

Blood pressure categories and mortality during a thirty-six-year follow-up

Research Article

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Abstract: Background. The aim of this study was to assess the mortality rate and risk of death in relation to the blood pressure (BP) categories during 36 years of follow-up period. Methods. 265 healthy middle-aged participants were included in the follow up for 36 years; 136 deaths occurred during this time. Causes of death (myocardial infarction (MI), stroke and other causes) were obtained from the death certificates. Participants were divided into four groups according to their blood pressure measurements (normal blood pressure, prehypertension, stage I and stage II hypertension). Hazard ratios (HR) for mortality from all investigated causes of death were calculated using measurements of normal BP as a reference. Kaplan-Meier method was used to calculate probability of survival for each BP category. Results. Participants with prehypertension and stage I hypertension have shared similar all-cause mortality rates (15 deaths per 1000 person-years), and MI mortality rates (7 per 1000 person-years). Participants with stage II hypertension had the highest risk of all-cause mortality (HR 2.78, 95% confidence interval 1.16 to 6.66). Conclusion. Prehypertension and stage I hypertension induced similar rates of mortality due to myocardial infarction or all-causes. The survival probabilities were lower for participants with hypertension and prehypertension in comparison with those who had normal blood pressure. Participants with stage II hypertension had the highest mortality rates and the lowest probability of survival during a 36-year follow-up period.

Keywords: Prehypertension • Hypertension • Myocardial infarction • Mortality • Survival • Follow-up studies

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1. Introduction

Cardiovascular diseases (CVDs) represent a serious public health problem in Serbia. The prevalence of all cardiovascular diseases in Serbia in 2009 was 269.6 per 1000 population, and a mortality rate for cardiovascular disease was 777.9 per 100.000 population (829.9 per 100.000 for women and 723.0 per 100.000 for men) [1]. The rising trend in the incidence of cardiovascular diseases has been reported in the past 30 years [2]. Arterial hypertension is one of the most fre-

quent cardiovascular diseases in Serbia, with a prevalence of 46.5% in 2006 [2,3].

The Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) defined several blood pressure (BP) categories, including prehypertension [4]. Despite its high prevalence worldwide, ranging from 14.5% in Turkey [5] to 31% in the United States [6], prehypertension does not have a status of a disease. Prehypertension and hypertension are associated with the traditional cardiovascular risk factors, such as obe-

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sity, smoking, diabetes and dyslipidemia [7-9], as well endothelial cell dysfunction [10], increased sympathetic activity [11], and systemic inflammation [12]. Furthermore, prehypertension and hypertension require similar modifications of lifestyle in order to prevent unfavorable cardiovascular events [7,13]. Patients in both BP categories are encouraged to reduce the intake of saturated fats [14] and salt [15], consume fruit and vegetables [16] and low-fat dairy products [17], give up smoking [18], and drink alcohol moderately [19]. Finally, both prehypertension and hypertension share similar adverse outcomes, including increased risk of cardiovascular mortality [6-9].

There is very limited data linking hypertension and prehypertension with cardiovascular and overall mortality in Serbia. We decided to undertake a prospective study on mortality and survival of persons with different categories of blood pressure from a small cohort. The aim of this study was to assess the mortality rate and the risk of death in relation to the blood pressure categories during a 36-year follow-up period.

2. Materials and methods

2.1 Sample

The study was designed as a 36-year prospective follow-up of healthy middle-aged participants. The study began in 1974 at the Institute for Chronic Diseases and Gerontology, Center for Hypertension in Belgrade (Serbia), by selecting 500 subjects, aged 30 to 60 years from both genders [20,21]. Originally this study was part of a large research on essential hypertension conducted by Serbia, Israel and the USA [22]. The goal of the study in 1974 was to assess the prevalence of hypertension in Serbian population. Therefore, the selection of participants was random by age, gender, ethnicity and socio-economic status in Serbia. The only exclusion criterion was the presence of chronic diseases. All 500 eligible participants were residing in a central municipality of Belgrade. Upon detailed clinical examination, 114 subjects were excluded from the study due to presence of chronic diseases (diabetes mellitus, angina pectoris, and kidney diseases; n=96), or refusal to participate (n=18). During the follow-up period, 121 patients have dropped out of 386 subjects enrolled. Some of them wanted to quit the study (n=100), whereas others have changed their contact addresses (n=21). The remaining 265 healthy middle-aged participants were enrolled in the final study, 136 men and 129 women.

