MEDICAL UNIVERSITY

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Dissertation work for awarding an educational and scientific degree "DOCTOR" on topic:

STUDY OF CLINICAL ACTIVITY OF RHEUMATOID ARTHRITIS IN PATIENTS, TREATED WITH BIOLOGICAL PRODUCTS

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The Dissertation work contains 189 pages and is illustrated with 33 tables and 62 figures. The bibliography includes 264 literary sources, including 2 in cyrillic and 262 in latin. The study was held at the Clinic of Rheumatology of the University Hospital “St. Marina” Varna, Bulgaria. The dissertation work was discussed and proposed for a defense at the department council of the Department of Propaedeutic of Internal Diseases at Medical University -Prof. Dr P. Stoyanov– Varna.

The defense of the dissertation will take place on .....2019 at ..... o’clock in ..... at an open meeting of the Scientific Jury. The defense materials are available at the library of the Medical University “Prof. Dr. P. Stoyanov” – Varna, Bulgaria.

CONTENTS

SHORT ABBREVIATIONS USED

ACR	American College of Rheumatology
BMI	Body Mass Index
CD	Concomitant diseases
CRP	C-reactive protein
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DAS	Disease Activity Score
ESR	Erythrocyte sedimentation rate
HTN	Hypertension
IHD	Ischemic Heart Disease
RA	Rheumatoid arthritis

I. INTRODUCTION

1. Actuality of the problem

The importance of the population aging is becoming increasingly apparent in industrialized countries, as birthrates are declining in parallel with increasing life expectancy. In an aging population, the number of patients with inflammatory arthritis, including rheumatoid arthritis (RA), is expected to increase proportionately.

RA itself is generally not considered a lethal disease. The mortality rate attributed to the RA as the main cause of death, has declined worldwide.

Patients with RA die earlier (live shorter) the risk of death is significantly higher for them. Trends have been identified to reduce this “excessive” mortality rate over the past 1-2 years, but a sustained, significant reduction in mortality rates for these diseases has not yet been proven.

What is the impact of modern rheumatology on the ultimate outcome for patients with RA? How does early diagnosis of RA, early and aggressive treatment for achieving the goal, and tight control strategy look at the strongest evidence of improvements in patients - the level of mortality?

The absolute one-year mortality rate for RA is 0.8% (1.4% in the general population), 5-year mortality is 5% (6% in the total population), 10-year mortality is 10% (10% in the total population) and 15 years after the diagnosis of RA, the mortality rate was 13% (versus 12% in the general population). Similar causes of death have been identified in patients with RA and the general population, such as cardiovascular disease, neoplasms and lung disease, which are the most common causes of death. The leading causes of death in patients with RA and in the general population are CVD (29% vs. 30%), carcinomas (26% vs. 33%) and respiratory diseases including respiratory infections (12% vs. 9%). All causes of death were elevated among patients with RA, with the exception of deaths due to diseases of the nervous system.

While the causes of death are similar, patients with RA die at a younger age.

2. Key findings from the Literary review

- Rheumatoid arthritis is a disease with an increasing social significance. Due to an increase in the average life expectancy of the entire population, in the coming decades RA will represent a bigger part of the pathology in everyday practice.
- Clear criteria for early diagnosis of RA, clear treatment goals and strategies to achieve them are established. There are modern, generally available target therapeutic molecules for use in everyday clinical practice.
- There is no single opinion on the combined indicators to assess the effectiveness of these therapeutic approaches and target molecules in everyday clinical practice.
- Patients with RA have an abnormal accumulation of concomitant diseases and conditions. The largest relative share is cardiovascular disease, which is the main reason for the shorter life expectancy of these people and the "excessive" mortality, even in the era of modern treatment.
- There is insufficient convincing evidence of a sustained, significant reduction in mortality for all causes, and in particular for CV death in RA patients. There are some trends that support a view of the role of prolonged inflammation process as the underlying cause of this "excessive" mortality.
- The medical community is aware that traditional risk factors are not able to explain the increased cardiovascular pathology in these patients.

II. PURPOSE, TASKS AND HYPOTHESIS

PURPOSE:

Optimize the assessment of clinical activity of rheumatoid arthritis in order to improve long-term prognosis of patients.

TASKS:

Analysis of the clinical activity of RA in patients undergoing treatment with biological agents with or without concomitant diseases;

Analysis of the dependence and extent of overlapping of RA activity score by DAS28(ESR) and DAS28(CRP);

Determination of the DAS28(CRP) thresholds corresponding to DAS28(ESR);

Determination of predicted probability of developing a CVD;

Offering an algorithm to improve the clinical course of RA patients and reduce CVD risk

HYPOTHESIS

The current approach to managing RA activity through tight control and treat to target strategy in the treatment of patients requires the use of secure combined assessment tools and dynamic monitoring of the response. Two variants of DAS28 (ESR and CRP) have been shown to allow a high level of residual activity in treatment that could be responsible for progression of RA despite the use of expensive medications. The use of these "more favorable" combined indicators in day-to-day clinical practice may be the cause of a lack of significant change in the development of concomitant cardiovascular disease, which ultimately leads to premature death in RA patients.

III. METHODOLOGY OF DISSERTATION WORK

1. Subject of the research

Investigation of the activity of RA in the course of treatment with biological agents, analysis of the factors allowing residual inflammation, analysis of the concomitant diseases and their interaction with the residual activity in RA patients on biological therapy.

2. Object of the research

The research was conducted at the Clinic of Rheumatology at the University Hospital “St. Marina” after approval by the Ethics Committee for Research (№83/16.05.2019) to the same hospital and in accordance with the Helsinki Declaration (WMA Declaration of Helsinki, 2008).

The medical records of a total of 209 consecutive patients with RA were analyzed. All patients have gone through the Diagnostic - Advisory Cabinet (DAC) at the Clinic of

Rheumatology, University Hospital "St. Marina" for the period 01 June 2017- 30 September 2018 under Ambulatory procedure № 38 for determination of a treatment plan and follow up of the therapeutic response in patients receiving expensive medicinal products by the order of art. 78, item 2 of the HIA (https://www.nhif.bg/page/1565).At first the study included 209 patients with RA. After applying selection criteria, the patients remained 197:

- Age over 18 years;
- Diagnosis of RA (ACR 1987 criteria);
- Positive rheumatoid factor (RF)
- Therapy with biological agents;
- Duration of the therapy with biological agents at least 6 months prior to the start of the study;

. Due to the development of serious adverse events during the study period (established lung tumor in one patient and multiple organ failure in another) the analysis eliminates 2 patients. The actual study was performed in 195 patients.

The analysis does not include patients who undergo biological treatment with diagnoses other than RA: Ankylosing Spondylitis, Psoriatic Arthritis, and Systemic Lupus Erythematosus.

Investigated, described, analyzed and followed for 12 months were the administrative medical records of 195 patients with rheumatoid arthritis who conducted 582 visits, the results of which were included in the dissertation work.

3. Conduct and organization of the research

The research was conducted in the period 16.05.2019-30.06.2019.

The period of treatment of patients with biological agents, which was studied is from 01 June 2017 to 30 September 2018.

All patients undergoing biological treatment are selected to meet the treatment criteria as required by the NHIF (Requirements of the NHIF for the treatment of seropositive rheumatoid and psoriatic arthritis with disease-modifying antirheumatic drugs (DMARDs) in outpatient care).

4. Methods

The following sets of metrics are analyzed:

Socio-demographic characteristics, including:

- Age;
- Sex;
- Height (cm);
- Weight (kg);
- BMI (kg/m^2);
- Smoking.

Characteristics of Rheumatoid Arthritis:

- Duration of RA (years)
- Age at the onset of RA;
- X-ray stage of RA;

Therapeutic variants with respect to the following groups of medication:

- Use of Non-Steroidal Anti-Inflammatory Drugs;
- Use of Corticosteroids;
    - Dose of corticosteroid product
- Treatment with synthetic disease-modifying agents:
    - Methotrexate;
        - Dose of Methotrexate.
    - Leflunomide.
- Treatment with biological products:
    - Time from onset of diagnosis to initiation of treatment with biological product;
    - Duration of treatment with biological products;
    - Type of biological product:
        - anti -TNFα;
        - anti -IL6;

- anti CD20.

Clinical indicators related to the level of RA activity and the safety of patients undergoing biological treatment.

Laboratory indicators related to the level of RA activity and the safety of patients undergoing biological treatment.

Indices to assess the activity of RA:

When analyzing the medical records of the patients during the 12 months of their treatment with biological drugs, the available data reflecting RA activity evaluations were derived according to DAS28.

In the secondary data processing, both DAS28 variants (ESR and CRP) were calculated. Thus, for each patient, two synchronous scores from each DAS28 variant were obtained for each visit. The calculation was made using online calculator formulas: https://www.das-score.nl/das28/DAScalculators/dasculators.html Formula for the average activity of RA during the analyzing period

The activity of RA was presented as the *average activity in each patient* in the course of biological treatment for the entire one-year period studied. The time average activity of RA is calculated by the formula (Fig.1):

$$\textit{Avarage activity of RA}\ (DAS28) = \frac{DAS28_1 + DAS28_2 + DAS28_3}{n}$$

Fig. 1 Formula for calculating the average RA activity over the analyzed period

Legend: n –number of visits; RA – rheumatoid arthritis; DAS28 - disease activity score 28; 1,2,3- consecutive visits during the 12-month treatment period

Concomitant diseases:

All available medical records of the patients included in the study, for the purpose of identifying concomitant diseases, are analyzed. Any illness included in the patient's medical records and encoded according to ICD 10 is classified.

Concomitant diseases are classified as:

- Diseases of the Cardio-Vascular System
- Diseases of the lung;
- Diseases of the genitourinary system;
- Diseases of the gastrointestinal tract and liver;
- Endocrine diseases.

Besides the available concomitant diseases, risk factors have also been analyzed:

- Hypercholesterolemia;

Statistical methods

Descriptive Statistics, Explore for Single-Variable Statistics, Student T-test for comparison of average values and relative shares with acceptance of a level of significance $p<0.05$, Pearson test and Fisher test to assess the qualitative variables in the single-variable analysis, non - parametric test for connectivity of category variables with acceptance of a significance level for χ^2 <0.05 .One-Way ANOVA analysis, post hoc analysis, correlation analysis, multifactorial classical and stepwise regression analysis with acceptance of a significance level for F<0.05 and less than the error $\alpha = 0.05$, the Bland-Altman method for analyzing the differences, Cohen's kappa test for determining the reliability of the results obtained by different methods. Statistical SPSS v 23 for Windows is used.

Graphic and tabular method for displaying the results.

IV. RESULTS

1. Indicators characterizing the patients in the study

The study includes 195 RA patients, who underwent treatment with biological products. The diagnosis is based on ACR criteria (1987).

Table 1. Demographic characteristics of RA patients included in the study

Characteristic		***n***	***%***	***p value***
Sex	women	168	85.28	<0.001
Age [years] mean ±SD (range)		58.84 ± 11.19 (19-87 years)		
Age [years] ≥ 55years.		133	67.5	<0.001
Age at diagnosis [years] mean ±SD (range)		46.88 ± 14.02 (1 – 77 years.)		
Age at diagnosis ≤ 40 years		47	23.8%	<0.001
BMI mean ±SD (range)		26.94 ± 5.34 (15-44)		
<18.5 - underweight		5	2.54	<0.001
18.5-24.9 - normal		60	30.96	
25-29.9 – overweight		75	38.07	
>30 – obesity		55	28.43	
Weight[kg] mean ±SD (range)		73.70 ± 16.45 (41-130)		
Height [sm.] mean ±SD (range)		163.50 ± 7.54 (145-185)		
Smoking	Smokers	60	30.46	<0.001

The sociodemographic characteristic of the examined group of patients is presented in table. 1. The results show the predomination- women (85.3%), patients over 40 years old (94.70%), BMI overweight (66.50%) and non-smokers (70.30%).

The average age of patients included in the analysis is 58.8 years (table.1, fig. 2), the relative share of the patients over the age of 55 is 67.5%, and the average life expectancy of patients without RA is 46.88 years. In a relatively small portion of patients, the diagnosis was made before age 40 (23.8%) (p<0.001).

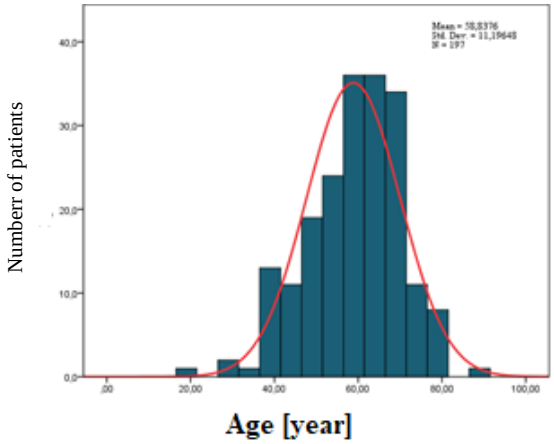


Fig. 2. Distribution of RA patients by age

In examining the socio-demographic signs, it was found that RA patients did not differ significantly with respect to the average age and BMI in terms of gender, with the average age of men and women being respectively 56 for men and 59 for women.

