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Combined effect of hypertension and alcohol consumption on the risk of death (27-year cohort prospective study)

Aim	To study the effect of arterial hypertension (AH) in combination with frequent alcohol consumption on the formation of risk for cardiovascular death and all-cause death according to results of a 27-year prospective cohort study.
Material and methods	This 27-year prospective cohort study of an unorganized population of the Tomsk city (1546 people aged 20–59 years, including 630 men and 916 women) investigated AH prevalence and alcohol consumption (1988–1991) and analyzed the predictive significance of the effect of AH in combination with frequent alcohol consumption on the formation of risk for all-cause and cardiovascular death. AH was diagnosed at blood pressure ≥140/90 mm Hg. Frequent alcohol users were defined as those who consumed alcohol more than once a week.
Results	The combination of AH and frequent alcohol consumption increased the risk of all-cause death 4.1 times compared to that for persons without these risk factors ($p<0.001$). This was true for all age groups of the total cohort (higher relative risk, RR, was observed for persons aged 20–39 years) and for men (except for the group aged 40–59 years). RR of cardiovascular death was 5.3 ($p<0.001$) for frequent alcohol users with AH. It was established that frequent alcohol consumption additionally increased RR of all-cause death for persons with AH (RR 1.89; $p<0.05$) primarily at the expense of persons aged 20-39 years. Prediction of 27-year survival for frequent alcohol users with AH was 35.3%.
Conclusion	A combination of AH with frequent alcohol consumption considerably increases the risk of all-cause and cardiovascular death. Frequent alcohol consumption significantly impairs the prediction of 27-year survival for persons with AH by additionally (1.9 times) increasing the risk of all-cause death. Binary AH combinations with frequent alcohol consumption exert a more pronounced adverse effect on young men and women.

Keywords	Сердечно-сосудистые заболевания; факторы риска; артериальная гипертензия; алкоголь; смертность; проспективное исследование
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Cardiovascular diseases (CVDs) are a major health care challenge. Every year CVDs cause the death of 17.9 million people (⅓ of all deaths). Risk factors (RFs) contribute largely to the development of cardiovascular pathology. Arterial hypertension (AH) and lifestyle-related RFs are the leading ones [1–3]. Every year, 9.4 million people die for reasons related to elevated blood pressure (BP), while alcohol abuse causes about 3 million deaths [4, 5]. In Russia, AH is the most significant factor contributing to cardiovascular morbidity and mortality [3, 6]. At the same time, alcohol abuse is a powerful prognostic factor for many medical conditions which contribute significantly to cardiovascular and all-cause mortality. However, this unhealthy lifestyle risk factor (RF) is still not classified as conventional and is not included in the prognostic risk models [5, 7, 8].

AH and alcohol abuse are quite common and often go hand in hand in today's world. However, there is little information on their synergistic effect on major adverse events, especially in young adults, since long-term follow-up periods are required to establish the correlation between alcohol use, CVDs, and mortality [7–10]. There are single reports on the combined effect of AH and increased use of alcohol on shaping the risk of death [11]. This, it is certainly interesting to study this issue in a long-term prospective study.

Objective

To study the effects of AH combined with alcohol abuse on the shaping of all-cause and cardiovascular death risk using the 27 -year cohort prospective study findings.

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Material and methods

The study was performed in accordance with the Declaration of Helsinki. The cohort was randomly collected from the resident lists. In 1988-1991, a baseline examination of the cohort was carried out, and the prevalence of AH and alcohol abuse was studied. The study included all individuals who had undergone baseline screening (1,546 people at the age of 20 to 59 years, including 630 males and 916 females).

BP was measured in a sitting position after a 5-minute rest (Korotkov method). AH was established at systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg.

The use of alcohol was studied using a standardized questionnaire and assessed by the frequency of alcohol consumption. Thus, the following groups were identified: Group 1 – no alcohol; Group 2 – drink alcohol once a month or less; Group 3 – drink alcohol once a week and less often, but more than once a month; Group 4 – drink alcohol several times a week (frequent alcohol use) [12].

In 2015, cardiovascular and all-cause mortality was studied in the cohort of interest. The prognostic value of AH, alcohol use, and AH combined with alcohol abuse were analyzed with regard to shaping the risk of all-cause and cardiovascular death. During the 27 years of the follow-up, 330 deaths were identified, of which 142 deaths were caused by CVDs. The fact and cause of death were established according to the Tomsk Regional Civil Registry Office archives. The vital status was determined for 1,501 (97.1%) subjects, while 2.9% were lost for follow-up.

