Cardiovascular drug use and differences in the incidence of cardiovascular mortality in elderly Serbian men

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Abstract
Objective: To assess whether the difference in risk of cardiovascular mortality between urban and rural areas of Serbia could be explained by differences in the use of cardiovascular medication.
Methods: The Serbian cohorts of the Seven Countries Study, Velika Krsna (VK), Zrenjanin (ZR) and Belgrade (BG), were enrolled in 1962-1964 and were followed up for 25 years. The survivors of these cohorts were re-examined in 1987, 1988 and 1989, respectively. This second examination of elderly men aged 65 to 84 years included a questionnaire about current use of cardiovascular medication, risk factors and diseases and a physical examination. All subjects were followed until death or the predefined censor date (10 years after baseline). The Cox proportional hazards model was used to calculate the risk of cardiovascular mortality in the rural cohorts compared to the urban cohort and to adjust for confounding.
Main outcome measure: Cardiovascular death.
Results: A total of 227 men from VK, 184 men from ZR and 287 men from BG were followed for a mean duration of 7.4 years and was complete for all subjects. After exclusion of 13 subjects with missing medication data, the incidences of cardiovascular mortality in VK, ZR, and BG were 60, 74, and 26 per 1000 person-years, respectively. The prevalence of cardiovascular medication use was 38% in VK, 52% in ZR, and 59% in BG. The greatest difference in use of specific medication was observed for betablockers (0% in VK and ZR, 13% in BG). After adjustment for cardiovascular risk factors, diseases and age, the relative risks (RRs) of cardiovascular mortality were 2.12 [95% CI: 1.44–3.12], and 2.27 [95% CI: 1.56–3.30] in VK, and ZR compared to BG. Additional adjustment for the use of cardiovascular medication increased these RRs to 2.40 [95% CI: 1.61–3.60] and 2.55 [95% CI: 1.72–3.78], respectively.
Conclusion: The variation in cardiovascular medication use could not explain the excess risk of mortality in the rural Serbian cohorts compared to urban Belgrade.

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Introduction

Cardiovascular diseases are the major cause of death in industrialized countries[1].

In central Serbia and Vojvodina, a northern province of Serbia, the contribution of cardiovascular deaths to deaths from all causes in men is greater than 50%[2]. Several cardiovascular drugs have been demonstrated to be effective in reducing cardiovascular deaths and morbidity. For instance, the benefits of antihypertensive drug therapy and lipid-lowering drug therapy have been clearly established in elderly subjects[3,4]. However, medical consumption by the elderly seems to depend on the place of residence. The urban elderly for example, pay more visits to the general practitioner and use more cardiovascular drugs than the rural elderly[5].

A longitudinal study on middle-aged men of the Serbian cohorts of the Seven Countries Study was initiated in the period 1962–1964[2]. The cohorts were inhabitants of the rural village of Velika Krsna, workers in an agro-industrial cooperative from Zrenjanin, and university professors from Belgrade. In this study, the age adjusted 25-year mortality from coronary heart disease appeared to differ between the cohorts and was lowest in Belgrade, intermediate in Velika Krsna and highest in Zrenjanin. Even after adjusting for cardiovascular risk factors, an unknown but significant protective factor was identified for the Belgrade cohort[2]. However, this study did not account for the use of cardiovascular medication. Considering the urban–rural contrast, patterns of drug use are likely to vary between the cohorts. This variation of drug consumption may possibly be a cause of the mortality rate differences. The present study is a continuation of the 25 years follow-up of the Serbian cohorts. This survey collected both medication data and information on classical cardiovascular risk factors. The aim of the present study was to assess whether the difference in risk of cardiovascular mortality between Belgrade, Zrenjanin, and Velika Krsna could be explained by differences in the use of cardiovascular medication.

