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The Sudden Cardiac Death Continuum. Message 2

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INTRODUCTION The study of the disease, including sudden cardiac death (SCD), as a consistent pathological process makes it possible to discover its mechanisms of formation, progression, and determine methods of prediction and prevention.

AIM OF THE STUDY To determine the risk of developing SCD in the chain of events of the cardiorenal continuum (CRC) using the example of 7,959 initially healthy workers of locomotive crews of the Trans-Baikal Railway.

MATERIAL AND METHODS Based on the material of a 6-year observation of a natural group of 7,959 men aged 18–66 years, predictors of microalbuminuria (microalbuminuria), creatininemia (creatininemia), reduced glomerular filtration rate (rGFR), retinopathy (retinopathy), and SCD were determined for 22 positions. A 2×2 table and multivariate analysis were used, the relative risk of risk factors (RF) was estimated, and survival analysis was performed, which made it possible to construct a chronic kidney disease (CKD) continuum from the studied prepared symptomatic blocks: microalbuminuria, retinopathy, creatininemia, rGFR using the synthesis method, to which the SCD block was added according to this principle. In the Cox proportional hazard model, the hierarchical significance of predictors of SCD, CKD, and the increase in risk when predictors are added to the SCD continuum were determined.

RESULTS The formation of SCD can occur from a risk factor from any peripheral point of the SCD continuum and depends on the set of risk factors, the proximity of the trigger to the outcome, its independent effect and (or) interaction with other risk factors. The most dangerous predictor of SCD is excessive alcohol consumption (EAC), causing damage to the heart and (or) kidneys, closing the dysfunctional circle of re-entry CRC, forming cardiorenal syndrome and the risk of events in the sequential chain of CRC:
EAC$\rightarrow^{+2677\%}$BCC$^{+9367\%}\leftrightarrow^{+10491\%}$sGFR$^{+6660\%}\leftrightarrow^{+3419\%}$creatininemia$^{+343\%}\leftrightarrow^{+304\%}$retinopathy$^{+793\%}\leftrightarrow^{+1257\%}$microalbuminuria$^{+1486\%}\leftarrow$EAC. All other risk factors for SCD and CKD also worsen the condition and bring SCD closer.

CONCLUSION Further research is needed into the continuum of sudden cardiac death to determine the primary nature of cardiac or renal involvement, the quantitative effects of risk factor damage, their increasing power with prolonged exposure, and the likelihood and timing of sudden cardiac death.

Keywords: alcohol, chronic kidney disease, continuum, sudden cardiac death, predictors, cardiorenal syndrome, risk factors, renocardial syndrome
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AH — arterial hypertension
ASP — atherosclerotic plaque
ATAO — atherosclerosis of the aorta
BMI — body mass index
CI — confidence interval
CHAI — chronic alcohol intoxication
CKD — Chronic Kidney Disease
CRC — cardiorenal continuum
CRS — cardiorenal syndrome
CVD — cardiovascular diseases
DM2 — diabetes mellitus, type 2, mild
EAC — excessive alcohol consumption
ED — endothelial dysfunction
FHCVD - family history of early cardiovascular disease
FR — risk factor
GFR — glomerular filtration rate
HUS — hemolytic uremic syndrome
LCW — locomotive crew workers
LVH — left ventricular myocardial hypertrophy
MCB — microcirculatory bed

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OB I–III — obesity grades I–III
OR — relative risk
RCS — renocardial syndrome
retinopathy I–II — retinopathy I–II degrees
SCD — sudden cardiac death
SF — survival function
sGFR — reduced glomerular filtration rate
TIM — thickening of the intima-media complex
TOD — target organ damage

RELEVANCE

In epidemiology, risk reflects the probability of a negative impact of external and/or internal factors on the incidence of certain population groups and combines the probability and consequences of adverse events [1]. Qualitative and quantitative assessment of the risk of developing a disease (condition) is performed in order to make a prognosis and determine preventive measures aimed at reducing the negative impact of risk factors (RF) and their consequences [2]. Modern concepts of many clinical conditions are built in a sequence of interrelated events (continuum) [3] - continuity representing the holistic nature of an object, homogeneity and interrelation of its individual parts and conditions [4]. The sudden cardiac death (SCD) continuum model, enriched with information on the qualitative and quantitative assessment of the risk of the impact of RF on the probability and consequences of the onset of each successive stage of SCD formation and development, will increase the effectiveness of forecasting and preventive measures aimed at preventing and developing SCD. According to *Chugh S.S.,* the total mortality from SCD cases per year can reach 5 million people [5]. Russian scientists estimate the annual number of losses worldwide from SCD at 3 million people [6], in the Russian Federation — at ¼ million people, which makes this disease one of the most pressing health problems in Russia [7] and worldwide [8]. Therefore, risk stratification of SCD is a major problem [9–11]. Current methods for detecting cardiac dysfunction do not solve it, since they do not have the proper diagnostic level [12, 13]. In a recent review article [10], the authors, having studied scientific publications, did not find universal, suitable models of SCD for all population groups (adults, children, and people involved in active sports). This paper shows such a model of SCD. We aim to provide valuable information on one of the parts of the study of this issue — determining the influence of SCD predictors on the risk of developing this disease.

Objective: to determine the risk of developing dysfunction and pathology of the heart and kidneys in the chain of events of the cardiorenal continuum (CRC) (continuum of the cardiac renal syndrome) using the example of a group of initially healthy workers of locomotive crews of the Trans-Baikal Railway.