The average BMI does not differ by gender (28.24 vs. 26.72, p> 0.05). The RA patients were overweight (26.94 kg / m2).73.3% of smokers are women (p = 0.002) and predominantly with BMI <30 kg / m2 (66.7%) (p = 0.039).

Characteristics of rheumatoid arthritis

The average continuance of RA in the monitored group was 11.95 years at the beginning of the study, with the largest relative part being the patients with a disease duration more than 10 years and the lowest being those between 1 and 5 years. (16.2 vs 46.1 %) (p<0.001).

In the IV-th X-Ray stages are more than 1/3 of the patients (36.04 %), and 55.3% of them are in II functional class (55.33 %) (p=0.135) (table 2).

Table 2. Characteristics in RA, in patients ongoing treatment with biological medication.

Indicator		***[n]***	***[%]***	***p value***
Duration of RA [years]	mean±SD (range)	11.95 ± 9.14 (2- 44)		
	< 1 year	0	-	<0.001
	1 – 5 years	31	15.90	
	5 – 10 years	73	37.44	
	> 10 years	91	46.19	
Rheumatoid factor	positive	195	100.00	
Rö stage [Conventional X-ray of palms and wrists]	Without Rö changes	0	-	<0.001
	I Rö stage	0	-	
	II Rö stage	67	34.4	
	III Rö stage	57	29.2	
	IV Rö stage	71	36.4	
Functional class	I func. class	0	-	NS
	II func. class	107	54.8	
	III func. class	88	43.2	
	IV func. class	0	-	
Time till the starting of biological treatment [years]	mean±SD (range)	8.28 ± 8.62 (0.5- 44)		<0.001
Duration of the biological therapy at the end of the treatment [years]	mean±SD (range)	4.69 ± 2.08 (1.5- 14)		

There was no established relationship between the continuance of the disease and the age of the patients. (p>0.05).

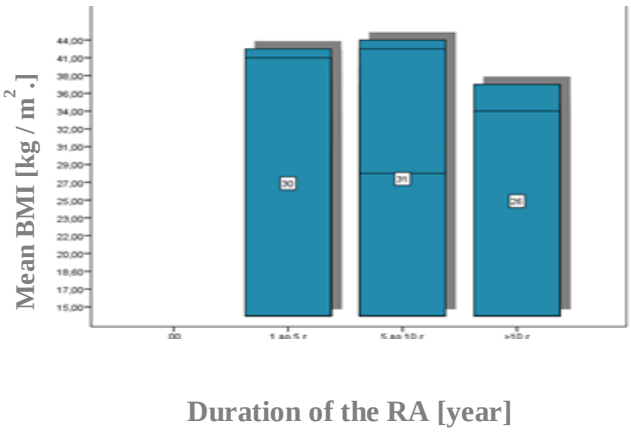


Fig. 3. Distribution of patients according to the continuance of RA and BMI

A significant difference in BMI value BMI (p = 0.002) was found in patients with different continuance of RA, with a consistent tendency to decrease the BMI value by increasing the RA continuance (fig. 3). Patients with a BMI of less than 18.5 kg/m^2 have the longest duration of RA- 23.8 years. There is a inverse proportionally low correlation between BMI and disease duration (r= -0.245; p < 0.001), 6.6 % in BMI changes are due to the duration of RA [years].

Even more significant are the results in terms of weight reduction of patients with RA with the increase in disease duration (p <0.001), with the difference in the average value of body weight between the patients with the lowest duration and those with the greatest 11.6 kg.

As major predictors of change in functional class, the motor deficiency in the study group of patients, the X-ray stage of RA and the disease status were determined.

60.3 % of changes in the functional class of motor deficiency are determined by the needs of RA and X-ray (p<0.001).

A total of 66.3% of the X-ray changes in RA in the patients studied are due to RA pause and time from diagnosis to initiation of treatment with biological products (p<0.001).

Concomitants diseases:

In 29.7% of patients with RA there are no concomitant diseases (p <0.001). In the remaining 70.3% of the patients there is an concomitant disease, which could be related to the prognosis of the patients (Fig.4)

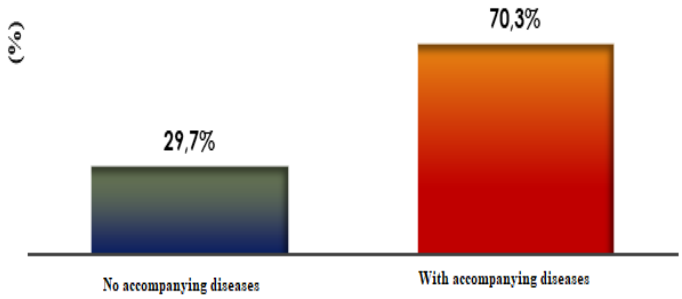


Fig.4. Relative share of patients with RA with and without concomitants diseases. (**- p<0.001)

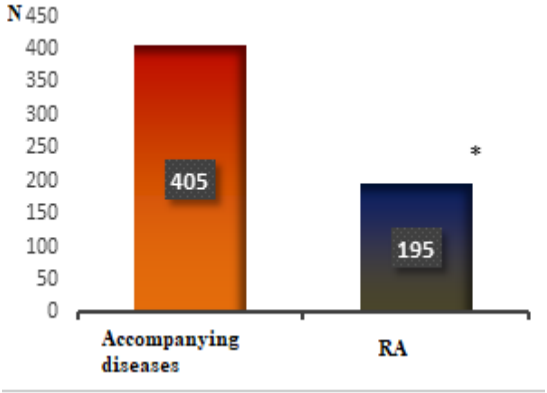


*Fig.5. Concomitant diseases in RA patients. The incidence of co-morbid diseases is more than twice the number of patients*** - p <0.001

The incidence of concomitant diseases is more than twice the number of patients. A total of 405 concomitant diseases were found in 195 patients (p <0.001) (Fig.5).

Patients with concomitant diseases (AD) are at a average age of 60.79 years (p <0.001), with a higher body weight of 75.21 kg. (p <0.001) and have a higher BMI (27.50 vs. 25.79) (p = 0.039) (Figure 6).).

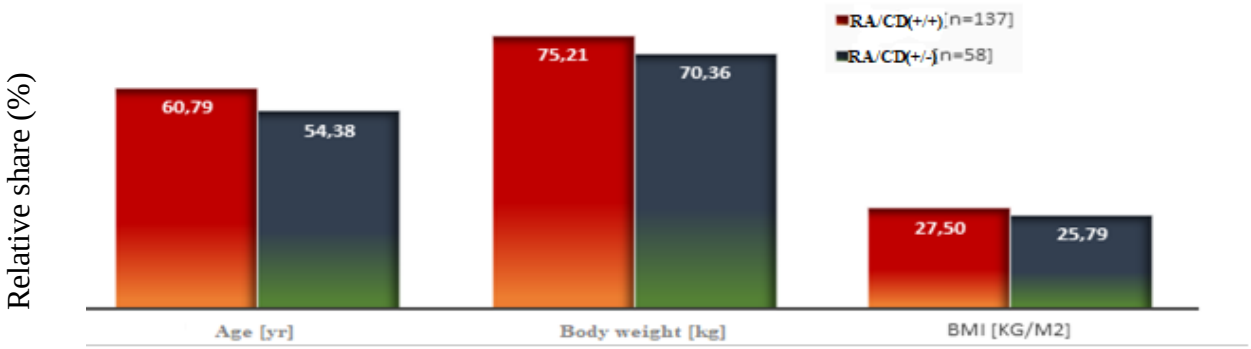


Fig 6. Age, weight and BMI in patients with RA according to the presence of concomitant diseases. Legend: CD – concomitant diseases

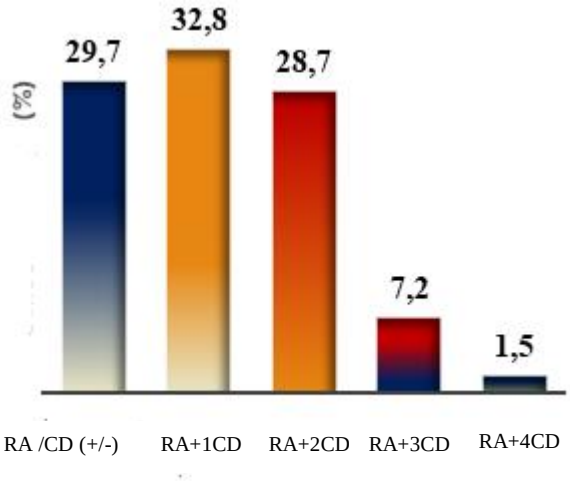


Fig 7. Relative share (%) of patients with RA without concomitants diseases, with one or more CD. There is a predomination of patients with one or 2 CD (60.54%) (p<0.001)

The largest portion is represented by the patients with one CD (32.8 %). Patients with three or more CD represent a relatively small portion of all RA patients treated with biological products (8.7%) (p<0.001) (фиг.7).

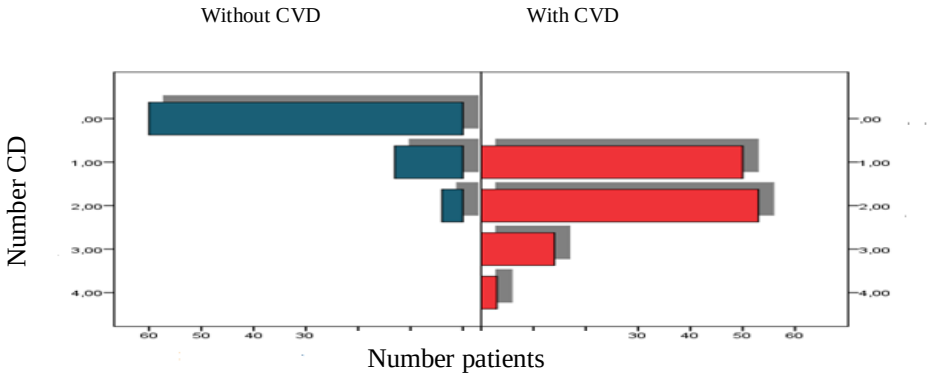
In 81% of patients with AD, RA's debut is after 40 years of age (p =0.015).

Patients with or without CD do not differ in gender, duration of RA, X-ray stage and functional class failure of RA(p>0.05).

Table 3. Concomitant diseases in RA patients

		[n]	[%]	p value
Without CD		58	29.74	<0.001
RA patients with CVD		120	61.54	0.002
HTN	yes	115	58.97	0.019
IHD	yes	24	12.31	<0.001
CVA	yes	20	10.26	<0.001
HF	yes	12	6.15	<0.001
Patients with pulmonary diseases		15	7.69	<0.001
COPD	yes	8	4.10	<0.001
Patients with gastrointestinal and liver diseases		36	18.46	<0.001
Liver diseases	yes	23	11.79	<0.001
Patients with endocrine diseases		42	21.54	<0.001
Diabetes	yes	29	14.87	<0.001
Patients with kidney diseases		18	9.23	<0.001
Chronic pyelonephritis	yes	10	5.13	<0.001
Total patients with concomitant diseases		137	70.26	<0.001

The largest portion of all concomitant disease is CVD (61.5%), followed by endocrine diseases (21.5 %). Gastrointestinal and liver diseases, mostly variants of ulcer disease were found in 36 patients, which represents a significantly small share of total CD. (p<0.001) (table.3).



Patients with RA and CVD usually have one more CD (fig.8).

Fig.8. Grouping of concomitant diseases.

Legend: Cardio vascular concomitant diseases

Of all 137 patients with concomitant diseases, only n=17 (12.4 %) had a concomitant disease, other than CV origin or not accompanied by CVD (p<0.001).

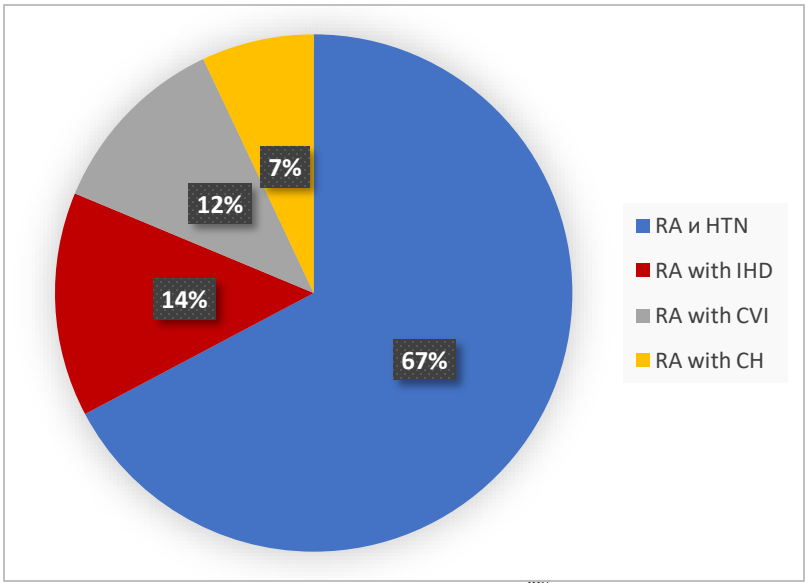


Fig.9. Distribution of cardiovascular disease and uncomplicated HTN in RA patients

Of all CVDs (n=171), the largest relative share were patients with HTN-67% (p<0.001), followed by IHD (14%), CVA (12%) and the lowest relative share was heart failure (7%). No significant differences were found in gender, body weight, BMI and RA duration in patients with and without CVD(p>0.05) (fig.9.).