During the follow-up period, total of 136 persons have died. Causes of death (all causes, myocardial infarction, stroke and other causes) were obtained from

the official death certificates. 'Other causes' of death included cancer and accidents. The scheme of the study is presented in Figure 1. Thirty-six years later (in 2010) the investigation was repeated in the Multidisciplinary center for Polyclinic Diagnostics, Assessment and Treatment of Blood Pressure Disorders, at the Clinic for Cardiology, Clinical Center of Serbia in Belgrade. Written informed consent was obtained from all participants in this study. Ethical Committee of the Clinical Center of Serbia, Belgrade, has approved this study protocol in 2010.

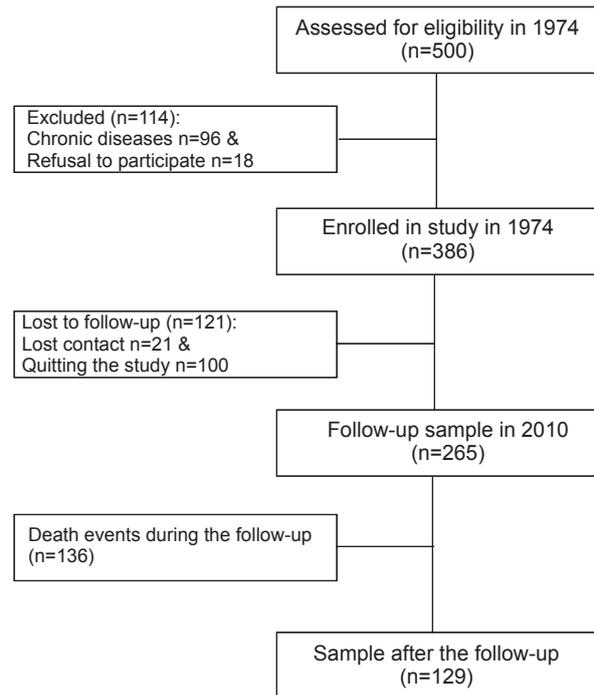


Figure 1. Scheme of the thirty-six years' follow-up study.

2.2 Outcome measures

All participants filled in a self-administered questionnaire concerning general characteristics, family history of hypertension and various health-related issues, including drinking and smoking habits. Subjects reported if they had never smoked or were former or current smokers; the latter two groups were united for further analysis.

Participants were asked to describe their intake of alcoholic drinks, separately for each beverage type (beer, wine and spirits). The choices were hardly ever or never, monthly, weekly, or daily. One standard drink is one bottled beer (350 ml), one glass of wine (150 ml), or one portion (40 ml) of distilled spirits. Each of these drinks contains approximately 10-12 grams of alcohol [23]. According to guidelines from the National Institute on Alcohol Abuse and Alcoholism, moderate drinking is defined as no more than one drink a day for women (not pregnant), and no more than two drinks a day for men [23]. The participants were classified into three groups, ac-

according to the total daily intake of alcohol: rarely or never drinking (less than 1 beverage a day), moderate drinking (one to two drinks a day) and heavy drinking (more than two drinks a day).

Anthropometric parameters were obtained in the morning. Body weight and height was measured with underwear and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Blood pressure was measured in the morning, at the end of physician's examination, with participant in the lying position. Mercury sphygmomanometer was used for all measurements, and the average of three consecutive readings was recorded (mmHg). Blood pressure values obtained at the beginning of the study (in 1974) were categorized according to the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure [4]. Four categories of blood pressure were established. Normal blood pressure was defined as systolic blood pressure (SBP) below 120 mmHg, and diastolic blood pressure (DBP) below 80 mmHg. Prehypertension was defined as SBP below 139 mmHg and DBP below 89 mmHg. Hypertension stage I was defined as SBP between 140 and 159 mmHg, or DBP between 90 and 99 mmHg; and hypertension stage II as SBP exceeding 160 mmHg, or DBP exceeding 100 mmHg.