Method

Setting

The Seven Countries Study is a longitudinal study of cardiovascular risk factors among 16 cohorts of middle-aged men, initiated in 1958[6]. The Serbian cohorts of Velika Krsna, Zrenjanin and Belgrade, were enrolled in the period 1962–1964 and were followed for 25 years. The survivors of these cohorts were re-examined in 1987, 1988 and 1989. This examination formed the baseline of the present study of elderly men aged 65 to 84 years. The study population consisted of 227 men from Velika Krsna, 184 men from Zrenjanin and 287 men from Belgrade. Subjects with missing medication data (n = 13) were excluded from the analyses. Velika Krsna is a rural village located about 70 km south of Belgrade and is inhabited mainly by farmers. The cohort from Zrenjanin represents the social class of workers and consists of former employees of the Agro-industrial Combine 'Servo Mikalj'. Zrenjanin is a town situated about 70 km north-west of Belgrade in the province of Vojvodina. The men from Belgrade were originally working as faculty members of the University of Belgrade and represent the social class of academics.

Baseline examinations and data collection

The elderly participants in the Serbian cohorts were examined at baseline, which took place in the period 1987–1989. The medical examinations were carried out by trained physicians according to the standard protocol of the Seven Countries Study[6]. The examination included questions about current medication use, an MRC (Medical Research Council) questionnaire on cardiovascular and respiratory symptoms, information on demographic and lifestyle factors and a physical examination. All men were asked closed-ended questions about their medication use. At the research centre subjects were asked to mention all the medication they used for cardiovascular diseases.

Diagnoses of angina pectoris, myocardial infarction and claudication were based on a short version of the MRC questionnaire[7,8]. Diagnoses from this questionnaire were categorized into present, possible, absent and unknown. Information on other morbidity was collected by the Rose questionnaire[9], clinical histories or supplementary questions asked by the examining physicians. Physician diagnoses were used to assess stroke, TIA, diabetes, bronchial asthma, emphysema, chronic bronchitis, malignancy and prostatic diseases. Smoking habits were examined using a standardized questionnaire, limited to cigarette smoking[6].

Physical examination included measurement of weight, height, blood pressure, total serum cholesterol, HDL cholesterol and a resting electrocardiogram.

Body weight was measured to the nearest Kilogram and height to the nearest centimeter. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Both diastolic and systolic blood pressure were measured using standard mercury sphygmomanometers with the men in supine position. Diastolic and systolic blood pressure were reported as the mean of two consecutive measurements. Total serum and HDL cholesterol (mmol/l) determinations were carried out in lipid laboratories standardized according to the criteria of the WHO Lipid Reference Laboratory[10].

Definitions

Medication data were coded according to the ATC system[11]. An additional code was created to define use of unspecified antihypertensives. Antihypertensive drugs included low-ceiling diuretics, betablockers, calcium antagonists, ACE inhibitors, and miscellaneous antihypertensives (centrally acting antiadrenergic agents, peripherally acting antiadrenergic agents, and other drugs such as ketanserin). Smoking was defined as currently smoking more than one cigarette a day. Total alcohol consumption was calculated as number of glasses, given the assumption that all alcoholic drinks (beer, spirits and wine) contain about the same amount of alcohol. Education was coded as number of years of education. Cerebrovascular disease (CVA) was defined as a positive clinical diagnosis of stroke or transient ischemic attack. Heart disease was defined as a positive clinical diagnosis of heart failure, myocardial infarction or angina pectoris. Diabetes represents the clinically known cases of diabetes. Hypertension was defined as a diastolic blood pressure > 95 mmHg, systolic blood pressure > 160 mmHg, or use of antihypertensive medication.

Outcomes

Data on deaths and their causes were obtained through official death certificates in the population areas. Death causes were coded by one experienced physician in a standardized way to ICD-9 categories. Cardiovascular mortality was defined as death from a cause belonging to the ICD-9 codes 390–459. A hierarchical order was used in cases where multiple death causes were given. The endpoint of the present study was restricted to the first cause of death only. Considering the advanced age of the subjects and frequent uncertainties about etiology of heart disease, there is a difference in hierarchy between the present coding and the classical Seven Countries Study (SCS) coding[6]. In the present coding, coronary heart disease (ICD-9 codes 410–414) is the only cardiovascular death cause taking precedence over stroke, whereas in the classical coding, cardiac dysrhythmias and heart failure (codes 427–428) also take precedence over stroke.