Patients with RA and CVD have the same duration of RA compared to the others (12.1 vs 11.1 years, p>0.05), but the average age of RA's debut is significantly higher in them (49.7 vs 42.4 years, p<0.001). In 66% of patients with concomitant CVD, RA debuted after the age of 40 (p=0.009).

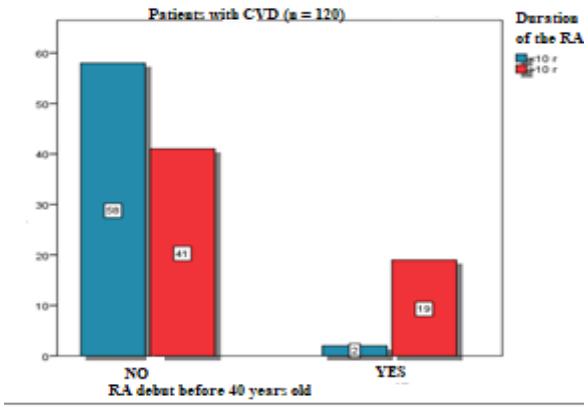


Fig.10 Correlation between the RA's debut before age 40 and the presence of CVD.

Of all patients with RA and CVD (n = 120), with a relatively small relative share - n = 21 (17.5%), RA debuted earlier before 40 years of age and with continuance more than 10 years at the time of the study (p <0.001) (Figure 10).

Patients with RA with CVD are predominantly in a lower X-ray stage (58.3% are in the II and III X-ray stages) (p = 0.040), with no significant difference in the functional class of motor failure (p>0.05).

Arterial hypertension

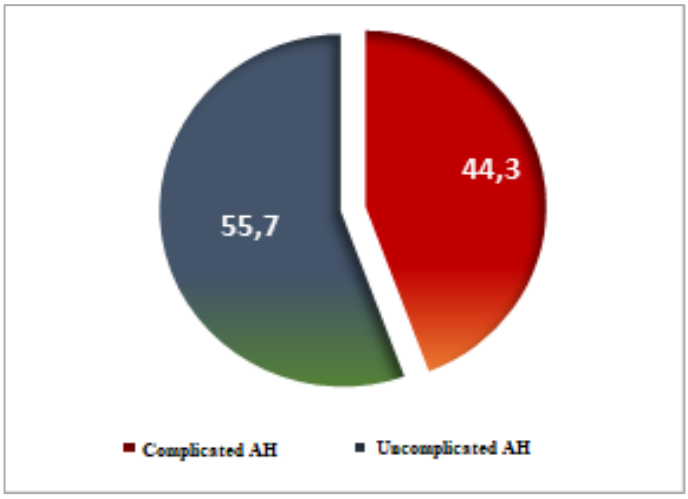


Fig. 11 Relative share of patients with RA with uncomplicated HTN.

The uncomplicated HTN prevails in the investigated patients. The relative share of patients with complicated HTN with IHD, CVA and HF in RA patients of biological products is significantly lower (44.3%) (p <0.001) (Fig.11)

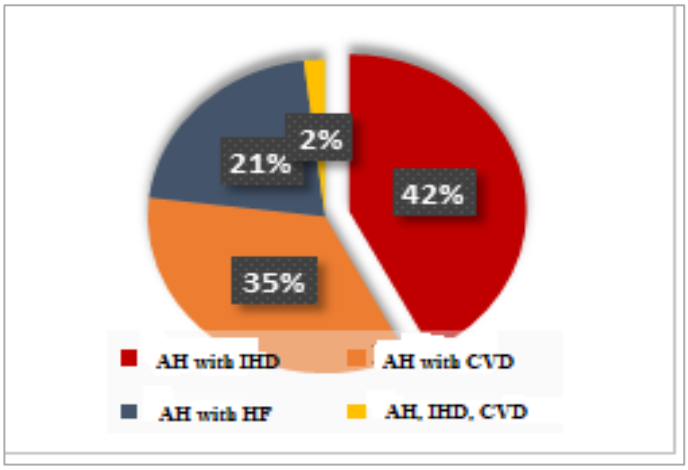


Fig. 12. Combined CVD.

Of all patients with complicated HTN (n = 52), the highest relative share is represented by the patients with HTN and IHD (n = 22) (42.3%), followed by patients with HTN and CVA (n = 18) (34.6%). HTN and HF (21%) were found in 11 patients. In 1patient from RA HTN is established with IHD and CVA (1.9%) (Figure 12). Patients with RA, HTN and IHD or CVA are at a higher average age than the others (p <0.001), no significant difference in body weight, BMI, RA pause, time to initiation of treatment with biological products and its duration (p>0.05).

Traditional CV risk factors:

Table 4 presents the traditional CV risk factors among the RA patients studied

Табл.4. Traditional CV risk factors in patients with RA (n=195)

Legend: BMI- Body Mass Index;HTN - arterial hypertension. Bold was used with a

Risk factors for CVD		*[n]*	*[%]*	*p value*
Men	yes	29	14.87	0.002
Age> 55 years	Yes	**132**	**67.69**	**<0.001**
Smokers	Yes	60	30.77	0.019
BMI>25 kg/m^2	Yes	**130**	**66.67**	**<0.001**
HTN	Yes	**115**	**58.97**	**0.019**
Hypercholesterolemia	Yes	**113**	**57.95**	**0.039**
Diabetes mellitus	Yes	29	14.87	<0.001
Blood sugar on fasted state >6 [mmol/l] in patients without diabetes	yes	19	9.74	<0.001

significantly higher prevalence of risk factor among the study group of patients

The most widely presented risk factor among the patient group is age. 67.6% of patients with RA are over 55 years of age (p <0.001). Second place is overweight and obesity (66.7%) (p <0.001) and third place HTN (58.9%) (p <0.001). Patients with RA and hypercholesterolemia account for 57.9% of all patients with RA (p = 0.039).

Patients with RA with HTN (n = 115) represent 58.97% of all patients enrolled in the study (p = 0.019), at an average age significantly higher compared to patients without HTN (61.8 years vs. 54.67 years) (p<0.001)

Among the patients with RA и HTN and those without HTN there was no difference in body weight, BMI, time to the onset of RA, as well as the continuance of RA (p>0.05). 35 от 47 patients with BMI over 30 kg/m^2 have concomitant HTN (p=0.010).

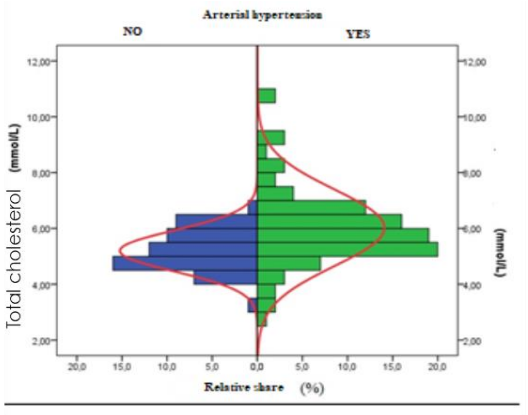


Fig.13 Correlation between HTN and hypercholesterolemia in patients with RA.

Between the two traditional risk factors for CVD (HTN and hypercholesterolemia), a moderate correlation was established in the monitored RA patients (p = 0.376, p <0.001) (Figure 13).

Among all patients with RA, registered endocrine diseases were reported at in 48 of them, with the largest proportion of them being diabetes (69.1%, p <0.001).

Therapeutic options in patients with and without the presence of CVD:

There were no significant differences in the type and duration of the ongoing biological therapy in patients with and without CVD (Table 5)

Therapeutics models in monitored group of patients with RA, data from the actual clinical practice are presented in Table. 5.

Table 5. Therapeutics models in the study group of patients with RA (data from actual clinical practice).

Indicator		**RA/CVD (+/+) [n=120]**		**RA/CVD (+/ -) [n=75]**		p
		[n]	**%**	[n]	%	
Biological products	anti-TNFα	60	50.00	45	58.44	NS
	non anti-TNFα	60	50.00	30	38.96	
Types of biological products:	Adalimumab	40	33.33	34	44.16	NS
	Certolizimab pegol	1	0.83	0	0.00	
	Etanercept	9	7.50	4	5.19	
	Golimumab	3	2.50	1	1.30	
	Infliximab	7	5.83	6	7.79	
	Tocilizumab	57	47.50	28	36.36	
	Rituximab	3	2.50	2	2.60	
Time till the start of biological therapy [years] mean±SD (range)		8.31 ± 8.15 (0 – 34.5)		8.15 ± 9.46 (0 – 41.0)		NS
Duration of biological therapy [years] mean±SD (range)		4.75 ± 2.04 (2 – 14.0)		4.60 ± 2.15 (1.5 – 13.0)		NS
Monotherapy with biological products	**Yes**	29	24.17	28	36.36	0.027
	no	91	75.83	47	61.04	
Combined disease-modifying therapy:	**Methotrexate [mg./week.]** mean±SD (range)	12.65±3.96 (7.5-25)		11.18±3.36 (2.5-20)		0.031
	yes n=121	66	55.00	55	71.43	0.028
	Leflunomide [mg./day mean±SD (range)	20.00±0.00 (20-20)		20.00±0.00 (20-20)		NS

Indicator		RA/CVD (+/+) [n=120]		RA/CVD (+/ -) [n=75]		p
		[n]	%	[n]	%	
	yes(n=8)	6	5.00	2	2.60	NS
	Total synthetic DMARDs (n = 129)	72	60.00	57	74.03	0.044
Biological products +symptomatic therapy	**NSAID**n = 85	57	47.50	28	36.36	NS
	Corticosteroids (mg/day) mean±SD (range)	5.48±2.34 (2-12)		5.51±2.39 (2-8)		NS
	yes (n = 110)	77	64.17	33	42.86	0.003
	Corticosteroids + NSAIDs (n = 60)	45	37.50	15	19.48	0.007
Biological + synthetic + combination of symptomatic therapy (n = 35)		25	20.83	10	12.99	NS

The average duration of treatment with biological products in patients with RA and CVD is 4.75 years versus 4.60 for patients with RA without CVD (p> 0.05).

The average time from the diagnosis of RA to the start of biological therapy did not differ significantly in patients with and without CVD (8.31 vs 8.15 years, p> 0.05). In all patients with RA, the onset of treatment with biological agents is significantly delayed (average 8.28 ± 8.62 years, (0.5-41 years).) This score determines the whole group of patients, such as patients with "established", long-labeled RA and the latest onset of biological therapy.

50% of patients with concomitant CVD and 45% of those without, start treatment with non-anti-TNF α inhibitors (anti-IL6 and anti-CD20 blockers) (p> 0.05).

The relative share of patients with RA with CVD who carry out monotherapy with biological products is considerably lower than those without CVD (24.2% vs. 36.4%) (p = 0.027).

Combined "basic" therapy - biological products with Methotrexate

55% of patients with RA and CVD performed combined "basic" therapy - biological products with Methotrexate, which is a significantly smaller share compared to patients with RA

without CVD (71.43%) (p = 0.028). Patients with RA with CVD receive a higher mean dose of Methotrexate than those without CVD (MD = 1.46, 95% CI -2.8.0.13) (p = 0.031).

In the study of the patients in comparison with the CV risk profile, a significantly more advantageous profile was found in the patients receiving MTX versus those of the monotherapy with biological products (Table 6)

Table 6. Combined therapy (biological products and MTX) and CV risk profile in patients with RA

Disease	CV risk profile in combined treatment with MTX (OR, 95%CI)		
	Total	TNF α inhibitors	Non-TNF α inhibitors
Hypertension	0.51(0.28-0.94)	0.38(0.16-0.84)	0.74(0.29-1.86)
Ischemic heart disease	0.32(0.13-0.77)	0.21(0.05-0.82)	0.44(0.13-1.43)
Cerebrovascular disease (CVA)	0.58(0.22-1.46)	1.01(0.46-2.8)	0.96(0.21-4.31)
Heart failure	0.59(0.18-1.91)	0.42(0.12-1.41)	0.86(0.14-5.44)
Hypertension with ischemic heart disease	0.31(0.12-0.76)	0.13(0.02-0.67)	0.52(0.16-1.80)
Hypercholesterolemia	1.30(0.73-2.32)	1.41(0.64-3.01)	1.14(0.46-2.8)
Hypertension with hypercholesterolemia	1.01(0.46-2.8)	1.05(0.47-2.36)	0.92(0.39-2.18)
Diabetes	0.52(0.23-1.14)	0.51(0.17-1.54)	0.52(0.16-1.64)

Treatment with symptomatic NSAIDs and corticosteroids

55.8% of all patients treated with biological drugs also use CS (p = 0.101).

A significantly smaller proportion of patients with RA without CVD received CS compared to those with CVD (42.9% vs. 64.2%, p = 0.003). A significantly greater proportion (37.5%) of patients with CVD use dual symptomatic therapy (NSAIDs and CS) compared with 19.48% of patients without CVD (p = 0.007)..

Average CS dose in patients with and without CVD did not differ significantly (MD = 0.034, 95% CI -0.94, 1.01) (Table 5).