MATERIAL AND METHODS

On the Zabaikalsky Railway from 2008 to 2013, 7,959 LCW — men aged 18–66 — were under observation [14–16]. The respondents, in addition to hypertension of stage 1 I or stage II, according to the inclusion criteria [17] did not have cardiovascular diseases (CVD), but had RFs to varying degrees: blood pressure not lower than 140/90, psychosocial stress, overweight or obesity of stage I–III (OI I–III) — body mass index (BMI) respectively = 25.0–29.9 or 30.0–34.9; 35.0–39.9; not less than 40.0, family history of early (FH) CVD, excessive alcohol consumption (EAC) - systematic alcohol consumption of more than 2 standard drinks per day for men with 1 standard drink of alcohol 13.7 g - 18 ml of ethanol, which corresponds to 330 ml of beer (content ≈5 vol.% ethanol) or 150 ml of wine (≈12 vol.% ethanol) or 45 ml of strong drinks (≈40 vol.% ethanol) [18], hyperglycemia, dyslipidemia. The LCW were determined by age, smoking history, left ventricular myocardial hypertrophy (LVMH), aortic atherosclerosis (AA), microalbuminuria, creatininemia, reduced glomerular filtration rate (GFR), retinopathy of grades I–II [17], pulse wave velocity of more than 12 m/s, ankle-brachial index less than 0.9, and mild type 2 diabetes mellitus (DM2). This information is presented in detail in the press [13, 19]. LCW were excluded from observation in the event of dismissal, death, and non-compliance with the health criteria of the order. According to the recommendations of the RMSAH (Russian Medical Society on Arterial Hypertension), ARSSC (All-Russian Scientific Society of Cardiologists) 2008, 2011. [18, 20] with the approval of the Local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education “Chita State Medical Academy” No. 30 dated 09.11.2011 [16] all LCW were examined during medical commissions using generally accepted diagnostic methods in the specified volume. Over 6 years of observation, 15 cases of SCD were identified and studied in the LCW group. To determine the relationship between possible predictors (RF, target organ damage (TOD)) and SCD, two groups of respondents were compared, those with and without SCD. Statistical data

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processing was performed in the *Statistica* v.6.0 (*StatSoft Inc.*, USA), *KrelRisk v.* 1.1 (Russia), *https://www.cog-genomics.org/software/stats software packages*. Quantitative variables were compared using the Mann–Whitney test. For binary variables, a 2×2 table, the χ^2 criterion (with Yates' correction if necessary), and Fisher's exact test were used. Then, a multivariate stepwise regression analysis was performed with the inclusion of variables, and the relative risk (RR) of the established predictors was estimated [21–25]. To determine the triggers that have the most significant and independent effect on the development of SCD, and to clarify the increase in the risk of SCD with the addition of each predictor to the latent pathological process, the Cox proportional hazard regression model was used [26]. To assess the significance of the Cox model, the χ^2 criterion is used, based on a comparison of the logarithms of the likelihood: a model with included predictors (L_1) and a basic model, where all predictors are equal to zero (L_0). If the obtained value of χ^2 is statistically significant, then the null hypothesis about the absence of influence of predictors on survival is rejected and a conclusion is made that independent variables have a significant effect on the time to event [27]. In our study, χ^2 of the models of each outcome (microalbuminuria, retinopathy, creatininemia, sGFR, SCD) was calculated by the iteration procedure after entering into the *Statistica* 6.0 program a set of triggers for each outcome, previously established in the 2 × 2 table, multivariate stepwise regression analysis with the inclusion of variables and assessment of the relative risk. The effectiveness of the constructed models of the outcomes microalbuminuria, rethinopathy, creatininemia, sGFR, SCD were shown in the table χ^2 and *p*. The significance of the triggers estimated in the Cox model was shown by *t, p* and the standard error, which will be explained below [27]. The probability and time of SCD development under the influence of each and every predictor were determined using the Kaplan–Meier curves [27]. Graphical assessment of the dynamics of the influence of predictors on the survival function (SF — probability of SCD absence) and its opposite value, the number of "failures" (probability of SCD), of each trigger as an independent effect and all together allowed us to determine the time of SCD development, its probability, and the stages of endothelial dysfunction (ED) progression. Kaplan–Meier analysis is shown outside the scope of this publication [14, 15, 19, 28–30]. The performed multivariate analysis revealed that SCD was preceded by damage to only one target organ — sGFR [14, 15, 18, 20] (table, fig. 1, 2). In accordance with the data of the multivariate analysis, the SCD module was attached to the chronic kidney disease (CKD) continuum model [13, 31, 32] (SCD ← CKD) using the synthesis method of the "assemble a whole from functional blocks" method. The model had previously been assembled in a similar way from the studied symptomatic blocks of CKD: microalbuminuria, creatininemia, eSCF, and retinopathy [13–15, 19, 22–25, 28–31]. SCD← eSCF↔ creatininemia ↔ retinopathy ↔ microalbuminuria (Fig. 1). The symbol "↔" denoted the interdependent relationship of target organs in the sequence of continuum events.

Based on the data of multivariate analysis, the predictors of CKD, retinopathy, and SCD were classified. The predictors of the outcomes microalbuminuria, retinopathy, creatininemia, sGFR, and SCD that showed a significant result in all statistical models were hypothetically assessed as the main predictors capable of independently implementing these outcomes without the participation of other risk factors. The predictors that had a statistically significant result in 4 models were assessed as interacting risk factors — implementing the final outcome with the participation of other risk factors by adding their damage effect into a joint effect. The predictors that had a statistically significant result in less than 4 models used were assessed as confounders — interfering factors influencing the final outcome and having a relationship with the main influencing variable [13–15, 19, 22–25, 28–31, 33] (see Table, Fig. 1, 2).

The interaction of RFs is manifested by the effect of modification in the overall influence of 2 or more variables. It can enhance the influence of factors on the end point or weaken their influence on it [34]. The following types of interaction of factors are distinguished: additivity - summation of the effect; synergism - mutual reinforcement; antagonism - mutual weakening of influence [35].

In the process of studying the scientific literature, it was concluded that the pathological connection between the heart and kidneys was interdependent, combined the failure of both organs and therefore in the chain of events, CRC was shown as cardiorenal syndrome (CRS) [13–15, 36]. SCD ↔ sGFR ↔ creatininemia ↔ retinopathy ↔ microalbuminuria. Further, the information content of the etiopathogenetic model of CRC [13] was increased by introducing the results established in the Cox proportional hazard model (table, figs. 1–5).

