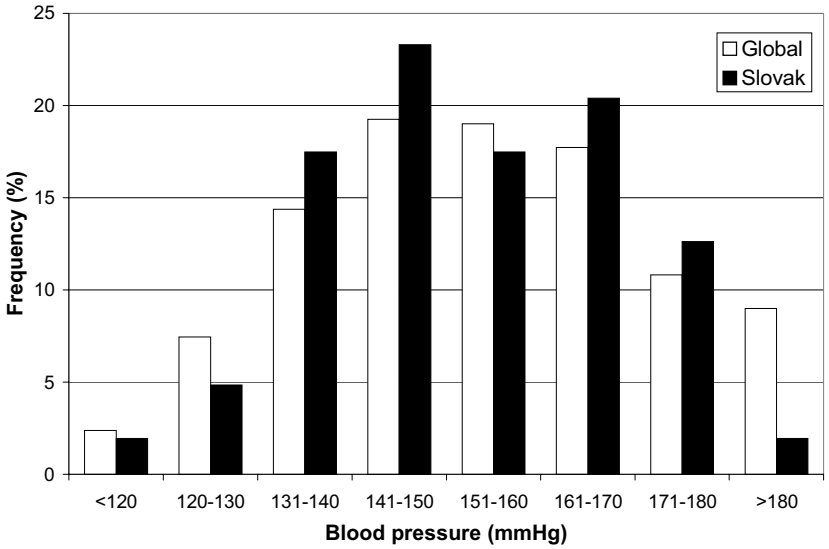

Fig. 4. Distribution of sitting systolic blood pressure at baseline.

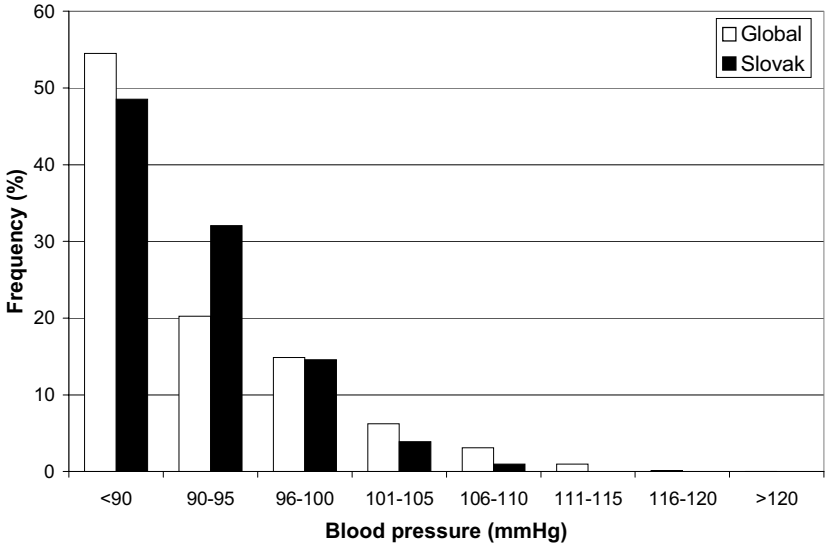

Fig. 5. Distribution of sitting diastolic blood pressure at baseline.

bal group included 3.6 % and Slovak group had none (p=0.0499). Coronary heart disease was more prevalent in the Slovak group (77.7 %) than in the global group (45.8 %, p<0.001). There were no differences in stroke or TIA, peripheral arterial occlusive disease and LVH with strain pattern.

Blood examinations

The values of minimum, maximum, mean, median and SD were available for the analysis of blood factors. There was no difference in values for serum GPT, total cholesterol and glucose. The mean value of hemoglobin was significantly lower in the Slovak group (138.0 g/l) compared to the global one (140.8 g/l, p=0.03).

The values for SGOT, creatinine, potassium, sodium and uric acid showed statistically significant results by F-test, therefore we could not analyze them further.

Discussion

Valsartan is an orally active, highly selective angiotensin II antagonist. The Valsartan Antihypertensive Long-term Use Evalu-

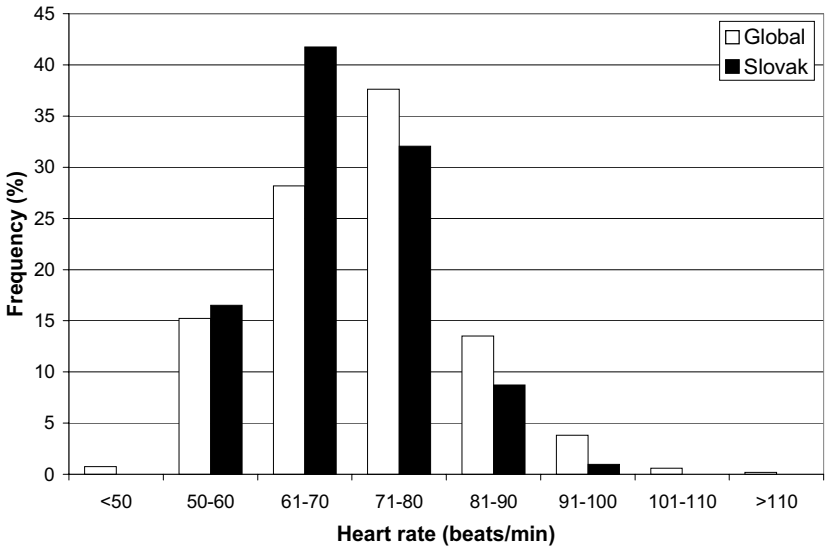

Fig. 6. Distribution of heart rate at baseline.

ation (VALUE) is a double blind, randomized multinational, multicenter, prospective, parallel group study. The primary objective of VALUE trial is to compare the effects of valsartan with those of calcium blocker amlodipine on the reduction of cardiac morbidity and mortality in patients aged 50 years of age or older with essential hypertension and a high risk of cardiovascular events (i.e. one or more a priori defined risk factor or a predisposing condition and a disease). A total of 15 314 patients from 31 countries were randomized. In Slovakia 103 patients were randomized. The population is being treated until at least 1450 patients experience primary endpoint, unless interim analysis is statistically significant.

The demographic and cardiovascular parameters were measured. The presence of risk factors and disease factors was determined. The blood factors were examined as well. Statistic analysis was made with F-test, t-test, chi-square test and binomial test.

This article aims to describe the baseline characteristics of a cohort of patients enrolled in Slovakia and compared them with those characteristics of patients enrolled globally. Sites in Slovakia enrolled a higher number of patients per site than global sites. The Slovak group had fewer men, more patients of Caucasian race and none of Black race. A difference in age distribution was noted. A higher proportion of patients treated for hypertension for at least 3 months at the time of study entry was found in the Slovak group. However, the mean values of sitting systolic and sitting diastolic blood pressures at baseline were similar in both groups. A greater part of patients with heart rate below 70 beats/min was found in the Slovak group.

The value of serum creatinine >150 μmol/l did not occur in the Slovak group. Coronary heart disease was more prevalent in the Slovak group and the mean value of hemoglobin was lower in the Slovak group.

The above baseline characteristics of 103 patients enrolled in VALUE trial in Slovakia indicated that the target population of patients with essential hypertension and a high risk of cardiovascular events was achieved. The results will provide important data on the impact of antihypertensive therapy on cardiac morbidity and mortality in this population.

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