Statistical analyses

All statistical analyses were carried out using the software package SPSS version 10.0. Two sample *t*-tests were used to compare continuous variables between cohorts. Chi-square tests were used to analyse categorical data. A *P*-value less than 0.05 was considered statistically significant. The Cox proportional hazards model[12] was used to compare the risk of cardiovascular death between cohorts and to calculate adjusted relative risks of cardiovascular death. The Belgrade cohort was used as the reference cohort. Subjects with missing categorical values were kept in analysis by using an indicator method. For missing continuous data, the cohort's mean value was imputed. The Cox model was used to adjust for age, systolic blood pressure, present smoking, heart disease, cerebrovascular disease, diabetes, total and HDL cholesterol and BMI.

Finally, cardiovascular medication variables were included to assess their influence on relative risks of cardiovascular deaths.

A second analysis assessed the risk associated with specific antihypertensive drugs. This analysis was restricted to hypertensive subjects only in order to reduce confounding by indication[13]. The purpose of this analysis was to assess whether use of antihypertensive drugs did reduce the risk of cardiovascular death in this population.

Results

Great differences in baseline characteristics were observed between the cohorts (Table 1). The men from Belgrade and Zrenjanin had a higher BMI, higher total cholesterol levels, more frequently had diabetes, angina pectoris and a history of myocardial infarction, compared to the men from Velika Krsna. The men from Velika Krsna and Zrenjanin smoked more often, had higher blood pressure, and suffered more often from claudication and heart failure. Educational level was completely different between the faculty members from Belgrade and the participants of the rural cohorts.

Great differences were also observed in cardiovascular medication use. At baseline, the men from Belgrade used more cardiovascular medication than the men from the two other cohorts (Figure 1; $P < 0.05$). Cardiovascular medication use was least frequent in the cohort from the rural village of Velika Krsna. The same trend was observed for antihypertensive medication. The use of betablockers was only reported in the baseline examination of the Belgrade cohort. Relative frequencies of subjects using ACE inhibitors, low ceiling diuretics and calcium channel blockers were also highest for the Belgrade cohort.

Only the group of miscellaneous antihypertensives appeared to be slightly more common among subjects from Velika Krsna and Zrenjanin, although the difference was not statistically significant. This group contained centrally acting antiadrenergic agents, the combination of rauwolfia alkaloids and diuretics, and alpha-adrenoceptor antagonists. Vasodilator use was similar in Belgrade and Zrenjanin but clearly lower in Velika Krsna. The use of cardiac therapy was highest in Belgrade, intermediate in Zrenjanin and lowest in Velika Krsna. In Velika Krsna, 15.3% of the subjects could not recall the name or type of their anti-hypertensive medication. In Zrenjanin this occurred in 7.7% of the subjects whereas in Belgrade this was only 1.4%.

The mean duration of follow-up was 7.4 years and was complete for all subjects.

The crude incidence rates of cardiovascular death in Zrenjanin, Velika Krsna and Belgrade were 74.5, 60.4 and 25.5 per 1000 person-years, respectively.

The subjects from Velika Krsna had a two-fold higher risk of cardiovascular death (RR, 2.32: 95% CI = 1.68–3.21) compared to the subjects from the reference cohort Belgrade (Table 2). The relative risk of cardiovascular death was highest in the Zrenjanin cohort (RR, 2.91: 95% CI = 2.09–4.04). After adjusting for traditional cardiovascular risk factors, the relative risks of cardiovascular death in Velika Krsna and Zrenjanin compared to Belgrade dropped to 2.12 and 2.27, respectively.

Finally, the use of antihypertensives and cardiac therapy were included in the model. The use of betablockers, ACE inhibitors, and unknown anti-hypertensives could not be included as separate variables in the model, because these drugs were not used in all cohorts. Therefore, we had to create one comprehensive variable that indicated whether subjects used antihy-