2.3 Statistical analysis

Descriptive statistics were presented as mean values \pm standard deviation (SD) for the numeric variables, or as percentages (relative numbers) for the categorical variables. Group comparisons were performed using parametric one-way analysis of variance (ANOVA), or Chi square test. Cox's regression analysis was performed in order to calculate crude and adjusted hazard ratios (HR) for mortality from all causes and from

specific causes (myocardial infarction, stroke and other causes) in relation to the categories of hypertension. Normal blood pressure was used as a referent category. Models were adjusted for gender, age, body mass index, smoking status, and alcohol consumption. Kaplan-Meier method was used for survival analysis. Statistical analyses were performed using SPSS software v15.0 for Windows (SPSS Inc. 1989-2006).

3. Results

At the beginning of the study (in 1974), 9% of participants had normal BP, 40.8% had prehypertension, 24.5% had hypertension stage I and 25.7% had hypertension stage II. Baseline characteristics of the study population are summarized in Table 1. Participants had similar age and gender, body mass index, smoking habits, alcohol consumption and family history of hypertension.

Table 2 summarizes general characteristics of the enrolled participants after a 36-year follow-up period (in 2010). Out of 265 patients from the beginning, 129 patients were re-examined in 2010. After the follow-up period, 14% of the study population had normal BP, 45.0% had prehypertension, 27.0% had hypertension stage I and 14% had hypertension stage II. All groups were comparable by age, gender, smoking habits, and alcohol consumption. Participants from all groups had their body mass index changed to a similar extent. Normotensive persons had the greatest increase in systolic pressure, whereas persons with baseline hypertension had the lowest increase in systolic pressure during the follow-up.

The majority of participants changed their blood pressure category during the study (data not shown). In 2010, only nine patients had normal blood pressure (7% of the baseline sample); 23 (17.8%) had prehy-

Table 1. General characteristics of study population (N=265) at the beginning of the study (in 1974) according to blood pressure categories.

Characteristics in 1974	Normal blood pressure	Prehypertension	Hypertension stage I	Hypertension stage II	p value
Number of participants (%)	24 (9.0)	108 (40.8)	65 (24.5)	68 (25.7)	
Age (years)	40.46 \pm 5.12	43.27 \pm 7.55	44.17 \pm 7.04	44.63 \pm 6.78	0.078 ^a
Men (%)	8 (33.3)	51 (47.2)	38 (58.5)	39 (57.4)	0.104 ^b
Body mass index (kg/m ²)	26.49 \pm 2.50	26.90 \pm 3.17	26.95 \pm 3.12	27.44 \pm 3.21	0.549 ^a
Smoking habits (%)					0.269 ^b
Never	11 (45.8)	47 (43.5)	21 (32.3)	33 (48.5)	
Current / former	13 (54.2)	61 (56.5)	44 (67.7)	35 (51.5)	
Rarely /never	12 (50.0)	54 (50.0)	26 (40.0)	30 (44.1)	
Alcohol drinking (%)					0.210 ^b
Moderate	7 (29.2)	25 (23.1)	16 (24.6)	10 (14.7)	
Heavy	5 (20.8)	29 (26.9)	23 (35.4)	28 (41.2)	
Family history of hypertension (%)	14 (58.3)	56 (51.9)	32 (49.2)	47 (69.1)	0.080 ^b

^a One-way ANOVA; ^b Chi square test

Table 2. General characteristics of study population (N=129) after a 36-year follow-up (in 2010) according to blood pressure categories, with changes in body mass index and blood pressure values.