The follow-up period was from 1 month to 27 years. Given that researchers did not intervene with the cohort for a period of 27 years, it can be assumed that all processes occurred naturally in the cohort and were governed by the objective laws of population.

The analysis database was generated in Microsoft Excel 2003. Statistical analysis was carried out using Statistica 6.0 and KRelRisk 1.0. Pearson's chi-square test and Fisher's test were used to process the data. The analysis results are presented in the contingency tables as the absolute and relative values. The differences were considered statistically significant at $p<0.05$.

Results

The 27-year prospective study revealed the pronounced effect of AH on shaping the risk of all-cause (odds ratio (OR) 2.2; $p<0.001$) and cardiovascular death (OR 3.38; $p<0.001$). The identified patterns were observed in all sex and age groups (only except for 40–59-year old males. In this group AH had no significant influence on the risk of cardiovascular death) [10].

Alcohol abuse was shown to have a significant effect on the risk of all-cause death (OR 2.55; $p<0.001$), which is true for both male (OR 1.79; $p<0.05$) and female individuals (OR 3.84; $p<0.01$) [8]. The study of the effects of alcohol on cardiovascular mortality found that alcohol abuse significantly increases the risk of premature death in 20- to 39-year-olds (OR 5.69; $p<0.05$). No adverse effects of alcohol on cardiovascular mortality were found in other sex and age groups.

The combination of AH and alcohol abuse was found to increase the risk of all-cause death 4.1-fold, when compared to individuals with no such RFs ($p<0.001$). The increased OR of all-cause death in the combination of AH and alcohol abuse was observed in all age groups of the total cohort and male individuals (except for 40-59-year-olds whose results were not statistically significant), with higher values of all-cause death OR in the younger age group. Due to the small number of female subjects with the combination of AH and alcohol abuse, it is not certain whether the effect of this RF combination on shaping the risk of all-cause death is significant in females (Table 1).

The combination of AH and alcohol abuse increases 5.32-fold the OR of cardiovascular death ($p<0.001$): 5.83-fold in 20–39-year-olds ($p=0.05$) and 3.10-fold in 40–59-year-olds ($p<0.05$). The gender-specific analysis showed a statistically significant increase in the risk of cardiovascular death only in 20–59-year old males (OR 3.30; $p<0.01$; see Table 1).

It has been established that alcohol abuse further increases OR of all-cause death (OR 1.89; $p<0.05$), mainly in the younger age group (OR 2.23; $p<0.05$). The gender-specific analysis did not reveal an additional risk of all-cause death associated with alcohol abuse in AH patients, which may be due to a small number of observations. There was also no significant additional OR of cardiovascular death due to alcohol abuse in AH patients (Table 2).

The analysis of survival prognosis based on the presence or absence of AH and alcohol abuse, and the combination of AH with alcohol abuse, showed that the 27-year survival prognosis was 78.5% for individuals without AH and alcohol abuse; 65.6% for AH patients without alcohol abuse ($p<0.001$); 66.7% individuals without AH who abuse alcohol ($p<0.001$); the combination of AH and alcohol abuse reduces chances of staying alive after 27 years to 35.3% ($p<0.001$; Figure 1).

Discussion

Most researchers now acknowledge the leading role of AH in shaping the mortality risk [3, 6]. The role of

Table 1. Odds ratio (OR) of all-cause and cardiovascular death in individuals with AH combined with alcohol abuse

Sex	Age, years	AH and alcohol abuse	N	All-cause mortality				Cardiovascular mortality			
				n	%	OR	95% CI	n	%	OR	95% CI
Male	20–39	No	250	43	17.2	1	1.99–6.63	11	4.4	1	0.42–19.42
		Yes	8	5	62.5	3.64**		1	12.5	2.84	
	40–59	No	173	59	34.1	1	1.03–3.26	29	16.8	1	0.86–5.81
		Yes	8	5	62.5	1.83		3	37.5	2.24	
	20–59	No	423	102	24.1	1	1.71–3.93	40	9.5	1	1.51–7.24
		Yes	16	10	62.5	2.59***		5	31.25	3.30**	
Female	20–39	No	450	29	6.4	–	–	4	0.9	–	–
		Yes	0	0	0			0	0		
	40–59	No	230	43	18.7	1	4.09–7.0	17	7.4	–	–
		Yes	1	1	100	5.35*		0	0		
	20–59	No	680	72	10.6	1	7.59–11.75	21	3.1	–	–
		Yes	1	1	100	9.44**		0	0		
Both sexes	20–39	No	700	72	10.3	1	3.40–10.85	15	2.1	1	0.87–39.02
		Yes	8	5	62.5	6.08***		1	12.5	5.83*	
	40–59	No	403	102	25.3	1	1.61–4.31	46	11.4	1	1.18–8.15
		Yes	9	6	66.7	2.63**		3	33.3	3.10*	
	20–59	No	1103	174	15.8	1	2.81–5.98	61	5.5	1	2.45–11.55
		Yes	17	11	64.7	4.10***			29.4	5.32***	