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Table

Results of the application of the Cox proportional hazard regression model for chronic kidney disease, sudden cardiac death [13–15, 19, 28–30]

Triggers (*n* =7959)	ν	*t* -value	*Wald*	*SE*	*p*	RR [±95% CI]	risk, %
Microalbuminuria (χ^2 = 28.38, p < 0.001)							
Excessive alcohol consumption	6	2.02	4.09	1.00	0.04	15.86 [1.98; 127.31]	+1486
Dyslipidemia	6	1.94	3.76	1.08	0.05	14.98 [1.84; 121.72]	+1398
Retinopathy grades I–II	6	1.37	1.88	0.83	0.04	13.57 [3.26; 56.54]	+1257
Family history of early cardiovascular disease	6	1.70	2.68	1.00	0.17	7.78 [1.95; 31.07]	+678
Arterial hypertension	6	0.65	0.43	1.00	0.51	4.86 [1.16; 20.31]	+386
Smoking	6	0,00	0,00	3565394	0.99	–	–
Creatininemia (χ^2 =68.23, p <0.001)							
Decreased glomerular filtration rate	11	5.36	28.34	0.63	<0.001	35.19 [15.48; 79.96]	+3419
Body mass index not less than 40.0	11	2.56	6.28	0.74	0.01	5.80 [1.52; 22.14]	+480
Retinopathy grades I–II	11	4.78	22.86	0.32	<0.001	4.43 [2.74; 7.15]	+343
Body mass index not less than 25.0	11	2.74	4.79	0.23	0.01	2.65 [1.70; 4.11]	+165
Dyslipidemia	11	1.74	3.11	0.20	0.08	2.37 [1.65; 3.40]	+137
27–66 years old	11	1.73	2.99	0.01	0.08	2.21 [1.08; 4.52]	+121
Hyperglycemia	11	0.91	0.88	0.31	0.36	2.13 [1.21; 3.76]	+113
Body mass index 35.0–39.9	11	1.42	1.76	0.41	0.15	2.11 [0.998; 4.50]	+111
Family history of early cardiovascular disease	11	1.25	1.64	0.24	0.21	2.03 [1.30; 3.17]	+103
Body mass index 30.0–34.9	11	2.13	2.87	0.23	0.03	1.94 [1.28; 2.92]	+94
Left ventricular myocardial hypertrophy	11	-0.40	0.13	0.33	0.69	1.83 [1.07; 3.13]	+83
Arterial hypertension	11	-0.99	0.87	0.27	0.32	1.78 [1.23; 2.58]	+78
Reduced glomerular filtration rate (χ^2 = 20.83, p < 0.001)							
Creatininemia	4	4.20	17.65	0.85	<0.001	67.60 [13.79; 331.44]	+6660
Hyperglycemia	4	1.76	3.08	0.93	0.08	8.44 [1.55; 45.97]	+744
Atherosclerosis of the aorta	4	0.55	0.30	1.02	0.58	8.19 [1.50; 44.59]	+719
Arterial hypertension	4	0.99	0.99	0.99	0.32	5.83 [1.07; 31.80]	+483

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Retinopathy grade I–II (χ^2=1080.06, p <0.001)							
Arterial hypertension	15	9.08	82.29	0.51	<0.001	242.63[90.64; 649.43]	+24163
26–66 years old	15	6.89	47.71	0,009	<0.001	73.60 [10.34; 523.62]	+7260
39–66 years old						12.27 [8.25; 18.27]	+1127
Thickening of the intima-media complex/atherosclerotic plaque	15	7.61	57.95	0.28	<0.001	14.33 [10.05; 20.43]	+1333
Left ventricular myocardial hypertrophy	15	4.52	19.89	0.12	<0.001	10.88 [8.94; 13.25]	+988
Microalbuminuria	15	1.31	1.66	0.59	0.19	8.93 [3.63; 21.97]	+793
Diabetes mellitus, type 2, mild	15	4.12	16.96	0.28	<0.001	7.62 [4.87; 11.93]	+662
Creatininemia	15	3.12	9.59	0.25	0.002	4.04 [2.64; 6.18]	+304
Body mass index 35.0–39.9	15	2.08	4.06	0.18	0.03	3.83 [2.76; 5.29]	+283
Family history of early cardiovascular disease	15	4.95	24.20	0.12	<0.001	3.72 [2.99; 4.63]	+272
Atherosclerosis of the aorta	15	-2.94	8.67	0.16	0.003	3.26 [2.49; 4.28]	+226
Body mass index 30.0–34.9	15	0.24	0.37	0.13	0.81	3.25 [2.63; 3.99]	+225
Body mass index not less than 40.0	15	-0.10	0.01	0.59	0.91	2.97 [1.02; 8.60]	+197
Dyslipidemia	15	1.48	2.17	0.11	0.14	2.48 [2.02; 3.06]	+148
Hyperglycemia	15	-1.33	1.80	0.20	0.18	1.59 [1.1; 2.30]	+59
Smoking	15	0.94	0.94	0.11	0.35	0.75 [0.61; 0.93]	–
Sudden cardiac death (χ^2 = 19.46, p = 0.003)							
Decreased glomerular filtration rate	6	2.61	6.87	1.22	0.01	94.67 [14.68; 610.68]	+9367
Excessive alcohol consumption	6	2.00	4.02	0.84	0.04	27.77 [8.01; 96.29]	+2677
Body mass index not less than 40.0	6	1.75	3.09	1.16	0.07	23.63 [3.23; 172.54]	+2263
34–66 years old	6	2.06	4.25	0.03	0.03	8.33 [1.10; 63.36]	+733
Arterial hypertension	6	0.60	0.36	0.66	0.54	5.82 [1.99; 17.03]	+482
Stress	6	0.87	0.76	0.58	0.38	1.93 [0.66; 5.65]	–

	independent risk factor;
	interacting risk factor;
	confounding [31]

Notes: Matching predictors of chronic kidney disease symptoms are shown in blue. CI — confidence interval; RR— relative risk; ν — degrees of freedom; *SE* — standard error of the regression coefficient [26]; *Wald* — Wald test; *t* -value — ratio of parameter estimates to their standard deviations