When examining the risk profile of patients with IHD with CS, it is found that patients are 68% more likely to have IHD than those who do not take CS. This probability is more than doubled in patients treated with non-TNF α inhibitors (anti-IL6, anti-CD20) (Table 7)

Table 7 Cardiovascular risk profile in RA patients taking corticosteroids.

Disease	CV risk profile in RA patients taking corticosteroids (OR, 95%CI)		
	Total	TNF α inhibitors	nonTNF-α inhibitors
Hypertension	2.51(1.41-4.50)	2.22(1.02-4.82)	2.63(1.06-6.49)
Ischemic heart disease	1.68(0.68-4.13)	1.25(0.35-4.37)	2.12(0.54-8.36)
Cerebrovascular disease	1.96(0.72-5.35)	1.02(0.31-3.39)	0.59(0.50-071)
Heart failure	1.11(0.34-3.64)	0.42(0.12-1.41)	0.86(0.14-5.44)
Hypertension with ischemic heart disease	1.80(0.70-4.64)	1.02(0.27-3.75)	3.29(0.67-16.08)
Hypertension with cerebrovascular disease	2.19(0.75-ов 6.42)	1.02(0.27-3.75)	0.59(0.50-0.71)
Hypertension with ischemic heart disease with cerebrovascular disease	1.05(0.23-4.85)	0.32(0.03-3.24)	NA
All cardiovascular diseases	2.38(1.32-4.28)	2.25(1.03-4.92)	2.33(0.94-5.76)
Hypertension with hypercholesterolemia	2.66(1.48-4.80)	3.04(1.33-6.92)	2.00(0.84-4.78)
Diabetes	1.35(0.60-3.03)	0.87(0.29-2.61)	2.39(0.61-9.28)
Hypercholesterolemia	2.53(1.41-4.52)	3.58(1.61-7.94)	1.41(0.57-3.44)

Legend: OR-odds ratio, CI – confidentiality interval, CV – cardiovascular

2. Activity analysis of RA in patients with and without CVD

Clinical indicators of RA and BP activity in patients with and without CVD.

Analyzed are: Blood pressure (mmHg), number of painful and swollen joints and VAS (table.8)

Table 8. Dynamics of clinical indicators presented as average difference in patients with and without depending on the presence of CVD

Indicator	At the beginning of the study period			At the end of the study period		
	RA/CVD (+/-) vs RA/CVD (+/+)			RA/CVD (+/-) vs RA/CVD (+/+)		
	MD (95%CI)		p value*	MD (95%CI)		p value*
SBP [mmHg]	-3.62 (-5.8-1.36)		0.004	-3.79 (-6.2- 1.37)		0..002
DBP [mmHg]	-1.87 (-3.28- 0.46)		0.010	-2.03 (-3.5- 0.54)		0.008
TJC	-0.58 (-1.31- 0.14)		NS	-0.6 (-1.06- 0.13)		0.012
SJC	-0.0007 (-0.59- 0.59)		NS	-0.09 (-0.4- 0.22)		NS
VAS (0-100 mm)	-6.8 (-9.59- 4.04)		<0.001	-6.05 (-8.2- 3.82)		<0.001
VAS<30mm (n)(%)‡	41(54.7)	52(43.4)	<0.001	60(80)	57(47.5)	<0.001

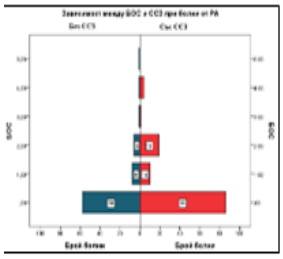
Legend: SBP- systolic blood pressure, DBP- diastolic blood pressure, TJC- number of tented joints, SJC-number of swollen joints, VAS- visual analogue scale; RA-rheumatoid arthritis, CVD = cardiovascular disease, * - Independent Samples Test; MD-average difference, CI - confidence interval, significance level for rejection of null hypothesis $p < 0.05$; ‡ - $\chi 2$ significance level for rejection of the null hypothesis $p < 0.05$.

Patients with RA with CVD had higher SBP and DBP values at the beginning and end of the study period. SBP values of ≥140 mmHg was found in 15.8% of patients with CVD and 1.3% of patients without CVD ($p = 0.001$). DBP≥90 mmHg was found in 11.7% of patients with CVD compared with 1.3% of patients without CVD ($p = 0.007$) (Table 8).

Patients with RA with CVD had a significantly higher number of painful joints at the end of the study (MD = -0.6, 95% CI (-1.06, -0.13)) ($p = 0.012$).

The number of swollen joints does not differ significantly in patients with RA, with or without (fig. 14).

Significantly higher VAS values were found in CVD patients both at the beginning of the study ($p < 0.001$) and at the end ($p < 0.001$) (Fig. 15).



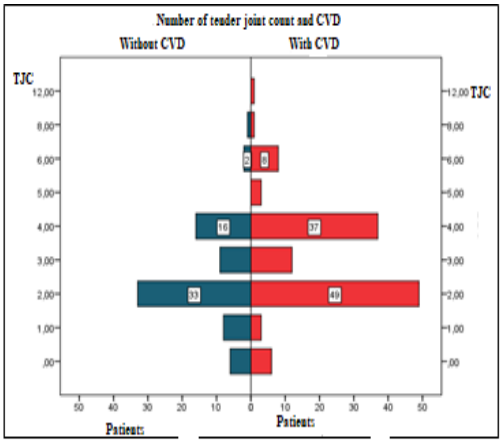


Fig. 14. Number of tender and swollen joints count in RA patients at the end of the study, depending on the presence of CVD

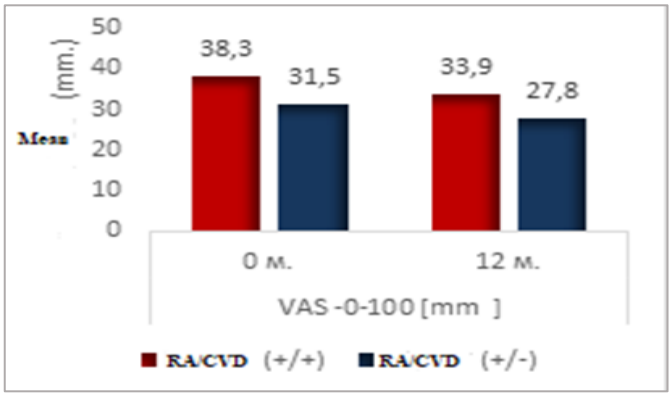


Fig.15. Change in VAS averages depending on the presence of CVD.

A significantly higher proportion of patients with CVD (65.8%) identified a VAS pain severity greater than 30 mm at the start of the study compared with patients without CVD (32.5%) ($p < 0.001$). A moderate inverse correlation was found between VAS score (less than 30 mm) and CVD in RA patients ($\rho = -0.326$, $p < 0.001$). Between 10.3% (at the beginning) and 12.5% (at the end) of the change in the value of VAS is determined by the presence of CVD ($F = 23.42$, $p < 0.001$.)

Laboratory indicators for RA and CVD activity

The average value of laboratory acute-phase indicators for the study period did not change significantly for the whole group.

CVD patients had significantly higher mean ESR and CRP values both at the beginning of the observation period and at the end (Table 9).

Table 9. Dynamics of laboratory parameters. in patients with and without CVD.

Indicator	At the beginning of the study			At the end of the study		
	RA/CVD (+/-) vs RA/CVD (+/+)			RA/CVD (+/-) vs RA/CVD (+/+)		
	MD (95%CI)		p value*	MD (95%CI)		p value*
CRP [mg/L]	-3.50(-5.33-1.67)		<0.001	-2.54(-4.81-0.27		0.028
CRP <1[mg/L] (n)(%)‡	15(19.4)	13(10.8)	NS	31(41.3)	18(15.0)	<0.001
CRP >3 [mg/L] (n)(%)‡	43(57.3)	90(75.0)	0.005	23(30.7)	84(70.0)	<0.001
ESR [mm/h]	-4.7 (-9.52-0.12)		0.011	-6.39 (-11.07-1.71)		0.002
ESR > 20 [mm/h] (n)(%)‡	29(38.7)	72(60.0)	0.002	24(32.0)	60(50.0)	0.004
Hemoglobin (g/L)	-1.99 (-5.9-1.97)		NS	-1.99 (-5..88-1.89))		NS
ALAT (U/L)	-2.38 (-6.09-1.31)		NS	-0.21 (-10.68-0.35)		NS
Creatinine (mmol/L)	-1.35 (-6.56-3.85)		NS	-5.51 (-6.09-1.31)		0.021

Legend: CVD - cardiovascular disease, CRP- C reactive protein, ESR - erythrocyte sedimentation rate, ALAT - Alanine aminotransferase, * - Independent Samples Test; AD-average difference, CI - confidence interval, significance level for rejection of null hypothesis p <0.05; ‡ - $\chi 2$ - significance level for rejection of the null hypothesis p <0.05

The average CRP value in patients with CVD at the beginning and at the end of the study period was significantly higher compared to patients without CVD (p = 0.028) (Fig. 16).

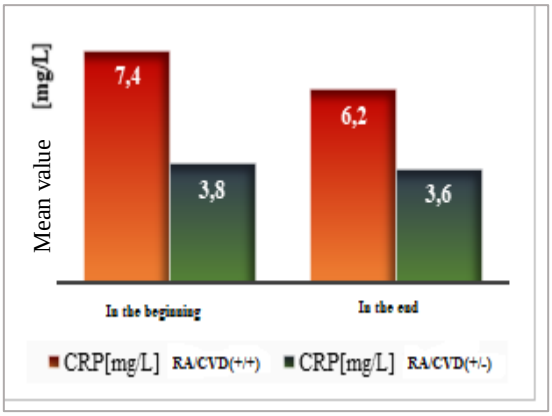


Fig.16 Dynamics of mean CRP during treatment with biological agents in patients with and without CVD.

A similar pattern is found in the analysis of the average ESR values. Patients with RA and CVD had significantly higher ESR values at the beginning of the study (p = 0.056) and at the end of the study period (p = 0.008) (Table 9).

No significant differences were observed in the mean Hb and ALAT values in patients with and without CVD. The mean creatinine at the end of the study was significantly higher in CVD patients (p = 0.021).

Analysis of combined indicators for evaluating RA activity.

Analysis of combined indicators for evaluating RA activity in all patients.

The activity of PA expressed by DAS 28 (ESR and / or CRP) is significantly altered during treatment with biological agents. The average of the two variants of DAS 28 decreased statistically significantly. The proportion of patients in remission and low disease activity increased, and the proportion of patients with moderate and high activity decreased (Table 10).

Table 10 Dynamics of RA activity over a 12-month treatment period in all patients studied.

Indicators			Beginning of the study			End of the study			p value
			[n]	[%]	p value‡	[n]	[%]	p value‡	
DAS 28 (ESR)	**MD (95%CI)**		0.37(0.27-47)						<0.001*
	Remission	Yes	12	6.09	p<0.001	23	11.79	< 0.001	p<0.001
	Low activity	Yes	30	15.23		53	27.18		
	Moderate activity	Yes	142	72.08		116	59.49		
	High activity	yes	13	6.60		3	1.54		
DAS 28 (CRP)	**MD (95%CI)**		0.41(0.32-0.49)						<0.001*
	Remission	Yes	23	11.68	< 0.001	62	31.79	< 0.001	< 0.001
	Low activity	Yes	66	33.50		72	36.92		
	Moderate activity	Yes	105	53.30		59	30.26		
	High activity	yes	3	1.52		2	1.03		

Legend: DAS – disease activity score, CRP- C-reactive protein, ESR- erythrocyte sedimentation rate* Paired Sample T-Test, MD-difference of means, CI – confidentiality interval, significance level for rejection of null hypothesis p <0.05; ‡ - $\chi 2$ significance level for rejection of the null hypothesis p <0.05

There was a significant difference between the mean values of DAS28 (ESR) and DAS28 (CRP) both at the beginning and at the end of the study period (p <0.001) (Fig.17).

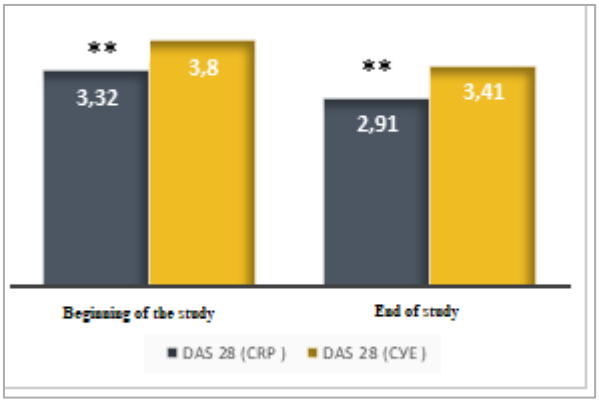


Fig. 17. Mean values of DAS28 (ESR) and DAS28 (CRP) at the beginning and end of the study period.

**Paired Sample T-Test was used to determine whether the mean difference between the two variants of DAS28 was a statistically significant difference. Significance level for rejection of the null hypothesis - p <0.05.

The mean DAS28 (CRP) values are significantly lower than the DAS28 (ESR) averages. The difference between the mean values of the two variants of DAS28 was a statistically significant difference both at the beginning of the study (MD = 0.48, 95% CI 0.40-0.55) (p <0.001) and at the end (MD = 0.51, 95% CI 0.44 -0.57) (p <0.001) (Fig. 17).