*, p<0.05; **, p<0.01; ***, p<0.001; N – total number of individuals with known risk factor status;
n, number of deceased individuals; CI, confidence interval; AH, arterial hypertension; CVD, cardiovascular disease.

Table 2. Additional risk of all-cause death due to alcohol abuse in AH patients

Sex	Age, years	Frequent AM in AH patients	N	All-cause mortality		OR	95% CI
				n	%		
Both sexes	20–39	No	114	32	28.1	1	1.21–4.11
		Yes	8	5	62.5	2.23*	
	40–59	No	274	101	36.9	1	1.11–2.94
		Yes	9	6	66.7	1.81	
	20–59	No	388	133	34.3	1	1.29–2.75
		Yes	17	11	64.7	1.89*	
Male	20–39	No	55	21	38.2	1	0.87–3.08
		Yes	8	5	62.5	1.64	
	40–59	No	106	50	47.2	1	0.75–2.35
		Yes	8	5	62.5	1.33	
	20–59	No	161	71	44.1	1	0.93–2.15
		Yes	16	10	62.5	1.42	
Female	20–39	No	59	11	18.6	–	–
		Yes	0	0	0		
	40–59	No	168	51	30.4	1	2.62–4.14
		Yes	1	1	100	3.29	
	20–59	No	227	62	27.3	1	2.96–4.53
			1	1	100	3.66	

*, p<0.05; AM, alcohol abuse; AH, arterial hypertension; OR, odds ratio; CI, confidence interval.

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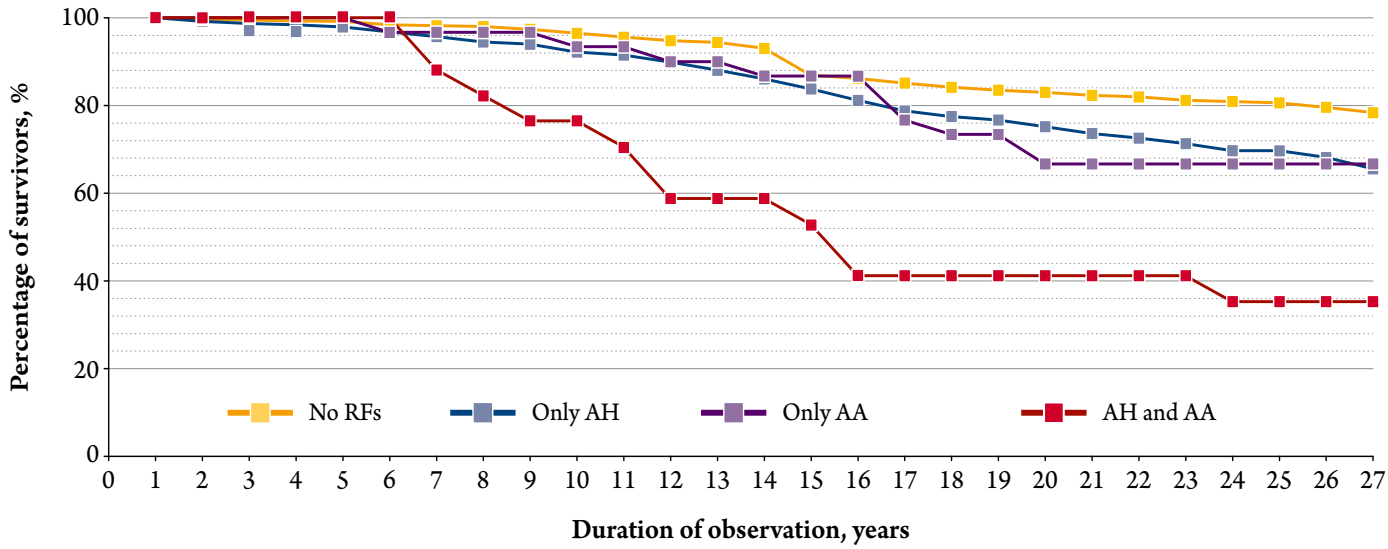
Рисунок 1. Chart pattern of 27-year survival in 20- to 59-year-old male and female individuals depending on the presence or absence of arterial hypertension (AH), alcohol abuse (AM), and combination of AH and AA