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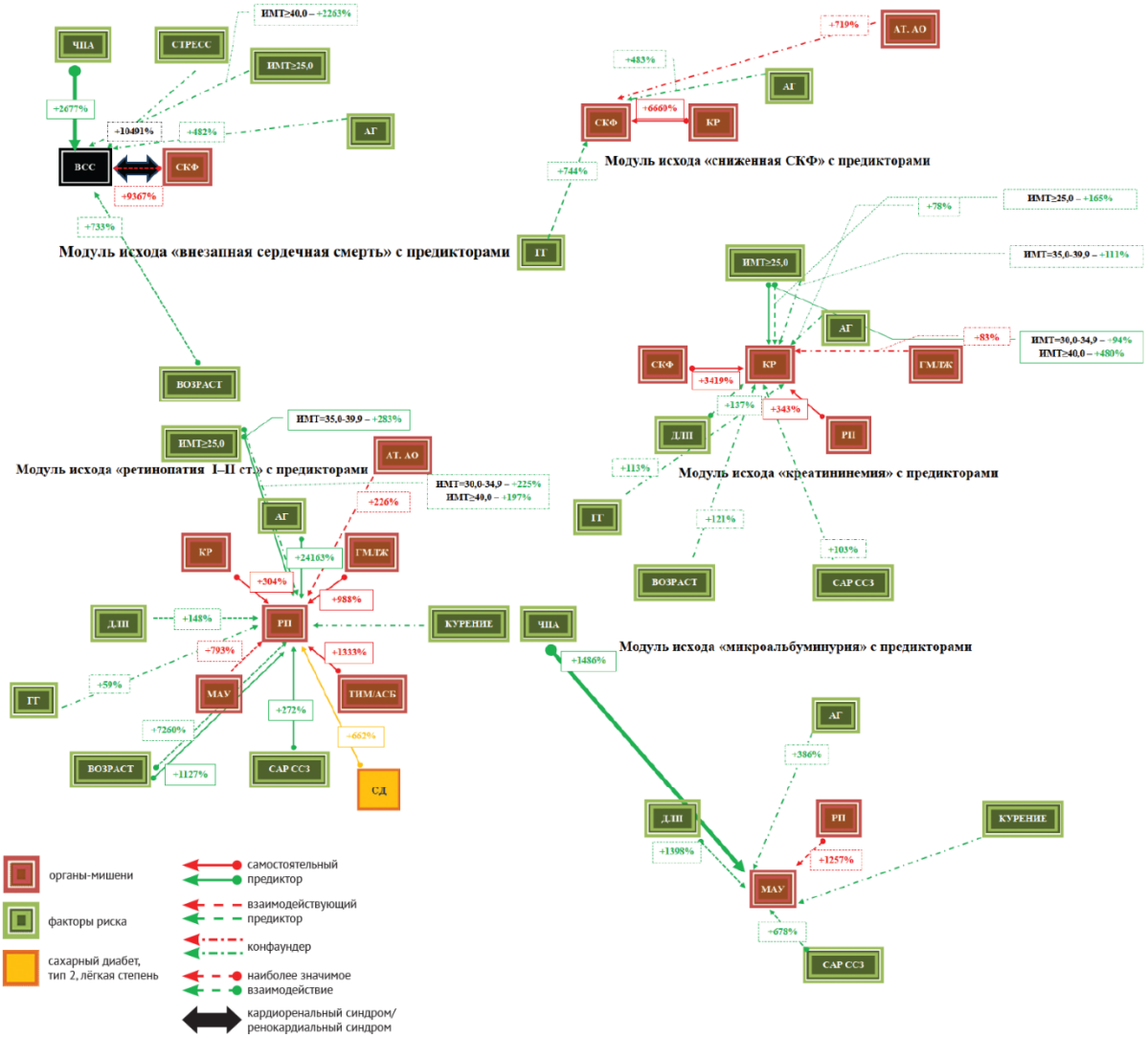

Fig. 1. Synthesis of modules of sudden cardiac death, chronic kidney disease. The influence of factors on the growth of the risk of formation of these outcomes

Notes: AH - arterial hypertension; ASB - atherosclerotic plaque; AT. AO - atherosclerosis of the aorta; SCD - sudden cardiac death; GG - hyperglycemia; LVMH - left ventricular myocardial hypertrophy; BMI - body mass index; FH CVD - family history of early cardiovascular disease; DM - Diabetes mellitus, type 2, mild; GFR - glomerular filtration rate; TIM - intima-media thickening; EAC - excessive alcohol consumption. The arrows show the direction of the predictor effect and its subclinical characteristics: independent effect or predictor/confounder interaction

At first glance, the constructed model (table, Fig. 5) looks quite complicated, which is true. It shows the sequence of CRC events and the risk of their occurrence in the endothelium of the cardiorenal basin vessels during the observation of the LCW population. Its creation required combining the results of a number of articles [19, 22–25, 28–31]. Understanding how the SCD model functions is quite simple if you study it from simple to complex. First, you need to understand how one factor works and that the event RF □ TOD or RF □ OUTCOME is impossible without initiating pathological processes of RF, and their negative impact should be minimized to achieve ED remission. The impact of each RF on the risk of events in the SCD continuum and the quality of RF can be assessed and compared in the table. At the next stage, it is necessary to study the modules of the abstract CRC model, their structure and the behavior of each individual RF in them and in their various combinations, assess the magnitude of the risks they generate and compare it in various CRC blocks, determine which of the triggers poses

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the greatest danger. Find out how the risk of tissue damage to organs will change as the RF is leveled (see Fig. 1–5, table). At this stage of planning a therapeutic and preventive intervention, it is necessary to remember the interacting qualities of the RF, since the elimination of some of the interacting triggers can weaken the influence of others or level them out. It is also necessary to remember the influence of protective factors, which we know little about, but they are probably present in the overall influence of factors (see Fig. 2). At the third stage of the study, begin to master the CRC model itself. In it, it is necessary to understand the sequence of POMs and how the risk changes when they are involved in the pathological processes of the CRC and how these events can be influenced by different RF (see Fig. 1–5). When stratifying the patient's CRC outcomes, it is necessary to determine its location in this model in order to determine its proximity to the outcome of interest, the locations of possible other pathologies and their progression directions in CRC, as well as the risk of subsequent probable events and the treatment and prevention strategy aimed at achieving RF remission during the zero-risk period. These treatment and prevention tactical considerations and manipulations to help them for convenience and to eliminate erroneous actions can be performed in medical documentation on pre-prepared templates.