Characteristics in 1974	Normal blood pressure	Prehypertension	Hypertension stage I	Hypertension stage II	p value
Number of participants (%)	18 (14.0)	58 (45.0)	35 (27.0)	18 (14.0)	
Age (years)	76.72±5.05	76.36±7.83	77.09±6.76	74.44±6.60	0.629 ^a
Men (%)	7 (38.9)	25 (43.1)	19 (54.3)	8 (44.4)	0.672 ^b
Smoking habits (%)	Never	11 (61.1)	33 (56.9)	14 (77.8)	0.400 ^b
	Current / former	7 (38.9)	25 (43.1)	4 (22.2)	
	Rarely /never	8 (34.6)	22 (38.6)	5 (27.8)	
Alcohol drinking (%)	Moderate	4 (22.2)	24 (42.1)	11 (31.4)	0.421 ^b
	Heavy	6 (33.3)	11 (19.3)	12 (34.3)	
Change in body mass index (kg/m ²)	1.53±2.29	2.25±2.70	2.09±1.95	1.73±1.95	0.805 ^c
Change in systolic pressure (mmHg)	41.39±18.28	30.39±24.21	17.14±24.83	2.89±19.99	<0.001 ^c
Change in diastolic pressure (mmHg)	11.78±11.85	5.51±18.17	3.23±15.39	10.39±22.52	<0.001 ^c

^a One-way ANOVA; ^b Chi square test; ^c Kruskal Wallis one-way ANOVA

hypertension; 39 (30.2%) had stage I hypertension; and 58 (45.0% of the baseline sample) had stage II hypertension. Amongst persons with prehypertension, 12 (20.7%) remained in the same category; 16 (27.6%) changed to stage I hypertension; 24 (41.4%) changed to stage II hypertension; and six patients (10.3%) changed to normal BP category after the follow-up.

During the follow-up period, total of 136 deaths occurred (51.3% of the baseline sample); 59 deaths were attributable to myocardial infarction, 32 to stroke, and 45 to other causes (data not shown). Fifty deaths occurred among persons with stage II hypertension (73.5% of the original group); thirty deaths among persons with stage I hypertension (46.2% of the original group); fifty deaths among persons with prehypertension (46.3%); six deaths occurred among persons with normal blood pressure (25.0% of the original group). All differences in the number of deaths by hypertension group were highly statistically significant.

Mortality rates (per 1000 person-years) for death from all causes, myocardial infarction, stroke and other causes in relation to the blood pressure categories are presented in Table 3. Persons with prehypertension and persons with stage I hypertension had similar mortality rates for all causes of death (15 per 1000 person-years),

Table 3. Mortality rate (per 1000 person-years) for death from all causes, myocardial infarction, stroke and other causes in relation to blood pressure categories.

Causes of death	Normal blood pressure	Prehypertension	Hypertension stage I	Hypertension stage II
All causes	7.18	15.38	15.98	29.38
Myocardial infarction	2.40	6.76	6.92	13.51
Stroke	2.40	4.61	2.13	6.46
Other causes	2.40	4.00	6.92	9.40

and for myocardial infarction (7 per 1000 person-years). Participants with stage II hypertension had the highest mortality rates for death from all causes (almost 30 deaths per 1000 person-years), myocardial infarction (13 per 1000 person-years), other causes (9 per 1000 person-years), and stroke (6 per 1000 person-years).

Crude hazard ratios for all-cause mortality, myocardial infarction, stroke and other causes of death are presented in Table 4. Persons with prehypertension and those with hypertension stage I had higher crude hazard ratios for all-cause mortality than the persons with normal blood pressure, but these hazard ratios were not statistically significant. Persons with hypertension stage II had the highest crude hazard ratios for all-cause mor-

Table 4. Crude hazard ratios (95% confidence intervals)^a for death from all causes, myocardial infarction, stroke and other causes, by blood pressure categories.