RF, risk factors, AH, arterial hyptertension, AA, alcohol abuse.

alcohol abuse in the origin of diseases and the place of this prognostic factor in shaping the mortality rates are being studied. This issue has some difficulties related to the peculiarities of statistical analysis of mortality and complex social and psychological aspects of alcohol abuse. Alcohol abuse is rarely regarded as a main cause of premature mortality, and the fact of alcohol use is not indicated as an etiological factor at diagnosis [13]. Moreover, it has been published that increased alcohol levels are reported in 18.4% of pathological studies. However, most commonly this fact is either not indicated at the final diagnosis or not taken into account in the statistical analysis [14]. Thus, it results in the underestimation of alcohol abuse as one of the most significant prognostic factors of premature death.

Our study is distinctive in that the severity of alcohol abuse was assessed by the frequency of alcohol consumption. This approach was chosen based on the 1980s findings. They showed that the northern type of alcohol use (strong spirits in large single doses) prevails in Russia, and the total consumption of alcohol is directly related to its quantity [12, 15].

The 27-year prospective cohort study showed that AH and alcohol abuse are significant independent prognostic factors of premature death [8, 10]. This is consistent with many large studies which established high OR of cardiovascular and all-cause death in individuals with these RFs [16, 17]. The increased OR of death in the combination of AH with alcohol abuse is also consistent with current knowledge of the combined effect of RFs on morbidity and mortality [7, 9, 18].

In a prospective study of the effects of alcohol abuse independent of the presence of AH, an additional risk associated with alcohol abuse was investigated in patients with AH. It was shown that this RF additionally (1.9-fold) increases the risk of all-cause death in AH patients compared to AH patients who do not consume alcohol often. Moreover, alcohol abuse significantly worsens the survival prognosis, reducing the chances of staying alive after 27 years to 35.3% compared to individuals with only one RF of interest.

There is evidence of the adverse effect of alcohol abuse on the development and course of AH. Several recent studies have shown that increased alcohol use causes higher BP levels and increased prevalence of AH in different populations. Reduced efficacy of antihypertensive therapy and a significant increase in the likelihood of cardiovascular and other complications were observed in individuals who abuse alcohol [18, 19].

Thus, an independent and significant contribution of alcohol to the origin of AH can largely explain the mechanism of increasing the risk of death in AH patients who abuse alcohol.

Moreover, alcohol abusers are reported to have more often long-QT syndrome, which is associated with the risk of sudden cardiac death due to fatal ventricular arrhythmias [20]. At the same time, AH is often combined with increased heart rate. This can contribute to trigger activity and reduces the threshold of ventricular fibrillation onset, thus increasing the risk of sudden death [21]. This demonstrates the synergistic, mutually reinforcing effects of high blood

pressure and alcohol abuse in the origin of fatal rhythm disorders.

The contribution of alcohol abuse and AH to the development of endothelial dysfunction may be a possible mechanism for increasing the risk of cardiovascular complications. It has been shown that high doses of alcohol cause imbalance vasopressor and vasodilator mechanisms: alcohol inhibits the formation and release of nitric oxide, stimulates the release of endothelin-1 and 2, and the formation of angiotensin II [22, 23]. High BP, in turn, determines the formation of structural and functional microcirculatory disturbances in the blood, which damages the endothelium and makes it unable to maintain a balanced synthesis of vasoactive compounds, thus accelerating the development of atherosclerosis [24, 25].

Moreover, alcohol affects the hemostasis system. It is reported that the use of high doses of alcohol causes the activation of platelets, while chronic alcohol abuse, on the one hand, causes chronic liver diseases, which reduces its synthetic function, including the production of anticoagulant factors. On the other hand it can induce systemic inflammatory reactions, and activate the coagulation system, thus increasing the risk of thrombosis [22]. Thus, alcohol abuse, causing endothelium dysfunction and having a procoagulant effect, is a significant pathogenic element of vascular thrombosis, which in combination with AH contributes substantially to the increased risk of cardiovascular death.

It is also important to consider common combinations of behavioral RFs, such as alcohol abuse and smoking [11], which certainly play a key role in shaping the risk of premature death. According to our findings, the percentage of smokers is 72.3% among alcohol abusers and 27.8% among individuals who consume alcohol less frequently.