Fig. 2. Example of the influence of sudden cardiac death factors on the end point, interaction of factors

Note: FR — risk factor

Fig. 3. Renocardial continuum (A) and cardiorenal syndrome (B), dynamics of cardiovascular risk

Notes: SCD - sudden cardiac death; GFR - glomerular filtration rate.The arrows show the direction of the predictor effect and its subclinical characteristics: independent effect or predictor interaction

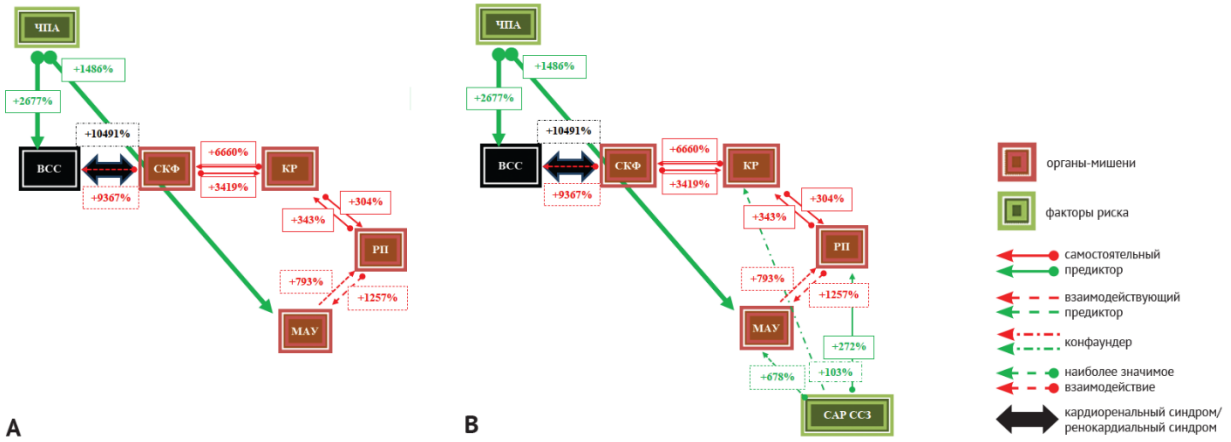

Fig. 4. SCD continuum, sequence of events, risk progression, risk factors for excessive alcohol consumption and family history of early cardiovascular disease

Notes: SCD - sudden cardiac death; FHCVD - family history of early cardiovascular disease; GFR - glomerular filtration rate; EAC - excessive alcohol consumption. The arrows show the direction of the predictor effect and its subclinical characteristics: independent effect or predictor/confounder interaction

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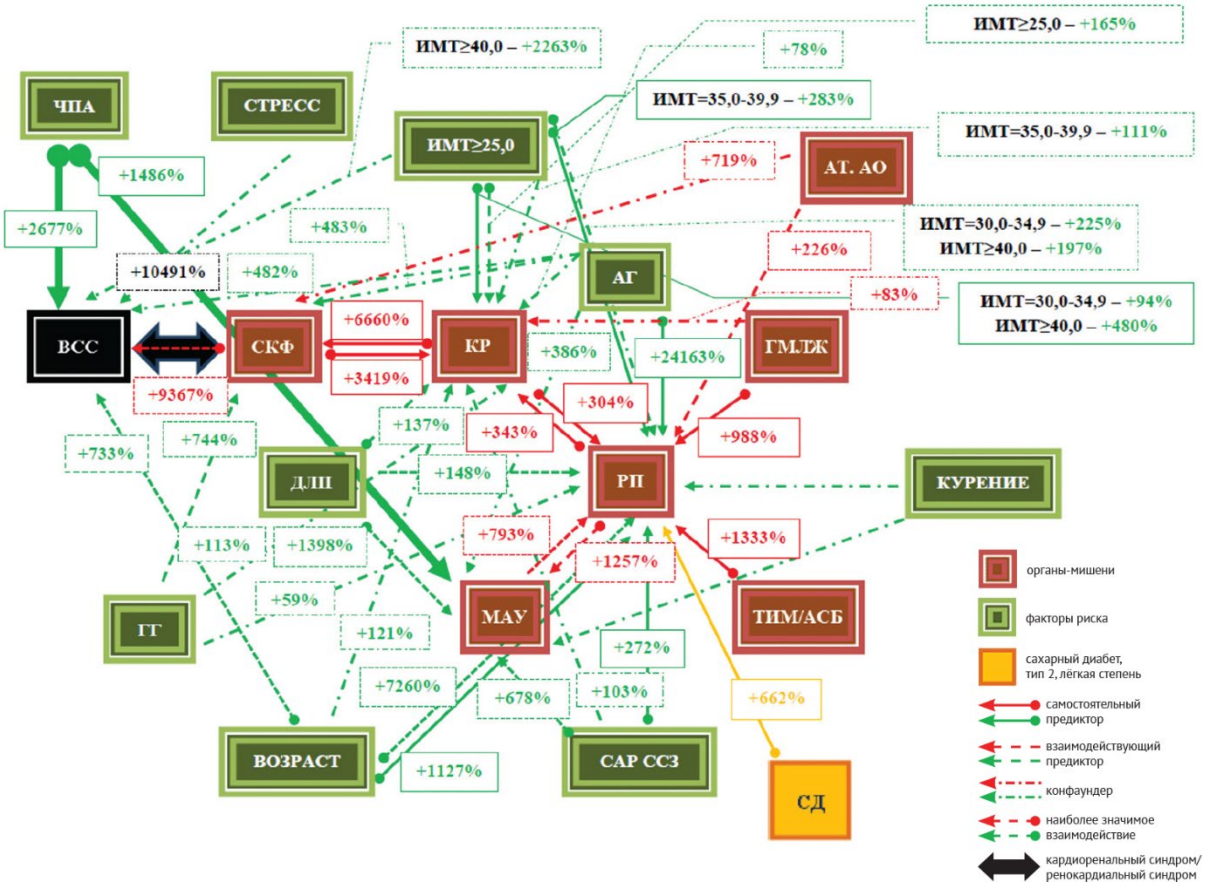

Fig. 5. Dynamics of risk in the sequence of events of the continuum of SCD and CKD, all risk factors

Notes: AH - arterial hypertension; ATAO - atherosclerosis of the aorta; SCD - sudden cardiac death; LVMH - left ventricular myocardial hypertrophy; BMI - body mass index; FH CVD - family history of early cardiovascular disease; DM - Diabetes mellitus, type 2, mild; GFR - glomerular filtration rate; TIM - intima-media thickening; EAC- excessive alcohol consumption. The arrows show the direction of the predictor effect and its subclinical characteristics: independent effect or predictor/confounder interaction

For morphologists and biochemists studying RF at the level of ultrastructural and biochemical transformations occurring in the endothelial cell in different organs of the CRC under the influence of RF, after selecting the CRC point of interest, using the information that comes from it, strategic thinking to help future scientific research can be simulated using other schemes modeling ED and shown in other works [29, 30].