At the beginning of the study period, according to DAS28 (CRP), the goal of biological treatment was achieved in 45.6% of patients, whereas according to DAS28 (CUE) it was achieved only in 18.4% of patients (p <0.001) (Table 10, Fig. 18). The same trend is observed at the end of the study. Patients in remission or low disease activity according to DAS28 (CRP) were 66% of all patients, whereas according to DAS28 (ESR) only 39% of them achieved this treatment goal (p <0.001) (Table 10)

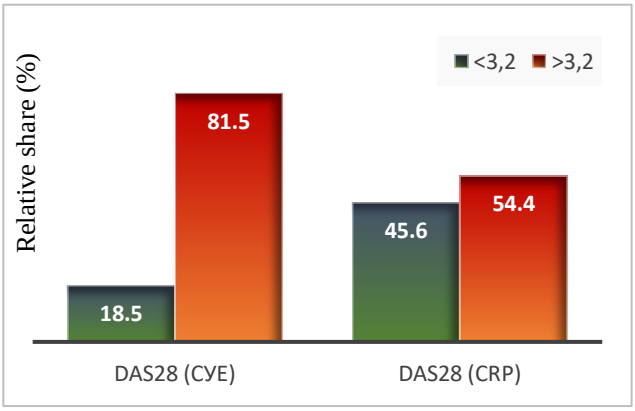


Fig.18. Relative share of DAS28 (CRP) and DAS28 (CEE) scores. Legend: <3.2-low activity and remission> 3.2 moderate and high activity at the beginning of the study.

Analysis of the combined indicators for evaluating the activity of RA depending on the concomitant CVD.

When examining the activity of RA depending on the presence of CVD, it was found that the mean values of the two variants of DAS28 were significantly higher in CVD patients throughout the analysis period. They decreased statistically significantly over the study period but remained higher than those in patients without CVD. The relative share of patients in remission and low disease activity is significantly lower in patients with CVD (Table 11).

Tab. 11. Evaluation of RA activity, during treatment with biological agents, in patients with and without CVD.

Activity Indicators	**RA/CVD (+/+) n=120**					**RA/CVD (+/-) n=75**					**- p -**	**- p -**
	0 m.		12 m		- p -	0 m.		12 m		- p -	CVD+/- 0 m.	CVD+/- 12 m.
	-n-	[%]	-n-	[%]		-n-	[%]	-n-	[%]			
DAS 28 ESR) Mean±SD (range)	3.92±0.81 (1.7-6.06)		3.59 ± 0.71 (2-6)		0.001	3.61±0.76 (1.7-6.06)		3.15± 0.71 (2-6)		< 0.001	0.001	< 0.001
Remission	7	5.83	8	6.67	0.001	5	6.49	16	21.33	< 0.001	0.001	<0.001
Low activity	9	7.50	27	22.50		21	27.27	26	34.67			
Moderate activity	93	77.50	83	69.17		49	63.64	32	42.67			
High activity	11	9.17	2	1.67		2	2.60	1	1.33			
Total	120	100	120	100		77	100	75	100			
DAS 28 (CRP) Mean±SD (range)	3.46 ± 0.67 (2-7)		3.06 ± 0.56 (1-5)		< 0.001	3.11 ± 0.58 (2-5)		2.69±0.59 (1 -6)		< 0.001	<0.001	< 0.001
Remission	8	6.67	23	19.17	< 0.001	15	19.48	39	52.00	< 0.001	0.01	<0.001
Low activity	36	30.00	47	39.17		30	38.96	25	33.33			
Moderate activity	73	60.83	49	40.83		32	41.56	10	13.33			
High activity	3	2.50	1	0.83		0	0.00	1	1.33			
Total	120	100	120	100		77.00	100	75.0	100			

Instantaneous RA activity in patients with and without CVD

DAS 28 (ESR)

The activity of RA, calculated and presented with a mean DAS 28 (ESR) in patients with RA with and without CVD differs significantly. Both at baseline and at the end of the observation

period, the mean DAS 28 (ESR) was higher in CVD patients (3.92±0.81 vs 3.61±0.76 at baseline (p=0.009)) (3.59±0.71 vs 3.15±0.71 at the end (p=0.009)) (fig.19)

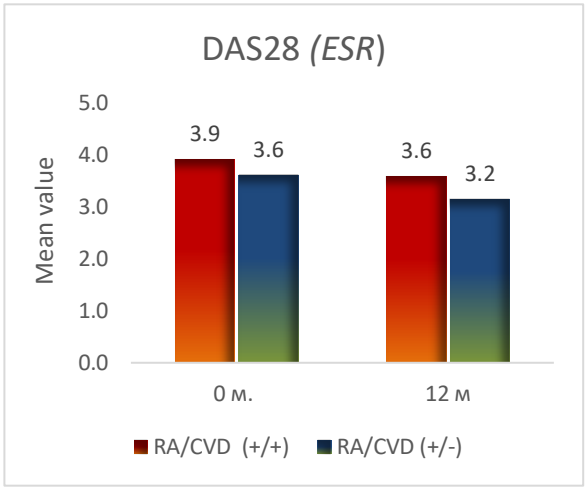


Fig. 19. Change in mean DAS 28 (ESR) during the 12-month biological treatment period in patients with and without CVD.

Significantly higher proportion of patients with CVD have moderate and high RA activity compared with non-CVD patients at the beginning and end of the study (86.7% vs 66.2% at baseline p=0.001), (70.9% vs 44 % at the end p=0.001).

They have not achieved the goal of treatment. Patients with CVD with an average RA activity above 3.2 presented by DAS 28 (ESR) were more than 2/3 of the cases (Fig. 20).

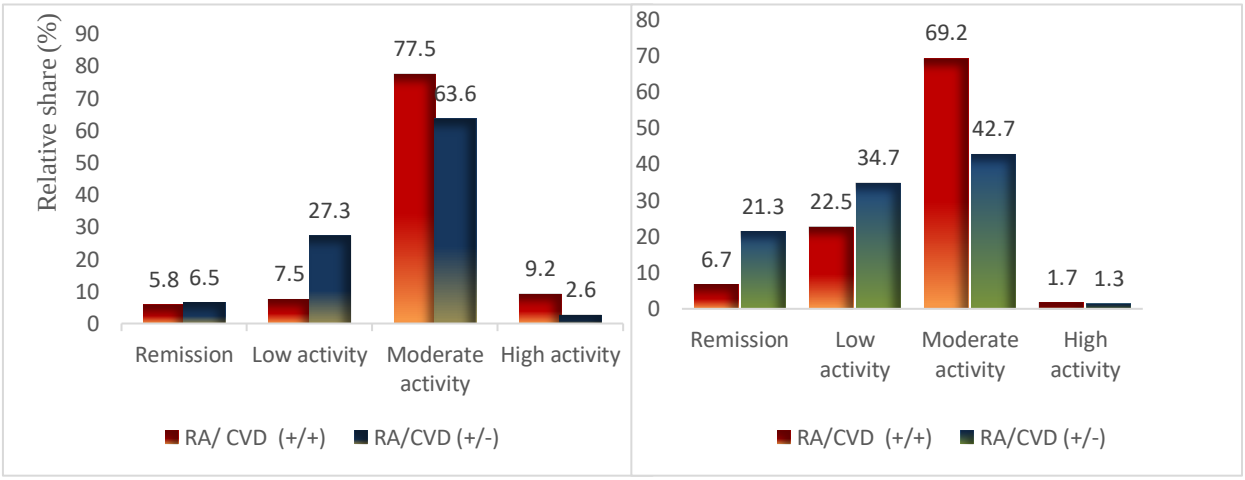


Fig.20. Relative proportion of patients in remission, low, moderate and high RA activity, assessed by DAS 28(ESR), in patients with or without CVD, at the beginning of the study (left panel) an at the end of the study (right panel).

DAS 28 (CRP)

The activity of RA, calculated and presented with average DAS28(CRP) in patients with RA with or without CVD differs significantly. Both at the beginning and at the end of the observation period, the average DAS28(CRP) in patients with CVD was higher than those without CVD, (3.46±0.67 vs 3.11±0.59, p=0.001), (3.06±0.55 vs 2.69±0.58, p<0.001) (fig. 21).

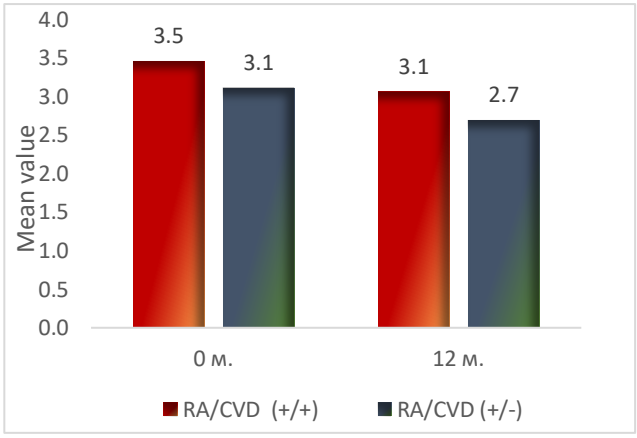


Fig. 21. Change in the mean value of DAS28 (CRP_ for 12 months of biological treatment in patients with and without CVD.

A significantly higher relative proportion of patients with CVD at the beginning of the study had moderate and high RA activity (63.33%) compared to patients without CVD (41.56%) (p=0.001) according to *DAS 28(CRP)* (fig.22). The desired goal of treatment was not achieved in these patients.

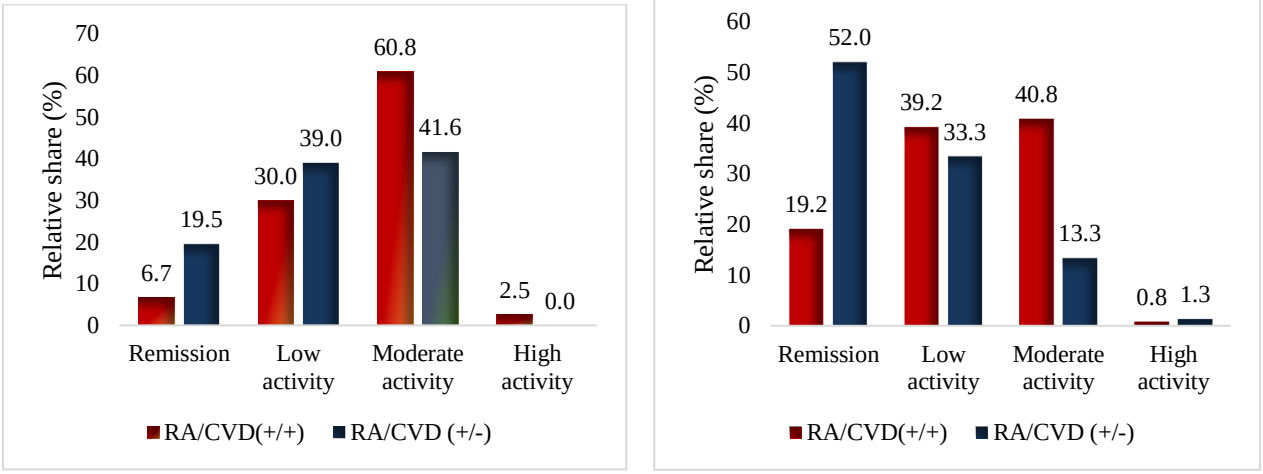


Fig.22. Relative proportion of patients according to RA activity depending on CVD at the beginning of the study (DAS28-CRP), at the beginning of the study (left panel) and at the end of the study (right panel)

Average activity of RA within the study period, expressed by DAS28 (ESR) and DAS28 (CRP), in patients with RA with and without CVD.

Factors that significantly alter the averaged values of the two DAS28 variants. Table. 12 presents the averaged values of DAS28 (ESR) and DAS28 (CRP), representing synchronous one-year activity of RA.

The influence of factors related to demographic characteristics was examined (age>55years, sex, BMI>30kg/m^2, smoking), *characteristics of RA* (duration of RA, X-ray stage, functional class motor insufficiency, averaged values of acute-phase parameters, averaged values of TJC, SJC and VAS*)*, *therapeutic features* (duration of treatment with biological drugs, biological monotherapy, treatment with anti-TNFα inhibitors, concomitant treatment with MTX, NSAIDs and CS), as well as the presence of co-morbidities, and in particular the presence of CVD, on the average activity of RA.

The values of the two DAS28 variants are influenced by: smoking, values of ESR and CRP, VAS, treatment with NSAIDs and / or CS, type of biological preparation, presence of concomitant conditions and in particular CVD (Table 12).

Table 12. Sociodemographic, clinical, therapeutic variants and accompanying diseases and average activity of RA within the study period.