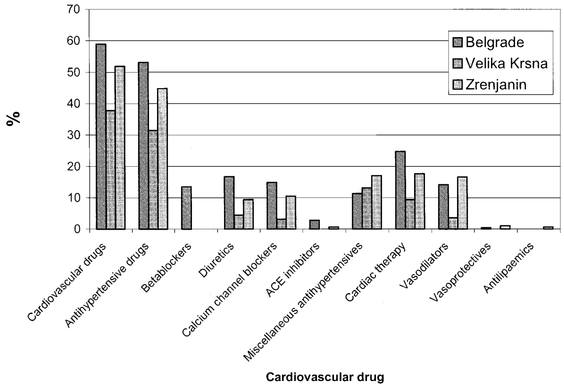

Figure 1 *Cardiovascular medication use at baseline (1987–1989) in Serbian men aged 65 to 84 years. Cardiovascular drugs includes all cardiovascular drugs. Antihypertensive drugs includes betablockers, low ceiling diuretics, calcium channel blockers, ACE inhibtors, vasodilators, miscellaneous anti-hypertensives, and unknown anti-hypertensives.*

Table 1 ***Characteristics of the 3 Serbian cohorts of men aged 65 to 84 at baseline***

	Belgrade		*Velika Krsna*		*Zrenjanin*	
	N[a]		N[a]		N[a]	
Number		282		222		181
Age, years	282	71.3ǂ#	222	72.3	181	72
Years of education	279		179		179	
0–12		0%		100%		100%
13–17		0%		0%		0%
18		100%ǂ#		0%		0%
Mycardial infarction, %	281	8.2ǂ	186	1.6#	176	6.8
Angina pectoris, %	281	10.3ǂ	187	3.7#	176	11.9
Claudication, %	279	5.0ǂ#	187	16.0#	178	30.3
Heart failure, %	280	2.5ǂ	222	6.3	177	5.6
Diabetes, %	279	11.1ǂ	222	0.9#	176	8.5
Currently smoking, %	278	11.9ǂ#	194	33.0	175	25.1
Never smoking, %	278	53.2ǂ#	194	35.6	175	36.6
Alcohol use, glasses/week	279	7.3ǂ	0	–	179	10.5
Blood pressure, mmHg	280	86.1#	219	88.0#	181	93.1
Diastolic		149.9ǂ#		154.2#		168.6
Systolic						
BMI, kg/m^2	259	26.1ǂ	196	23.3#	155	26.6
Total serum cholesterol, mmol/l	194	6.34ǂ	163	5.41#	147	6.29
HDL, mmol/l	193	1.26#	144	1.31	145	1.37

Data are given as means unless otherwise indicated.
[a] Number of subjects with measurements.
ǂ $P < 0.05$ *versus* Velika Krsna; # $P < 0.05$ *versus* Zrenjanin.

pertensive drugs or not. The use of vasoprotectives, serum lipid lowering agents, high ceiling diuretics and potassium sparing agents was too infrequent to be included the model. The inclusion of the cardiovascular medication variables resulted in increased adjusted relative risks of cardiovascular death in Velika Krsna (RR: 2.33, 95% CI: 1.57–3.45) and Zrenjanin (RR: 2.46, 95% CI: 1.68–3.60) compared to Belgrade (Table 3).

In a second analysis we compared users of specific antihypertensive drugs with untreated hypertensive subjects. The adjusted relative risks of cardiovascular death were 0.97 (95% CI: 0.53–1.77) for calcium channel blockers, 1.26 (95% CI: 0.71–2.22) for vasodilators, 0.71 (95% CI: 0.42–1.20) for miscellaneous antihypertensives, 1.81 (95% CI: 0.84–3.94) for low ceiling diuretics and 1.43 (95% CI: 0.81–2.51) for combinations of anti-hypertensives. The use of ACE inhibitors was too infrequent, whereas the risk associated with the use of betablockers could only be assessed in Belgrade. The relative risk of cardiovascular death associated with the use of betablockers was 0.53 (95% CI: 0.21–1.36) in Belgrade.

The adjusted relative risk of cardiovascular death among antihypertensive users (n = 284) was 0.91 (95% CI: 0.64–1.30) compared with the untreated hypertensives (n = 125).

Discussion

Cardiovascular mortality rates were substantially different between the cohorts. Highest death rates were observed in Zrenjanin (74.5/1000 person-years), intermediate death rates in Velika Krsna (60.4/1000 person-years), and lowest death rates in Belgrade (25.5/1000 person-years). The great differences in cardiovascular drug use between the cohorts did not explain the observed differences in cardiovascular mortality.

Several studies have examined patterns of medication[14–16] or cardiovascular mortality differences[17,18] among the elderly, but few studies have assessed associations between drug use patterns and cardiovascular mortality.