RESULTS

The Cox model has the form: $\lambda_i(t) = \lambda_0(t) \exp\{\beta_1 X_1 + \beta_2 X_2 + ... + \beta_k X_k\}$, where $\lambda_i(t)$ is the risk of subject i at time t, $\lambda_0(t)$ is the baseline risk of the subject, $X_1, ..., X_k$ are the studied risk factors, $\beta_1, ..., \beta_k$ are the coefficients. Let $b_1, ..., b_k$ be the estimates of $\beta_1, ..., \beta_k$ obtained using a type of maximum likelihood. The exponent of these values ($\exp\{b_j\} = e^{b_j}$) is the estimate of the OR or the risk ratio of the outcomes SCD, microalbuminuria, retinopathy, creatininemia, eSCF. For a specific value of RF (X_j), the OR increases or decreases the risk of achieving these outcomes, which is associated with a single increase to (X_j+1), taking into account other RFs. OR greater than 1.0 means an increased risk, less than 1.0 - a decreased risk, at 1.0 there is no risk [21]. Based on this position, we considered the value of 1.0 OR as the base (initial) risk equal to 100%. To determine the specific value of the OR of an increase or decrease in the RF (X_j) of the risk of achieving a specific outcome, the base risk of 1.0 = 100% was subtracted from the obtained result of its OR. The difference of this action was shown in percentages (see table). In the Cox model, the predictors of NPA, sGFR, and age had a significant result in the outcome of SCD. In the outcome of microalbuminuria - NPA.

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In the outcome of creatininemia: sGFR, BMI not less than 25.0, OS I, III, retinopathy. In the outcome of sGFR — only the predictor of CRS. In the outcome of retinopathy I–II: hypertension, age, intima-media thickening/atherosclerotic plaque, left ventricular hypertrophy, type 2 diabetes, CRS, obesity II, cardiovascular disease, AT. AO. The influence of the age factor on the approximation of CRS through the formation of pathology of the microvascular system (retinopathy I–II) was shown separately [37]. The remaining predictors did not withstand the assessment of the ratio of the parameter value to its standard error (*t* -value), and (or) the application of the Wald criterion, since the condition: *t >2.0 with* $\rho < 0.05$ calculated according to the Wald criterion, was not met [27, 38]. The model also contains the Wald criterion for each coefficient and *p* [27]. In the Cox proportional hazards model, the Wald criterion is used to test the assumption of the absence of a relationship between the predictor and the dependent variable, which is equivalent to testing the equality of the regression coefficient to zero. If it is statistically significantly different from zero, this indicates that the independent variable has a significant impact on the predictive power of the model [26]. The data from the table were entered into the CRC model.

DISCUSSION

The development of sciences requires searching for promising directions and improving methodology. Their improvement is ensured by analysis and synthesis of knowledge [39, 40]. Analysis is a method of decomposing an object into parts and properties. Synthesis is a study from simple to complex, a method of connecting disparate things (concepts) into a whole from pre-prepared modules by determining their location and creating a non-existent abstract model for its further study [39]. In complex systems, synthesis is preceded by analysis. Together with analysis, synthesis makes it possible to obtain an idea of the relationships between the components of the subject of study [41]. For this purpose, using the synthesis method, the abstract modules of the SCD and CKD were combined into the CRC — SCD ↔ CKD (see Fig. 1, 3). SCD ↔ sSCF ↔ creatininemia ↔ retinopathy ↔ microalbuminuria. The synthesis of the designated modules of CKD, SCD is shown outside the scope of this publication [13–15, 19, 28–31]. The relationship of the impaired heart, CKD through CRS and (or) renocardial syndrome (RCS), acting in both directions, impart stability to the entire cardiorenal system and close the pathological circle of CRC by the type of *re-entry mechanism* [13, 42, 43]. The earliest kidney damage is manifested by microalbuminuria [44]. Since the RF of the EAC in the LCW of the ZabzhD preceded microalbuminuria and heart damage, was the main independent predictor in these outcomes, SCD could develop in 2 variants of sequential events. Their simultaneous formation is also possible. Each stage of CRC events was accompanied by an increase in risk, which was determined by the ability of the RF to transform function into dysfunction, into pathology and ensure the occurrence of the next CRC event as it progresses to SCD (see Table). Since the possibility of correlation of the total intensity of RF and the severity of RF, which persists in further clinical stages and participates in the formation of manifestations of the initial chronic endothelial injury and the "response to injury" of its later variants, has been established [45, 46] (see Fig. 3–5). The affected target organ turns into RF. Version 1 — primary kidney damage and formation of CRS: EAC $\rightarrow^{+1486\%}$ microalbuminuria $^{+1257\%} \leftrightarrow^{+793\%}$ retinopathy + 304% $\leftrightarrow^{+343\%}$ creatininemia $^{+3419\%} \leftrightarrow^{+6660\%}$ sGFR $\rightarrow^{+9367\%}$ SCD (see Fig. 4 *A*). Alcoholic latent chronic glomerulonephritis is manifested by microalbuminuria, hypertension and microhematuria. Its exacerbations are associated with excesses of EAC, an increase in clinical symptoms and a decrease in SCF [47]. The risk of CVD increases with an increase in microalbuminuria, RF is manifested [23, 29, 44, 48] and the transition to the next stage of development of events of the CKD continuum: microalbuminuria ↔ retinopathy. The changes are interdependent, the microalbuminuria level correlates with the thickness of the choroid and retina of the eye [19, 23, 25, 29, 49]. Their manifestations are considered signs of systemic damage to the microcirculatory bed (MCB) and a pathological process in the kidneys. The GFR of the kidneys and eye are anatomically similar and react in the same way with complications in these organs [50]. The progression of CKD is accompanied by an increase in the level of serum creatininemia, sGFR and pathology of the MCB of the eye [51]. microalbuminuria $^{+1257\%} \leftrightarrow^{+793\%}$ retinopathy $^{+304\%} \leftrightarrow^{+343\%}$ creatininemia $^{+3419\%} \leftrightarrow^{+6660\%}$ sGFR. It is believed that an elevated level of creatininemia in the blood serum forms sGFR through renal hyperfiltration [22, 24]. On the contrary, with sGFR, tubular secretion of creatininemia and an increase in its concentration in the blood are compensatorily enhanced [52, 53]. creatininemia $^{+3419\%} \leftrightarrow^{+6660\%}$ sGFR. RF of FH CVD may precede microalbuminuria (FH CVD $\varepsilon^{678\%}$ microalbuminuria) [23, 29], creatininemia (FH CVD $\varepsilon^{103\%}$ creatininemia), and retinopathy (FH CVD $\varepsilon^{272\%}$ retinopathy) [14, 15, 19, 22, 25, 30] and