Indicators		**Average DAS28 (CRP)**	**p value**	**Average DAS28 (CYE)**	**p value**
		mean±SD (range)		**mean±SD (range)**	
Age [year]	<55 [years]	3.04± 0.51 (2.12–4.36)	NS	3.50± 0.64 (2.29–5.39)	NS
	>55 [years]	3.10± 0.58 (2.04–5.45)		3.61± 0.70 (1.73 –6.21)	
Gender	female	3.07± 0.56 (2.04–5.45)	NS	3.58± 0.68(1.98–6.21)	NS
	male	3.13± 0.52 (2.46–4.31)		3.53± 0.69(1.73–4.96)	
BMI [kg/m^2]	<30 [kg/m2]	3.03 ± 0.57 (2.04-5.45)	NS	3.54 ± 0.69 (1.98-6.21)	NS
	>30 [kg/m2]	3.24 ± 0.49 (2.2-4.31)		3.69 ± 0.66 (1.73-4.84)	
Smokers	No	3.00 ± 0.57(2.04-5.45)	0.003	3.48 ± 0.70 (1.73-6.21)	0.002
	Yes	3.26 ± 0.49(2.28-4.31)		3.80 ± 0.58 (2.39-4.96)	
Duration of RA [years]	<10 [years]	3.10 ±0.56 (2.07-5.45)	NS	3.57 ± 0.72(1.73-6.21)	NS
	>10 [years]	3.06 ± 0.56 (2.04-4.57)		3.59 ± 0.63(1.98-5.39)	NS
Rö-stages	≤ III	3.12 ± 0.58 (2.07-5.45)	NS	3.58 ± 0.73 (1.73-6.21)	NS
	IV	3.03 ± 0.52 (2.04-4.49)		3.56 ± 0.59 (2.07-5.19)	NS
Functional class	II	3.33 ± 0.57 (2.07-5.45)	NS	3.60 ± 0.74 (1.73-6.21)	NS
	III	3.01 ± 0.54 (2.04-4.57)		3.55 ± 0.60 (2.07-5.19)	NS
Average ESR [mm / h]	< 20 [mm/h]	2.94 ± 0.49 (2.04-4.57)	0.000	3.21 ± 0.51 (1.73-4.45)	0.000
	>20[m/h]	3.26 ± 0.59 (2.08-5.45)		4.04 ± 0.58(2.07-6.21)	
Average CRP [mg / L]	< 3 [mg/L]	2.66 ± 0.34 (2.07-3.64)	0.000	3.31 ±0.55 (1.98-4.64)	0.000
	> 3 [mg/L]	3.31 ±0.52 (2.04-3.64)		3.72 ± 0.70 (1.73-6.21)	
Average TJC [n]	≤ 1	3.18 ± 0.64 (2.46-4.40)	NS	3.76 ± 0.84 (2.83-5.19)	NS

	≥2	3.08 ± 0.56 (2.04-5.45)		3.76 ± 0.84 (2.83-5.19)	
Average SJC [n]	≤ 1	3.05 ± 0.53 (2.04-4.49)	NS	3.53 ± 0.66 (1.73-5.39)	NS
	≥2	3.25 ± 0.69 (2.12-5.45)		3.81 ± 0.73 (2.31-6.21)	
Average VAS [mm]	< 30 [mm]	2.96 ± 0.55(2.04-4.49)	0.036	3.51± 0.68(1.73-5.19)	NS
	≥ 30 [mm]	3.14 ± 0.56 (2.12-5.45)		3.61 ± 0.68 (2.07-6.21)	
Duration of bDMARDs [year]	< 3 [years]	3.2 ± 0.65 (2.07-5.45)	0.038	3.67 ± 0.75 (2.34-6.21)	NS
	> 3 [years]	3.02 ± 0.5 (2.04-4.49)		3.53 ± 0.64 (1.73-5.39)	
Treatment with Methotrexate	Yes	3.19 ± 0.62 (2.15-5.45)	0.02	3.69 ± 0.79 (1.98-6.21)	NS
	No	3.00 ± 0.51 (2.04-4.49)		3.51 ± 0.60 (1.73-4.96)	
Treatment with NSAIDs	No	2.99 ± 0.52 (2.07-4.40)	0.010	3.48 ± 0.64 (1.73-5.19)	0.023
	Yes	3.20 ± 0.60 (2.04-5.45)		3.69 ± 0.72 (1.98-6.21)	
Treatment with CS	No	3.02 ± 0.53 (2.07-4.31)	NS	3.47 ± 0.65 (2.07-4.97)	NS
	Yes	3.19 ± 0.58 (2.04-5.45)		3.63 ± 0.70 (1.73-6.21)	
Monotherapy with biological agents	No	3.14 ± 0.56 (2.04-5.45)	0.04	3.64 ± 0.70 (1.73-6.21)	0.032
	Yes	2.96 ± 0.55 (2.07-4.31)		3.42 ± 0.63 (2.31-4.97)	
Anti-TNFα inhibitors	No	3.04 ± 0.55 (2.04-4.57)	NS	3.45 ± 0.65 (1.73-4.96)	0.024
	Yes	3.12 ± 0.57 (2.07-5.45)		3.67± 0.69 (2.07-6.21)	
Concomitant diseases	No	3.04 ± 0.54 (2.07-5.45)	<0.001	3.45± 0.67 (1.98-6.21)	0.003
	Yes	3.11 ± 0.54 (2.04-4.57)		3.67± 0.67 (1.73-5.39)	
CVD	No	2.86 ± 0.52 (2.07-5.45)	<0.001	3.35± 0.64 (1.98-6.21)	<0.001
	Yes	3.21 ± 0.54 (2.04-4.57)		3.70± 0.67 (1.73-5.39)	

Legend: Legend: DAS disease activity score, SD standard deviation, BMI body mass index, RA-rheumatoid arthritis, Rö-X-ray stage, ESR-erythrocyte sedimentation rate, CRP-C - reactive protein, BBS-number of painful joints, BOS number of swelling joints, VAS-visual analog scale, bDMARDs-biological disease agents, NSAIDs-nonsteroidal anti-inflammatory agents, CS-corticosteroids, TNF-tumor necrosis factor, CVD-cardiovascular diseases. * - Independent Samples Test, significance level for rejection of null hypothesis p <0.05. The lines marked in gray show significant differences.

Patients with concomitant diseases, and in particular CVD patients, have significantly greater value for both DAS28 variants.

Table 13. Sociodemographic, clinical indicators, therapeutic options and concomitant diseases and average activity of RA <3.2.

Indicators	MD (95%CI *	DAS28 (CRP)				p value	DAS28 (CУE)				p value
		<3.2		>3.2			<3.2		>3.2		
		[n]	[%]	[n]	[%]		[n]	[%]	[n]	[%]	
Age[years]		-0.31(-3.4-2.22)				NS	3.60(1.8-7.02)				0.039
Age >55 [years.]	Yes‡	80	67.8	52	67.5	NS	36	62.1	97	69.8	NS
Gender	male	16	55.2	13	44.8	NS	21	72.4	8	27.6	NS
Weight [kg]		5.75(0.59-10.92)				0.017	2.64(-1.43-8.97)				NS

Indicators	MD (95%CI *)	DAS28 (CRP)				p value	DAS28 (CYE)				p value
		<3.2		>3.2			<3.2		>3.2		
		[n]	[%]	[n]	[%]		[n]	[%]	[n]	[%]	
BMI [kg/m^2]		1.45(-0.15-3.06)				NS	0.99(-0.65-2.64)				NS
Smokers	Yes	29	48.3	31	51.6	0.02	9	15.0	51	85.0	0.003
Duration of RA [years.]		0.59(-3.36-1.93)				NS	0.32(-2.50-3.15)				NS
Rö stage	II	36	53.7	31	46.3	NS	40	33.3	26	34.7	NS
	III	34	59.7	23	40.4		30	25	28	37.3	
	IV	48	67.6	23	32.4		50	41.7	21	28	
Functional class	II	59	55.1	48	44.9	NS	32	29.4	77	70.6	NS
	III	59	67	29	33		29	29.5	62	70.5	
Average ESR [mm / h]		7.79(3.38-12.19)				<0.001	14.5(10.4-18.59)				<0.001
Average CRP [mg / L]		5.97 (4.09-7.84)				<0.001	2.58 (0.73-4.43)				0.006
Average TJC		0.81 (0.33-1.28)				0.001	0.91 (0.43-1.39)				<0.001
Average SJC		0.13 (-0.19-0.46)				NS	0.16 (-0.16-0.50)				NS
Average VAS [mm]		2.60 (0.29-4.92)				0.027	2.20 (-0.27-4.68)				NS
Duration of bDMARDs [years.]		-0.32 (-0.93-0.27)				NS	0.26(-0.37-0.91)				NS
Treatment with Methotrexate	Yes	81	66.4	41	33.6	0.03	39	32	83	68.0	NS
Treatment with NSAIDs	Yes	57	47.5	28	37.3	NS	57	47.5	28	37.3	NS
Treatment with CS	Yes	63	57.8	46	42.2	NS	27	24.5	83	75.5	NS
Monotherapy with biological agents	Yes	24	40.7	35	59.3	0.024	62	59.0	43	41.0	NS
Anti-TNFα inhibitors	Yes	62	59.0	43	41.0	NS	28	29.4	79	73.8	NS
Concomitant diseases	No	48	80.0	12	20	<0.001	27	45.0	33	55.0	0.002
CVD	No	58	77.3	17	22.7	<0.001	34	44.2	43	55.8	<0.001

Legend: * - Independent Samples Test; MD-mean difference, CI - confidence interval, significance level for rejection of null hypothesis p <0.05; ‡ - $\chi 2$ significance level for rejection of the null hypothesis p <0.05. The lines marked in gray show significant differences.

Patients with less than 3.2 DAS28 (CRP) had a lower body weight, a lower relative proportion are smokers, a lower average ESR and CRP value, a significantly lower number of painful joints, a better evaluation. according to VAS, a larger relative share of them take MTX, a smaller relative share of them perform monotherapy with biological agents, and a significantly smaller proportion of them have concomitant diseases and in particular CVD (Table 13).

Patients with DAS28 (ESR) <3.2 are significantly younger, only 15% were smokers, had significantly lower ESR values throughout the study period, lower CRP, and fewer painful joints. No significant difference was found in VAS values and the number of surrounding joints. A significantly smaller proportion of patients have concomitant diseases and in particular CVD.

Age is a factor affecting DAS28 (ESR) but not DAS28 (CRP), whereas body weight is associated with DAS28 (CRP) but not DAS28 (ESR). MTX administration and biological monotherapy have an effect on DAS28 (CRP) but not DAS28 (ESR). Values of VAS significantly influence the assessment of DAS28 (CRP) but not DAS28 (ESR).

Both variants of DAS28 are significantly influenced by the presence of concomitant diseases and in particular CVD.

CVD and average values of the components included in DAS28

Patients with CVD had significantly higher average values of CRP ($p < 0.001$) and ESR ($p = 0.031$) (Fig. 23) compared to patients without CVD within the study period. No significant difference was observed in the averaged values of the subjective and objective indicators forming the clinical part of the nucleus of DAS28 ($p > 0.05$) (Table 14).

Table 14. Average clinical and laboratory parameters included in the core of DAS28

Indicators	**RA /CVD (+/+)[n=120]**	**RA /CVD (+/-)[n=75]**	
	mean±SD(range)	**mean±SD(range)**	p value*
CRP [mg/L]	6.41 ± 5.78 (0.12-39.86)	3.86 ± 6.27 (0.14-51.04)	<0.001
ESR [mm/h]	23.95 ± 15.02 (2.67-96)	19.31 ± 14.02 (3.67-78.33)	0.031
TJC	3.39 ± 1.62 (0.33-10.00)	3.26 ± 1.61 (0.67-8.67)	NS
SJC	0.53 ± 1.01 (0.00-4.00)	0.50 ± 1.17 (0.00-8.00)	NS
VAS[0-100mm]	34.01 ± 8.20 (20-56.67)	33.09 ± 7.93 (18.33-53.33)	NS

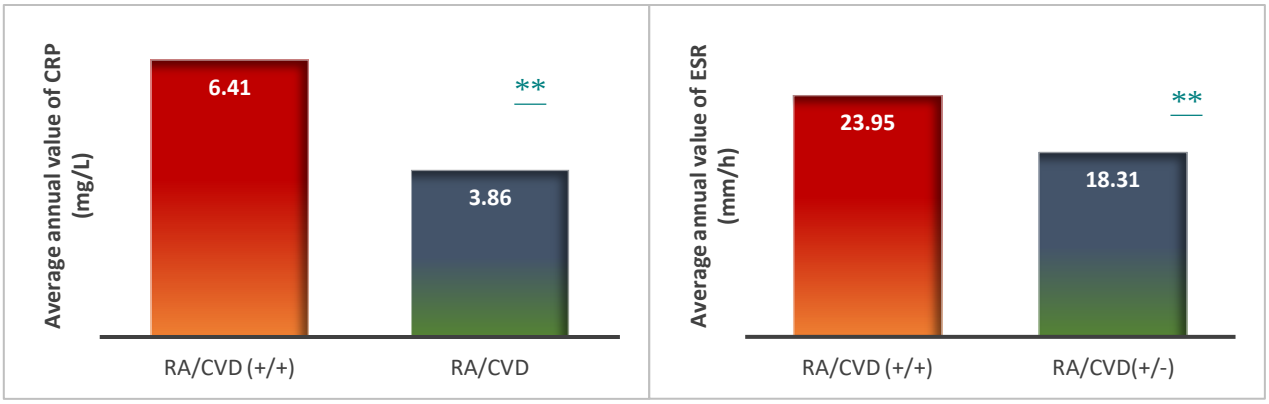


*Fig. 23. Averaged CRP (mg / L) and ESR (mm) over a one-year period in patients with RA with and without CVD. Legend: ** - p <0.001. In the left panel - CRP, in the right panel - ESR.*

The tables present the averaged values of the two variants of DAS28 in patients with and without CVD (Table 14) and for different CVD, compared with patients without CVD (Table 15).