A possible causal factor for the observed differences in cardiovascular survival between the cohorts may be the great differences in socioeconomic status. Socioeconomic status was found to be a strong and consistent predictor of cardiovascular mortality in a large number of studies[19–22], and this effect seems to persist after retirement[23].

There is substantial evidence that socioeconomic status is inversely associated with cardiovascular risk factors, particularly hypertension[24]. This is in agreement with the present study as the average blood pressure values were higher in the cohorts of Velika Krsna and Zrenjanin than in the cohort of Belgrade. However, cardiovascular risk factors could only explain a small part of the difference in risk of cardiovascular death between the Serbian cohorts. In other studies, confounding by risk factors only partly explained the association between socioeconomic status and cardiovascular mortality[23,24]. Therefore, socio-economic status is likely to have an independent, additional effect on cardiovascular mortality.

The mechanism through which socioeconomic status affects cardiovascular mortality is not certain, but psychosocial factors and economic factors as well as an influence on lifestyle factors, problem-solving abilities and values may play an important role[23,24]. In this study, lifestyle factors were partly considered by including smoking and cholesterol variables. However, these variables only explained a small part of the mortality differences between Belgrade and the two other cohorts.

Another factor that may have caused mortality rate differences is access to medical services. It has been shown that the urban elderly make more use of local health services than the rural elderly[25,26]. In addition, quality of care may have been better in the Belgrade cohort and this may have been a cause of the lower mortality rate in this cohort.

The main strength of the study is the standardized mode of data collection and the prospective design. Due to the extensive monitoring system, no subjects were lost to follow up. Several limitations of this study have to be considered. As the cohorts represented three different social classes, no adjustment could be made for this potential predictor of cardiovascular death. Data on alcohol use was not collected in Velika Krsna and therefore could not be included in the models. Medication variables that could not be included in the model were vasoprotectives, serum lipid lowering agents, high ceiling diuretics and potassium sparing diuretics. However, because of the low prevalence of these medications, their influence is negligible. Medication use was based on self-reports and physician or pharmacy data were not available. It might be possible that underreporting of medication occurred in the rural and instrial cohorts compared to the academic cohort. However, this would have resulted in an underestimation of the effect of differences in medication use on cardiovascular mortality between the cohorts.

Another factor which was not considered in the analysis was adherence to drug instructions. Most studies, however, do not find a clear relationship linking socioeconomic status measurements to poor adherence in hypertensive patients[27]. Therefore, we

Table 2 *Relative risk of cardiovascular death in Velika Krsna and Zrenjanin compared to Belgrade*

	N	*Cardiovascular deaths (no.)*	*Person-years*	*Crude RR*	*95% CI*	*RR adjusted*[a]	*95% CI*	*RR adjusted*[b]	*95% CI*
Belgrade	282	61	2389.8	1.00		1.00		1.00	
Velika Krsna	222	95	1572.2	2.32	1.68–3.21	2.12	1.44–3.12	2.40	1.61–3.60
Zrenjanin	181	85	1140.9	2.91	2.09–4.04	2.27	1.56–3.30	2.55	1.72–3.78

[a] Adjusted for age, systolic blood pressure, present smoking, heart disease, cerebrovascular disease, diabetes, total serum cholesterol, HDL cholesterol and body mass index.
[b] Adjusted for risk factors and medication variables (anti-hypertensives and cardiac therapy).

have no indications that adherence was substantially different between the cohorts. However, poor compliance could diminish the impact of differences in medication use between the cohorts. Another limitation is that all analyses were based on single point measurements (medication use, blood pressure, etc.) and changes over time were not considered.

An important message for health care professionals may be that our findings suggest that the impact of cardiovascular drug therapy on cardiovascular mortality in the population at large may be less important than life style, which is strongly associated with socioeconomic class. Therefore, efforts to improve cardiovascular risk in the population should not only focus on drug therapy, but should also include the promotion of life style modifications.

Conclusion

In conclusion, the variation in cardiovascular medication use could not explain the greater risk of cardiovascular mortality in the rural Serbian areas compared to the urban Belgrade area. Other factors such as socioeconomic class are more important in risk of CVD mortality.

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