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predispose to the development of CKD in patients with a congenital small number of nephrons [54] (see Fig. 4B *)*. This may be the case in individuals with low birth weight [54, 55] or congenital microangiopathy, manifested by an increase in microalbuminuria, creatininemia, and rGFR[56]. This also occurs in premature infants [57] and/or in individuals with a genetic defect of MCB [58].

Hemolytic uremic syndrome (HUS) in children is the main cause of acute kidney injury [59] and can be a cause of SCD. In children with HUS, polymorphism of the genes of the blood coagulation system is detected in 100% of cases: MTHFR C677T, FVLeiden G1691A, PTGG20210A, FGBG(455)A, ITGB3 (glycoprotein IIIa) C176T (L33P), PAI-1 4G(675)5G [60].

Thrombotic microangiopathy is a special type of damage to small intraorgan vessels, mainly renal. Genetic thrombophilia affects the severity of kidney damage, activates blood coagulation inside the glomeruli [61] and progresses thrombotic microangiopathy [60]. Five atypical cases of HUS in newborns have been described, caused by absolute deficiency of vWF protease associated with a hereditary defect of this enzyme [62, 63] and, probably, with the cause of SCD in infants.

In the whole organism, specialized functional systems are closely interconnected. If the result of the activity of one of the functional systems deviates, the activity of other related functional systems of the organism immediately undergoes reorganization. Violation of the hierarchical and multiparametric harmony of information relationships of the functional systems of the organism leads to dysfunctions and then to pathology [64]. Since the LCW ZabZHD initially did not have heart diseases, the 2nd path of SCD formation is possible as acute CRS, manifested by a sudden deterioration in cardiac activity and leading to acute kidney injury, which can occur with acute coronary syndrome [65], caused by latent EAC [14–16, 66]. Or chronic primary kidney damage can lead to a violation of the functional state of the heart [67]. In order to clarify the pathological influence of the impaired heart on the kidney, the SCD $\rightarrow$ sGFR in cattle was re-examined as the final outcome and the SCD (impaired heart) data were included in the set of variables determining this outcome. This variable showed a statistically significant result in multivariate analysis and in the assessment of RF - 105.91 [13.15; 853.22]. The obtained result was shown in the SCD model.

EAC $\rightarrow$ $^{+2677\%}$ SCD $^{+9367\%}$ $\leftrightarrow$ $^{+10491\%}$ eSCF $^{+6660\%}$ $\leftrightarrow$ $^{+3419\%}$ creatininemia $^{+343\%}$ $\leftrightarrow$ $^{+304\%}$ retinopathy $^{+793\%}$ $\leftrightarrow$ $^{+1257\%}$ microalbuminuria $^{+1486\%}$ $\leftarrow$ EAC (see Fig. 1, 3–5). A single consumption of a large dose of alcohol in any form of drink is a statistically significant risk factor for SCD [65]. However, it was found that in patients with alcohol dependence, high concentrations of all proinflammatory cytokines were detected on the 3rd–5th day after alcohol detoxification, of which the most prominent fractions were interferon γ and interleukin-17. The remaining cytokines exceeded the control concentrations 2–6-fold. After 2 weeks of standard anti-alcohol therapy, the concentration of the cytokine profile did not change and remained high [68], which indicates long-term oxidative stress, inflammation, ED, and their persistence in patients regularly using EAC in a dangerous dose [18, 66]. In acute and chronic alcohol intoxication (CAI), ethanol intake initiates the formation of reactive oxygen species, reduces the production of relaxing endothelium-dependent factors, increases the concentration of vasoconstrictor factors and the development of ED [69]. With systematic EAC, ED becomes permanent with all the ensuing consequences, since ED is involved in the pathogenesis and clinical course of all CVD and is associated with the risk of subsequent adverse cardiovascular events [70], including SCD. The RF of SCD, having the quality of "risk" - the ability to disrupt the stability of the norm, transform the function into dysfunction, pathology and ensure movement to the next event of CRC, having its significant quantitative values, closes the pathological circle of CRC, and making it continuous, can lead to dysfunction and failure of initially healthy kidneys and heart. All other RF of SCD and CKD also aggravate the condition and bring the time of SCD closer (see Fig. 5). At the same time, a screening study [71] of the causes and pattern of consumption of alcoholic beverages in professional male athletes showed the presence of significant alcoholization, the absence of absolute abstinence and a preference for consuming strong alcoholic beverages in the amount of 401.7 ± 271.2 ml of absolute ethanol per month. About a third of athletes - EAC, 2-3 times a week and more than 5 standard portions per day. About 93% of athletes-respondents experienced negative consequences of EAC. *BF Grant et al.* consider alcohol to be the most frequently consumed substance in general and among adolescents [72]. In the study *by Marshall et al.*, 79% of US schoolchildren and students (mean age 15.8 years) consumed alcohol at least once in the last 12 months, 57% at least once in the last month [73]. *Martinsen et al.* note that up to 36.5% of elite adolescent athletes in Norway resort to alcohol consumption. In the control group, consisting of adolescents not involved in sports, this figure was

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63% [74]. E.D. Koroleva et al. [75] demonstrated widespread alcohol consumption among elite football players aged 11–21 years with a negative impact on sleep. Respondents consumed alcohol from the age of 17, most often at the age of 19–21 years. These data and the research of the LCW ZabZhD identified risk groups in which the likelihood of favorable consequences from preventive measures aimed at diagnosing CAI and correcting problems associated with EAC and preventing SCD will be especially successful [66, 76]. SCD in athletes evokes a significant public response, since such tragedies occur with apparently healthy people who are the most physically prepared part of the population. Each person instinctively asks the question of what could have prevented this phenomenon [9].