Alcohol abuse is associated with reduced efficacy of antihypertensive therapy, which may be due to lower compliance in this category of patients and possible direct interaction of ethanol and its metabolites with antihypertensive drugs [18]. Lack of efficacy of antihypertensive therapy or even its absence can contribute significantly to the increased risk of all-cause and cardiovascular death.

Gender-specific studies of the combined effects of AH and alcohol abuse have shown that this combination of RFs has the worst prognostic value in shaping the risk of death in females. In the total cohort the higher rates of cardiovascular death OR than in males are of interest. This situation can be explained by more pronounced adverse effects of alcohol on the female body, which may be partly due to a lower rate of ethanol metabolism and thus higher blood levels of alcohol in females when they consume the same amount of alcohol as males [26].

The contribution of alcohol to shaping the risk of malignancies in female patients compared to males is much higher [27].This to some extent may explain a higher risk of all-cause death in female alcohol abusers.

Moreover, a higher risk of all-cause and cardiovascular death in female AH patients than in males may be caused by more frequent combinations of AH with other metabolic syndrome components (obesity and insulin resistance) in females [10].

Instable sex hormone levels due to alcohol may worsen prognostic indicators in female AH patients [28]. This situation can also be exacerbated by age-related endocrine changes and hormonal fluctuations caused by combined oral contraceptives or hormone replacement therapy.

Thus, the synergism of the RFs of interest with respect to the increased risk of death may result from the adverse effects of alcohol abuse on the course of AH. It may also be a result of the negative influence of alcohol on the development and progression of metabolic syndrome components; the arrhythmogenic, vasopathogenic, and thrombogenic effects of both RFs; the effects on the development of heart failure, lower compliance to antihypertensive therapy among alcohol abusers. There might be other mechanisms of direct interaction between alcohol abuse and AH yet to be studied.

Our findings suggest that healthcare authorities and society as a whole should focus on alcohol abuse, particularly in young patients with AH. Successful implementation of the relevant measures will significantly reduce the risk of premature death and also contribute to longer life expectancy. New data should be considered when designing and planning future preventive programs.

Conclusion

The long-term prospective study has shown that arterial hypertension and alcohol abuse are among the most powerful preventable risk factors for premature death. It has been established that the combination of arterial hypertension and alcohol abuse increases by 4.1-fold the risk of all-cause death and by 5.3-fold the risk of cardiovascular death.

Alcohol abuse has been shown to significantly worsen the prognosis of 27-year survival in patients with arterial hypertension, further increasing by 1.9-fold the risk of all-cause death.

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Пресс-релиз

Переход на новую форму

Уважаемые коллеги!

Компания АО «Сервье» сообщает о завершении с января 2018 г. производства формы лекарственного препарата Предуктал МВ 35 мг и полном переходе на новую форму выпуска – Предуктал ОД 80 мг.

Новая лекарственная форма – Предуктал ОД (МНН триметазидин) – капсулы с пролонгированным высвобождением, дозировка 80 мг, упаковка №30 и №60.

Режим дозирования новой формы Предуктал ОД 80 мг – одна капсула в сутки. Благодаря инновационной технологии при приеме препарата обеспечивается пролонгированное высвобождение триметазидина в ЖКТ с поддержанием его стабильной концентрации в плазме крови в течение 24 часов. Применение новой формы препарата позволит значительно увеличить приверженность пациентов лечению за счет однократного приема, что в свою очередь позволит более эффективно контролировать симптомы стабильной стенокардии.

Фармакокинетическая эквивалентность Предуктала МВ для двукратного приема (35 мг) и новой формы Предуктала ОД 80 мг для однократного приема доказана в сравнительном исследовании, необходимом для регистрации препарата и проведенном согласно европейским требованиям и стандартам.

Предуктал ОД 80 мг сохраняет все свойства Предуктала МВ 35 мг, обеспечивая:

- высокую эффективность по снижению приступов стенокардии;
- улучшение функционального класса ИБС и ХСН;
- уменьшение ремоделирования миокарда и повышение выживаемости больных.

Компания АО «Сервье» направляет максимум своих усилий на удовлетворение потребностей пациентов благодаря вкладу в терапевтический прогресс. Именно это послужило стимулом для создания инновационной, более удобной и эффективной формы выпуска. Использование Предуктала ОД 80 мг позволит повысить приверженность большинства пациентов проводимой терапии на фоне высокой эффективности и переносимости.

Один День Пациента с ИБС

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A more severe negative effect of the binary combination of arterial hypertension and alcohol abuse on younger male and female individuals has been revealed.

No conflict of interest is reported.

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