Causes of death	Prehypertension	Hypertension stage I	Hypertension stage II
All causes	2.268 (0.972 – 5.290)	2.161 (0.899 – 5.192)	4.677 (2.001 – 10.933) ^b
Myocardial infarction	3.126 (0.735 – 13.297)	2.911 (0.657 – 12.901)	6.539 (1.538 – 27.799) ^b
Stroke	2.190 (0.501 – 9.581)	0.919 (0.168 – 5.021)	3.877 (0.856 – 17.552)
Other causes	1.685 (0.380 – 7.469)	2.721 (0.614 – 12.063)	3.994 (0.915 – 17.435)

^a Normal blood pressure used as reference category; ^b p<0.05

tality or mortality from myocardial infarction. After adjustment for age, gender, body mass index, smoking status, and alcohol consumption, hazard ratios for all-cause mortality remained statistically significant for patients with hypertension stage II (Table 5).

The general survival of patients per four blood pressure categories during a 36-year follow-up period is presented in Figure 2. The overall survival model was statistically significant (Cox regression omnibus test of model coefficients: Chi-square = 26.010, $p < 0.0001$). Persons with stage II hypertension had the lowest probability of survival during the investigated period. Persons with prehypertension and stage I hypertension

shared similar survival probability that was lower than that of persons with normal blood pressure, but higher than that of persons with stage II hypertension.

4. Discussion

This study has shown that persons with stage II hypertension (defined by JNC-7 criteria) had the highest mortality rates from all-causes and from myocardial infarction during a thirty-six year follow-up period, in comparison with persons with the normal blood pressure. Patients with prehypertension and those with hyperten-

Table 5. Adjusted hazard ratios (95% confidence intervals)^{a,b} for death from all causes, myocardial infarction, stroke and other causes, by blood pressure categories.

Causes of death	Prehypertension	Hypertension stage I	Hypertension stage II
All causes	1.570 (0.665 – 3.704)	1.607 (0.662 – 3.897)	2.780 (1.160 – 6.663) ^c
Myocardial infarction	2.150 (0.498 – 9.286)	1.875 (0.416 – 8.451)	3.500 (0.790 – 15.495)
Stroke	1.257 (0.279 – 5.663)	0.782 (0.141 – 4.326)	2.519 (0.545 – 11.639)
Other causes	0.749 (0.208 – 2.693)	1.340 (0.373 – 4.811)	1.530 (0.423 – 5.533)