According to A.B. Palchik et al. [77], 20.3% of pregnant women in Russia consume alcohol, 2.7% are heavy drinkers, which can lead to the birth of a child with varying degrees of manifestations of CAI [78, 79]. Therefore, when determining the main cause of SCD at any age, CAI should first of all be excluded by all means, including the study of alcohol-oxidizing enzyme systems in the tissues of the liver, kidneys and myocardium of the anterior wall of the left ventricle [80, 81], since every year many SCDs in people under 35 years of age remain undiagnosed. Autopsy-negative death is recorded at autopsy in the absence of any specific structural changes in the heart [82].

Identification of the timing of the onset of the risk period and the period of time without risk has an important prognostic value. When comparing the time intervals of risk and zero risk, it is possible to significantly advance in personalized and population forecasting and prevention of SCD, CKD and other outcomes, and take correct effective treatment and preventive measures aimed at counteracting RF.

CONCLUSION

Current methods of diagnosing cardiac dysfunction are imperfect, and therefore, in the preventive strategy of sudden cardiac death, the priority should be the diagnosis of a dysfunctional kidney, the time of the risk of its symptoms when identifying risk factors and the time of the absence of risk when they are eliminated. Especially the most dangerous predictor of sudden cardiac death - excessive alcohol consumption. At the same time, each individual should be informed about the safe and dangerous dose of this factor.

In this regard, it is necessary to continue the study of the sudden cardiac death continuum model in order to determine what occurs first - heart or kidney failure, to determine the strength of the effect of damage to triggers, the increase in their power in target organs with prolonged exposure and the addition of each predictor to the sudden cardiac death continuum, as well as the time of onset of reversible and irreversible changes.

1. The development of sudden cardiac death can be determined by the influence of traditional risk factors from any peripheral point of the sudden cardiac death continuum (from risk factors) and the reciprocal recurrent effect of damage emanating from the affected target organs (eyes, heart, large arteries and from the dysfunctional kidney itself), impairing the function of a separate organ or target organs associated with each other. By increasing the risk of events, reciprocal damage of target organs probably occurs through a *re-entry mechanism*. According to statistically significant multivariate regression ($p < 0.05$), comparisons in a 2 × 2 contingency table and risk ratios of factors, the relative risk of cardiac dysfunction increases (94.67-fold). The risk of a decrease in the glomerular filtration rate increases interdependently (105.91-fold). Also, according to statistically significant multivariate regression ($p < 0.05$), comparisons in the 2 × 2 contingency table and risk ratios of factors, the risk of decreased renal filtration function increases (67.60-fold) with an increase in the level of creatininemia, the indicators of which with an increase in risk (35.19-fold) interdependently simultaneously increase with a decrease in the glomerular filtration rate. At the same time, an increase in the level of creatininemia with an increase in risk (4.43-fold) is stimulated by pathology of the microcirculatory bed. At the same time, an elevated creatinine level increases the risk (4.04-fold) of changes in the microcirculatory bed. At the same time, the progression of changes in the microcirculatory bed is stimulated by microalbuminuria, increasing the risk of capillary disorders (8.93-fold), and changes in the microcirculatory bed, increasing the risk (13.57-fold), initiate the appearance of microalbuminuria. The chronic kidney disease continuum is a component of the sudden cardiac death continuum and includes microcirculatory bed damage. According to statistically significant multivariate regression ($p < 0.05$), comparisons in the 2x2 table and risk ratios of factors, with damage to the endothelium of large arteries, aorta, left ventricular hypertrophy, the risk of microcirculatory bed changes increases (14.33, 3.26 and 10.88-fold respectively), and atherogenic changes in the aorta increase (8.19-fold) the risk of decreased renal filtration function.

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2. The development of sudden cardiac death depends on a specific set of trigger factors in each case and is determined by the predictor's proximity to the end point. Its independent effect or interaction with other risk factors or confounding effect. Also, it depends on the possession of the "risk" quality in quantitative measurement - the ability of the trigger to transform function into dysfunction, into pathology and to ensure the occurrence of the next event of the cardiorenal continuum as it moves toward sudden cardiac death. The most dangerous predictor of sudden cardiac death is excessive alcohol consumption. This factor, by disrupting the functional balance of the endothelium, is capable of causing damage to the heart and (or) kidneys, forming a dysfunctional pathological circle of cardiorenal syndrome, making it continuous through a *re-entry mechanism*. According to statistically significant multivariate regression ($p < 0.05$), comparisons in the 2x2 table and the risk ratios of factors, excessive alcohol consumption, increasing the risk of events (27.77-fold), disrupting the heart function, triggers a series of events of the cardiorenal continuum. In primary kidney damage, excessive alcohol consumption disrupts their function by forming a symptom of microalbuminuria, increasing the risk of its occurrence (15.86-fold), and triggers a series of events of the renocardial continuum. All other negative factors, if present in an individual, also progress the pathology of the cardiorenal and (or) renocardial continuum.

3. Within the population, those with the highest risk of sudden cardiac death are those with an initially low nephron count and/or a congenital microcirculatory defect and/or a genetic microcirculatory defect and an initially unfavorable starting position in the cardiorenal continuum. According to statistically significant multivariate regression ($p < 0.05$), comparisons in a 2×2 table and risk ratios of factors, the risk of an initial microcirculatory defect increases (3.72-fold), the occurrence of a creatininemia level above the norm (2.03-fold) and microalbuminuria (7.78-fold). These individuals require lifelong dispensary observation.

4. The interdependence of pathological processes of the cardiovascular system and kidneys in a certain continuous sequence of events of the cardiorenal continuum leads to cardiorenal or renocardial syndrome and sudden cardiac death.

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