The average RA activity over the one-year study period was significantly higher in patients with CVD compared with patients without CVD, expressed with both variants of DAS28 ($p < 0.05$) and significantly above the target value of 3.2 expressed by DAS28 (ESR) ($p < 0.001$) (Table 14, Figure 24).

Table 14. Average activity of RA for one year, represented by the two DAS28 variants

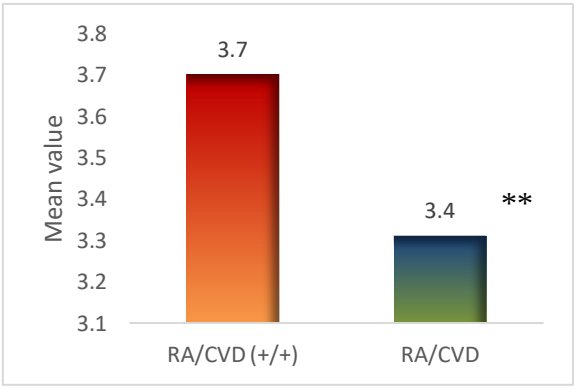
Indicators	**RA/CVD (+/+)**				**RA/CVD (+/-)**			**p value *-**
Average activity of RA		[n]	[%]	p value	[n]	[%]	p value‡	
(DAS 28 CVE)	Mean±SD (range)*	3.70±0.66 (1.73-5.39)			3.39±0.66 (1.98-6.21)			<0.001
Remission		9	7.50	0.001*	6	8.00	<0.001	0.001
Low activity		15	12.50		28	37.33		
Moderate activity		94	78.33		40	53.33		
High activity		2	1.67		1	1.33		
(DAS 28 CRP)	Mean±SD (range)*	3.21±0.53 (2.04-4.57)			2.88±0.53 (2.07-5.45)			0.002
Remission		16	13.33	<0.001	28	37.33	<0.001	<0.001
Low activity		44	36.67		30	40.00		
Moderate activity		60	50.00		16	21.33		
High activity		0	0.00		1	1.33		

Legend: RA- rheumatoid arthritis, CVD-cardiovascular disease, DAS- disease activity score28, CRP-C reactive protein, ESR-erythrocyte sedimentation rate, *- Independent Samples Test; SD-standard deviation, significance level for rejecting the null hypothesis p <0.05; ‡- $\chi 2$ significance lever for rejecting the null hypothesis p<0.05

Table 15. Average activity of DAS28 over a twelve-month study period in CVD

CVD	Average DAS28 (12 months)			
	DAS28(ESR) mean ± SD (min, max)	p value**	DAS28(CRP) mean ± SD (min, max)	p value**
RA without CVD	**3.35±0.63(1.98-6.21)**		**2.86±0.52(2.07-5.45)**	
RA with HTN	3.71±0.67(2.04-5.39)	<0.001‡	3.19±0.57(2.04-4.57)	<0.001‡
RA with IHD	3.73±0.61(1.73-4.8)	0.001‡	3.30±0.41(2.47-4.49)	<0.001‡
RA with CVA	3.60±0.77(2.39-4.88)	0.19‡	3.16±0.53(2.14-4.03)	0.027‡
RA with HF	3.38	0.5	3.09	0.63

Legend: DAS28- disease activity score, CRP- C-reactive protein, ESR – Erythrocyte Sedimentation Rate, CVD-cardiovascular disease, HTN- hypertension, IHD- ischemic heart disease, CVA- cerebrovascular accident, HF- heart failure,** ANOVA, Kruskal Wallis Test, ‡-Mann-Whitney U-between DAS28 values in patients with and without CVD, significance level for rejecting the null hypothesis- p<0.05. *The DAS28 value in patients without CVD was considered as a reference for the study.*



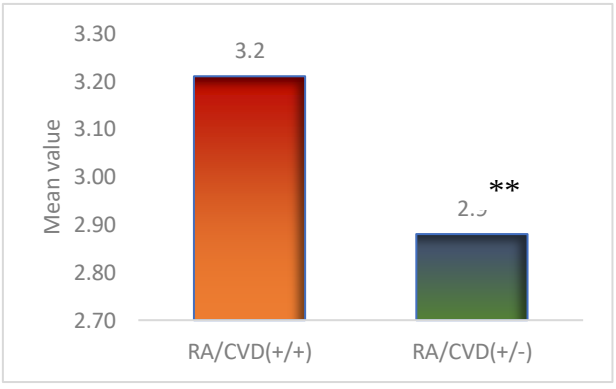


Fig. 24 *Average RA activity (12 months) in patients with and without CVD, expressed by DAS28(ESR) (left) and DAS28(CRP) (right) p<0.05*

RA patients with HTN, IHD and CVA had higher average activity within the study period, expressed by the two DAS28 variants (Table15, fig. 25) (p<0.05

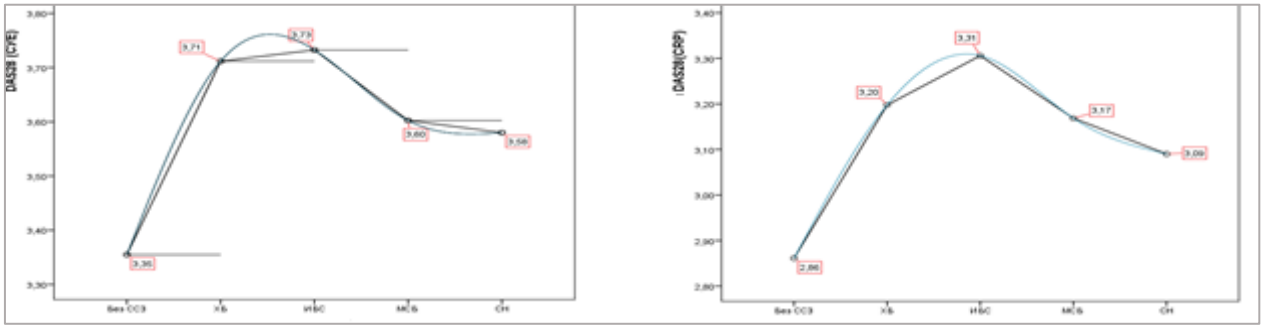


Fig. 25 Distribution of DAS28 values according to the presence of CVDs and their type. Legend: Left -DAS28 (ESR), right DAS28 (CRP).

3. *Analysis of the dependence and degree of overlap between the two DAS28 variants.*

There is a significant discrepancy between the estimates of DAS28 (CRP) and DAS28 (ESR) classifying patients in remission, low, moderate and high activity.

Rated with DAS28 (CRP), a higher relative proportion of patients present themselves as low-activity patients (DAS28 (CRP) <3.2 - 60.51 %. The same patients, for the same period, the same RA activity calculated by DAS28 (ESR) are presented as moderate and high activity. (70.26%) (p<0.001) (Table 16) (fig.26).

Table 16. RA activity presented in synchrony with the two DAS28 variants

Indicators		Average activity represented by DAS28 (ESR)		
		Moderate and High activity (n)	Low activity and Remission(n)	Total(n)
Average activity represented by DAS28(CRP)	Moderate and High activity(n)	74	3	77
	Low activity and Remission(n)	63	55	118
	Total(n)	137	58	195

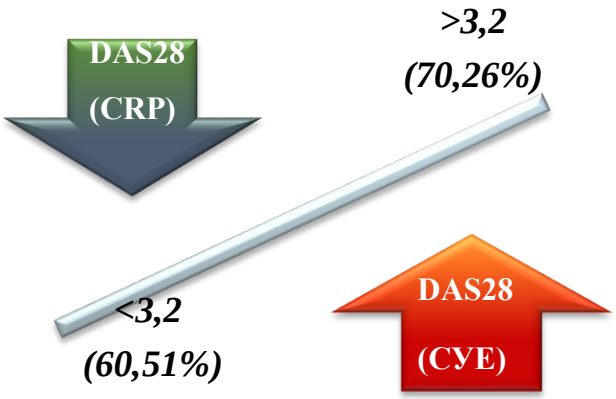


Fig.26. Presentation of the average one-year activity of RA over the study period, using the two variants of DAS28 (DAS28 (CRP) on the left and DAS28 (ESR) on the right)

Significant differences are found between the scores expressed by the two most commonly used indexes in daily clinical practice (p<0.001) (table16.). According to DAS28 (ESR) only 15 patients (7.69 %) were in remission throughout the study period, whereas according to DAS28 (CRP) the patients in remission were 44 (22.56 %) (p<0.001). Similar discrepancies in the determination of one-year RA activity are also found for low, moderate and high activity rates. (p <0.001).

When comparing the momentary activity of RA at the beginning and at 12 months, a similar discrepancy between the estimates of the two variants of DAS28 was also found. This low degree of overlap between the two assessments is not affected by the type of biological product. (Table 17).

Table 17 Proportion of discrepancy, correlation and level of agreement between the two DAS28 variants.

All patients (N=195)	Proportion of <3.2 [n (%)]		PD n (%)	ρ*	K ▼	p value ‡
	DAS28(CYE)	DAS28(CRP)	DAS28(CYE) vs (CRP)			
In the beginning	36 (18.4)	89 (45.6)	65(33.3)	0.361	0.296	<0.001
At the end	79 (40.51)	136 (69.7)	63(32.3)	0.481	0.405	<0.001
Non-anti-TNFα inhibitors (n=90) n (%)						
In the beginning	24 (26.6)	42(46.6)	28(14.3)	0.393	0.358	0.001
At the end	41 (45.5)	62 (68.8)	69 (35.4)	0.517	0.462	<0.001
Anti-TNFα inhibitors (n=105) n (%)						
In the beginning	12 (11.4)	47(44.8)	37(18.9)	0.34	0.235	<0.001

All patients (N=195)	Proportion of <3.2 [n (%)]		PD n (%)	ρ*	K ▼	p value ‡
	DAS28(CYE)	DAS28(CRP)	DAS28(CYE) vs (CRP)			
At the end	38 (36.2)	74 (70.4)	39(20.2)	0.453	0.361	<0.001
‡ McNemar's Test, *Spearman's rank correlation (ρ coefficient), ▼Kappa statistic						

Legend: PD- proportion of discordance, DAS28(ESR)- Disease Activity Score28 with Erythrocyte Sedimentation Rate, DAS28(CRP) - Disease Activity Score28 with C-reactive protein, TNFα- tumor necrosis factor α, Remission and low disease activity ≤3.2;, ρ-coefficient of correlation, κ coefficient-kappa coefficient of agreement between two measurements, level of significance p<0.05.

The correlation between the averages of the two indicators is strongly proportional (r> 0.700, p <0.001), while the correlation between their estimates is moderate (ρ = 0.340 ÷ 0.517, p <0.001).The level of agreement between the estimates of the two DAS28 variants is low (k <0.300, p <0.001). A disproportion was found in the range of 14.3% to 35.4% between the two evaluation options (Table 17).

The Bland-Altman graph comparing the average of the two variants of DAS28 over the one-year study period shows that the mean difference between the values of DAS28 (ESR) and DAS28 (CRP) is 0.49 (95% CI 0.42-0.55) (p < 0.001) (Fig. 27).

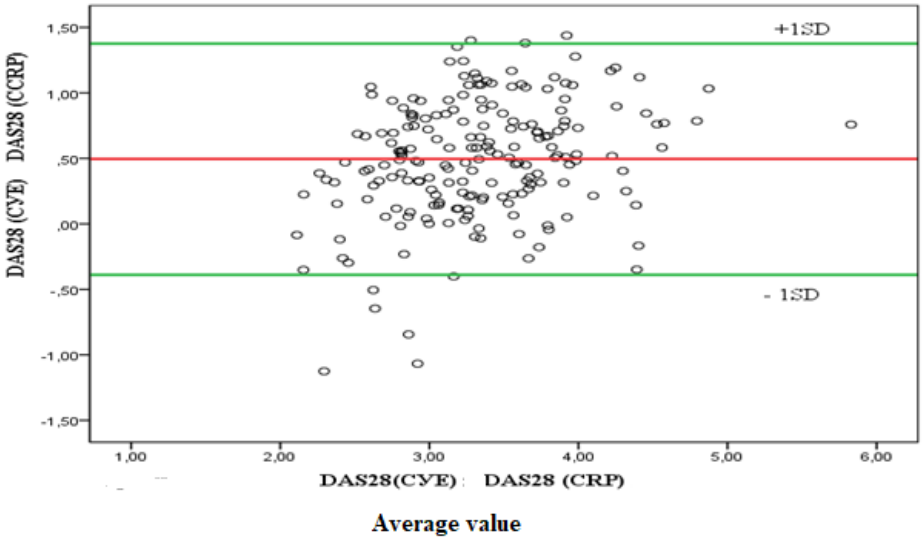


Fig. 27. Bland-Altman graph comparing the average of the two variants of DAS28 for the one-year study period calculated simultaneously.