^a Adjusted for age, gender and body mass index at the beginning of the study

^b Normal blood pressure used as reference category

^c $p < 0.05$

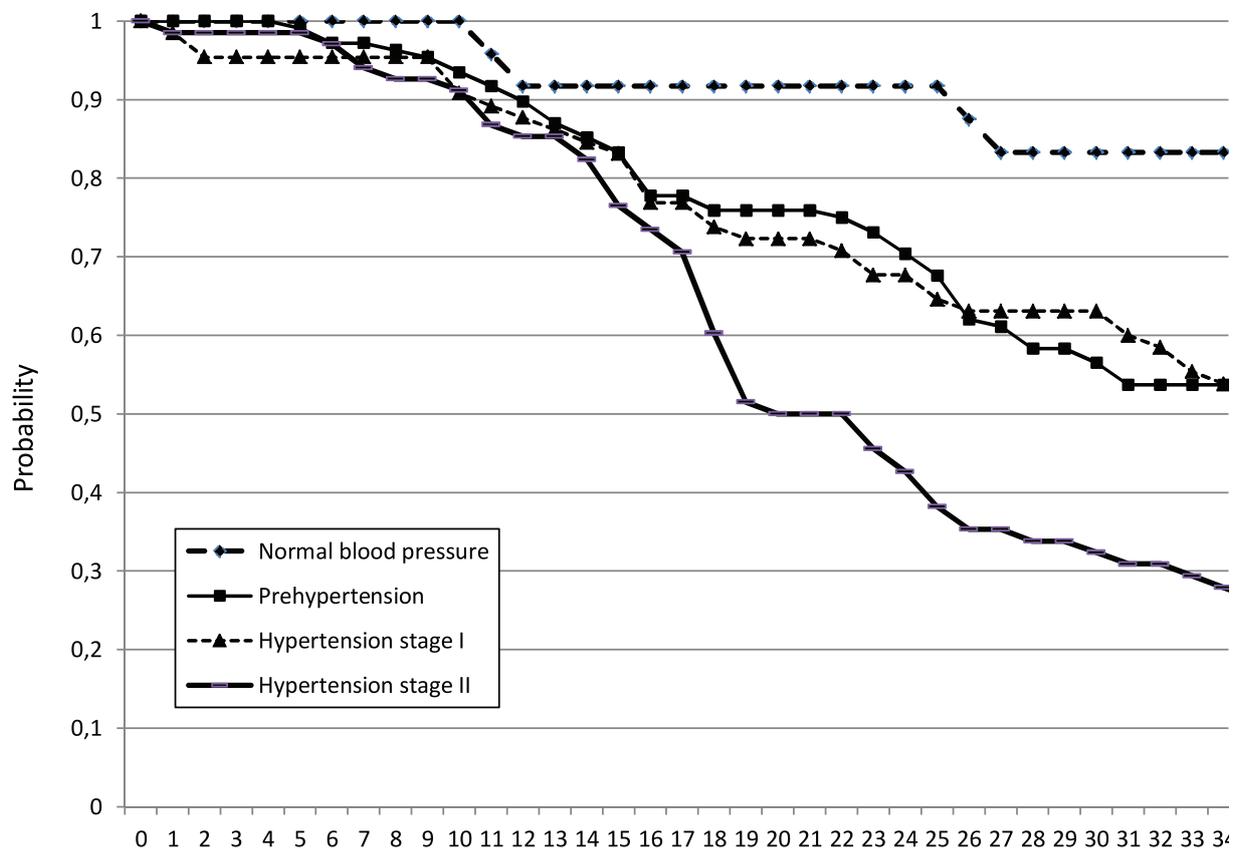


Figure 2. The general survival by blood pressure categories during a 36-year follow-up period.

sion stage I shared similar mortality rates for cardiovascular mortality; this relationship, however, was not statistically significant after adjustment for age, gender, body mass index, smoking or alcohol consumption. The probability of survival during a 36-year period was the lowest for persons with hypertension stage II and somewhat higher for persons with prehypertension and hypertension stage I in comparison with the persons with normal blood pressure.

The presented results are supportive of other studies. During a ten-year follow-up in the Framingham Heart Study, hypertension (SBP \geq 140 mmHg, DBP \geq 90 mmHg) was associated with increased risk of myocardial infarction (adjusted hazard ratio 7.4), all strokes (HR 7.1), and coronary artery disease (HR 3.2), adjusted for several risk factors including smoking, obesity, and hypercholesterolemia [9]. Furthermore, prehypertension was associated with increased risk of myocardial infarction (HR 3.5), and coronary artery disease (HR 1.7), but not with stroke [9]. In another nationally representative cohort, persons with hypertension (SBP \geq 140 mmHg, DBP \geq 90 mmHg) were at highest risk of all-cause mortality (adjusted HR 1.36) and cardiovascular disease mortality (adjusted HR 1.92), after control for several traditional risk factors [8]. At the same time, persons with prehypertension were at higher risk of all-cause mortality (unadjusted hazard ratio 1.27), and cardiovascular mortality (unadjusted hazard ratio 1.66), but this risk was no longer significant when other risk factors were taken into account [8]. These two studies, however, failed to separate the stages of hypertension. Such an approach would have enabled a better comparison with the presented study.

Other studies demonstrated that subjects with prehypertension, compared with the individuals with normal blood pressure, were at higher risk of developing cardiovascular diseases (HR 1.45) [24], myocardial infarction (HR 1.93) [25], and stroke (HR 1.36). In the Women's Health Initiative study, an eight-year follow-up of postmenopausal women, women with prehypertension had an increased risk of cardiovascular death (HR 1.76) [25]. In the Framingham Study, persons with prehypertension had significantly higher risk of developing hypertension over time, compared with the subjects with normal blood pressure [9,26].

To our knowledge, this is the first survey of survival of patients with prehypertension and hypertension during a follow-up period of 36 years in Serbia. A similar survival pattern was observed over a period of 154 months (almost 13 years) in the USA. Persons with hypertension had the lowest probability of survival during the investigated period, whereas persons with prehypertension had a lower probability over persons with

the normal blood pressure [8]. This finding is significant given the fact that all blood pressure categories shared similar baseline characteristics. At the beginning of the study, groups were comparable by age, gender distribution, body mass index, smoking, alcohol consumption, and family history of hypertension. During the follow-up period, participants changed their body weight and lifestyle habits (smoking, alcohol consumption) to a similar extent. Frequent weight changes (more than three weight variations for 10% of body weight) and more intense weight variations (weight gain or weight loss over 10 kg) during a ten-year period were significant predictors for the coronary heart disease, independent of age, gender, body mass index and blood pressure [27].

The differences between presented studies may be explained by nutrition, ethical, cultural and social factors [28]. In addition, the discrepancies may also reflect the volunteer bias in the study population. At the beginning of the study, healthy individuals who agreed to take part might have differed from those who refused, primarily regarding some psychological traits, educational level, socio-economic status, and presence of chronic diseases. These factors could have influenced participants' eating habits, smoking and alcohol consumption behavior, and quality of life. Therefore, obtained results must be interpreted carefully, since the study sample may not be representative of the whole population.

Another important finding of this study was the similarity between the mortality rates and the survival probability of persons with prehypertension and persons with stage I hypertension. To authors' knowledge, this is the first study showing similar mortality rates for prehypertension and hypertension stage I. In similar follow-up studies, hypertension was analyzed as a single variable, and hypertension stages were not defined [5,6,8,24].

The presented research implies a need to modify the attitudes toward addressing prehypertension. Persons with prehypertension believe to be healthy, and are rarely motivated to change their lifestyle habits or to treat their blood pressure. At the same time, health practitioners consider patients with prehypertension as healthy (unlike persons with hypertension), and are not stimulating them to involve in medical treatment. We propose that prehypertension should be considered a disease, rather than a state between health and disease. In which case, both physicians and persons with prehypertension would be more concerned about improvement of patient's health and treatment of prehypertension.

The limitations of this study comprise a small sample size and a considerable loss of participants during the follow-up. However, to authors' knowledge, this is the longest follow-up study in any population. Secondly, we failed to assess dietary habits, but accomplished to con-

sider smoking habits and alcohol consumption. Thirdly, we did not control for participants' physical activity level. Fourthly, we did not control for the number of variations of body weight during investigated period; although we were able to control for body-weight change. Lastly, total cholesterol, triglyceride, fasting glucose and insulin levels were not controlled for, and glucose-loading tests were not routinely performed at the beginning of the study. Patients with history of diabetes (confirmed by endocrinologist) were excluded from the study. This population had a relatively low cardiovascular risk profile at the beginning of the study, potentially limiting the generalizability of the present findings to a broader population. At last, we did not control for medication history, i.e. antihypertensive drugs, adherence to medication, and changes of treatment over time. Control for all these confounding factors would have strengthened the above-described statistical conclusions; yet their function remains to be examined in future studies.

Here presented study highlights the need to raise the awareness of the general public and health professionals with regard to prehypertension. Individuals with prehypertension, as well as those with hypertension, should be informed about the seriousness of their condi-

tion, advised to change their lifestyle, and be prescribed with blood pressure-lowering medications. These actions would reduce the risk of further adverse cardiovascular complications. In addition, health policy initiatives and guidelines must be introduced to emphasize the extent of this problem in Serbian population.

5. Conclusion

This study showed that stage II hypertension was associated with the highest mortality rates and the lowest probability of survival during the 36-year follow-up period. Prehypertension and stage I hypertension shared similar mortality rates of all-cause and MI mortality. The probability of survival at every time point was lower for persons with hypertension or prehypertension in comparison with persons with normal blood pressure.

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