4. Determination of DAS28 (CRP) thresholds, better in line with those of DAS28 (ESR)

The combination of factors: ESR [mm / h] and TJC were statistically significant for DAS28 (ESR) (F = 141.06, p <0.001). The adjusted R2 is = 0.590. 59.00% of changes in the value of DAS28 (ESA) are determined by a change in these two indicators. SJC and VAS were excluded from the model (p> 0.05).

Of these 59.00% of the value of DAS28 (ESR) - 54.3% are determined by the value of ESR and only 4.7% of TJC.

The combination of factors: CRP [mg / L] and number of painful joints was statistically significant for DAS28 (CRP) (F = 85.57, p <0.001). Adjusted R2 is = 0.466, 46.60% of the changes in the value of the average activity of RA expressed by DAS28 (CRP) are determined by a change in these two indicators. The number of swollen joints and VAS were excluded from the model (p> 0.05). Of these 46.60% -42.7% are determined by the value of CRP and only 3.89% by painful joints.

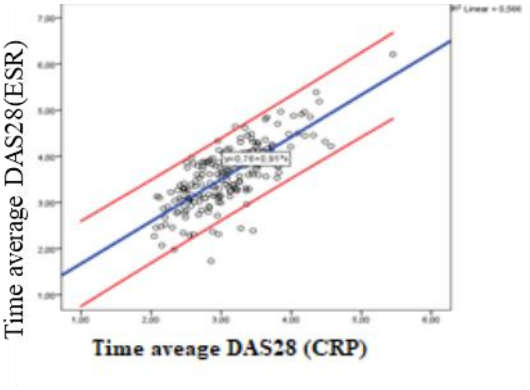


Fig. 28 Linear regression between the two variants of DAS28 to study and represent the average activity of RA.

There was a statistically significant relationship between the two variants of DAS28 (ESR and CRP) (F = 254.183, p <0.001). The adjusted R^2 is = 0.564. 56.6% of the changes in the average value of DAS28 (ESR) were determined by the change in the average value of DAS28 (CPP) within the study period (Fig.28).

A linear regression model for determining the relationship between the two DAS28 variants is represented by the equation (Fig. 29).

Time average activity (DAS28 ESR) =
0,759+ 0,915* DAS28 (CRP)

Fig. *29. A formula expressing the relationship between the two variants of DAS28.*

Replacing the DAS28 (ESR) formula with commonly accepted, validated remission, low, moderate, and high activity thresholds, new, optimized DAS28 (CRP) thresholds are obtained.

DAS28 (ESR) remission (2,6) = 0.759 + 0.915 * x

При заместване в така получената формула, на DAS28 (СУЕ) със общоприетите, валидирани стойностите на прагове за ремисия, ниска, умерена и висока активност, се получават нови, оптимизирани прагове за DAS28 (CRP).

$$\text{DAS28 (СУЕ) ремисия } (2.6\ ) = 0.759 + 0.915 * X$$

$$x = 2.01$$

x = 2.01 DAS28 (CRP) remission value = 2.01. DAS28 (CRP) values for low, moderate and high activity were obtained. The optimized values of DAS28 (CRP) are presented in Fig. 30

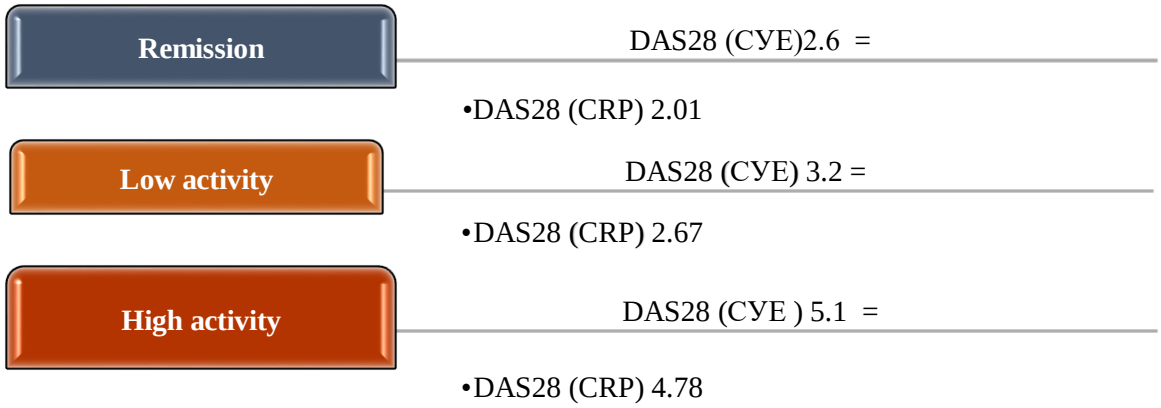


Fig. 30. Optimized remission values, low, moderate and high RA DAS28 (CRP) activity.

5. *Determination of prognostic probability for CVD development*

To investigate CVD-related factors in RA patients, a logistic regression model (MODEL 1) was developed, including:

- *demographic indicators (*age, gender, BMI, smoking*);*
- *characteristic of RA (*duration of RA, X-ray stage and functional class*);*
- *laboratory parameters (*ESR, CRP, hemoglobin, creatinine, ALAT U / L blood sugar, cholesterol, triglycerides*);*

- *Average RA activity during the study period (*DAS28-ESR and DAS28-CRP*);*
- *therapeutic models (*duration of biological treatment, type of biological drug, combination with Methotrexate, combination with corticosteroids, combination with NSAIDs*).*

A statistically significant MODEL-1 (χ 2 = 50.42, p <0.001) is detected with a sensitivity of 59.5% and specificity of 90.9%. In table 18 and figure 31, the main predictors of CVDs identified by model -1, their ORs and 95% CIs are presented.

Table 18 Predictors of CVD in RA patients in the study group.

INDICATOR	OR	95% C.I. for EXP(B)	
		Lower	Upper
Average time activity of RA [DAS28 (CRP) <3.2]	0.182	0.060	0.558
Age [year]	1.064	1.014	1.116
Function. class	3.379	1.280	8.922
Blood glucose [mmol / L]	2.057	1.110	3.812
Total cholesterol [mmol / L]	2.091	1.226	3.568

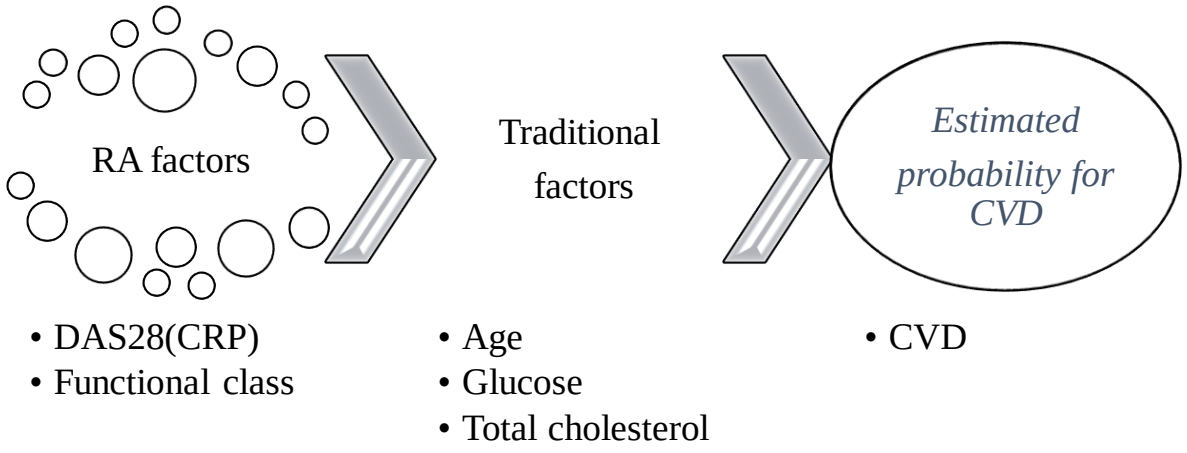


Fig. 31 Factors associated with the risk profile of RA patients with CVD.

The main traditional risk factors that determine the likelihood of CVD in RA patients are age, blood sugar, and total cholesterol. Of these, the highest factor in value is total cholesterol, followed by blood sugar and the lowest value is age.

Of the factors associated with RA, the determinant is DAS28 (CRP) and functional impairment class.

DAS28 (ESR) was not identified as a significant predictor of the prognosis of CVD in the study group (p> 0.05).

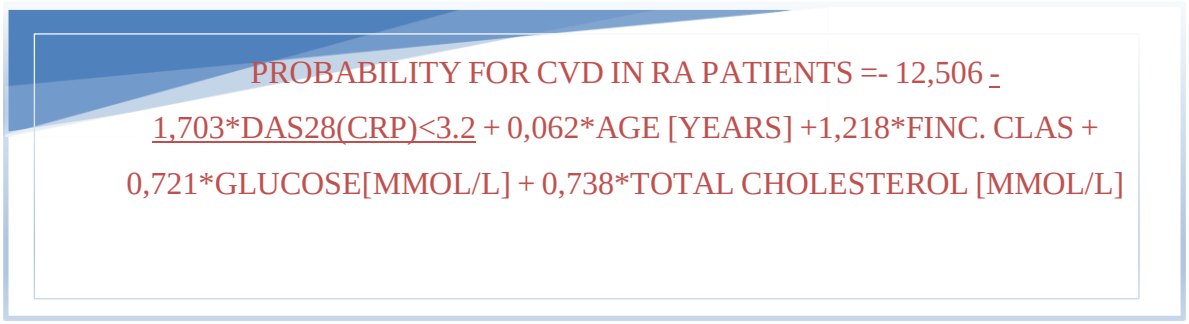


Fig. *32. Model-1 representing the factors determining the probability of CVD in the study group.*

If DAS28 (CRP) values of 0 or 1 (remission / low or moderate / high RA activity) are entered in this formula, functional class motor deficit, age in years, functional class, blood sugar and total cholesterol can be calculated OR value for forecasting CVD probability. Using the formula of Fig. 33, one can determine the prognosis for CVD of each patient or group of RA patients.

$$\frac{Exp\ (B)}{1 + Exp\ (B)}$$

Fig. 33 Formula for calculating the CVD probability through OR. To test the reliability of MODEL 1, MODEL 2 was compiled. The DAS28 (CRP) predictors of CVDs in Model 1 were removed and DAS28 (ESR) plus all other predictors in MODEL 1 were left.

A new statistically significant MODEL-2 ($\chi 2$ = 40.97, p <0.001) is detected with a sensitivity of 50.00% and specificity of 89.1%.

Predictive probability for CVS in model-2 = - 9.777 + 0.055 * Age [yr] + 0.648 * Blood sugar [mmol / L] + 0.714 * Total cholesterol [mmol / L].

Averaged RA activity of 12 m expressed in DAS28 (ESR) <3.2 was not determined as a predictor of CVD.

When in regression MODEL-1 DAS28 (CRP) <3.2 is replaced by an optimized value of DAS28 (CRP) for low disease activity DAS28-CRP <2.67, a different statistically significant MODEL-3 (χ 2 = 36.17, p <0.001) is obtained sensitivity 47.60% and specificity 88.6%.

When examining the risk profile of patients through MODEL 3 with a view to a predictable probability of CVD, DAS28-CRP <2.67 was not recognized as a predictor of CVD development. The factors that remain in the model are not directly related to RA. Traditional risk factors remain - age, blood sugar and total cholesterol (Table 19).

Table 19. Predictors of CVD in RA patients - MODEL 3 (DAS28 CRP <2.67)

Predictor	OR	95% C.I.за EXP(B)	
		Lower	Upper
Age [year]	1.059	1.015	1.105
Blood Sugar [mmol / L]	2.158	1.233	3.777
Total cholesterol [mmol / L]	1.897	1.208	2.978

Once it was determined that DAS28 (CRP) <or> of 3.2 was determined as a predictor of CVD, a logistic regression model was drawn up that included all therapeutic options except DAS28 (CRP) <or> 3.2. A statistically significant MODEL - 4 (χ 2 = 27.24, p <0.001) was detected with a sensitivity of 34.7% and specificity of 91.7% (fig.34).

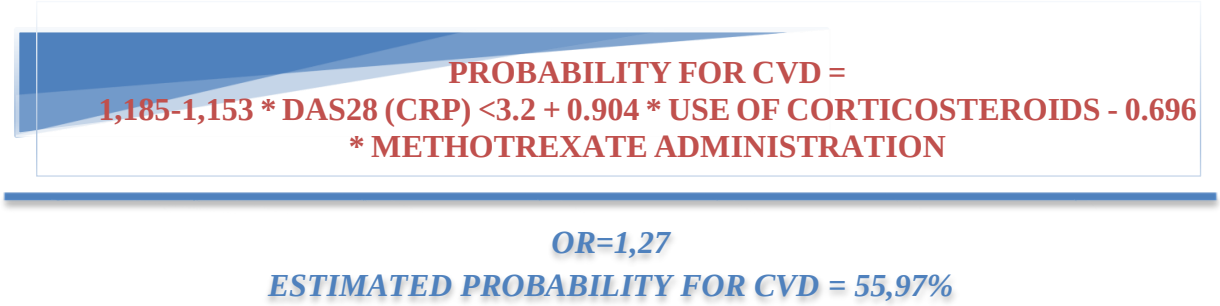


Fig. 34. Estimated probability for CVD-MODEL - 4.

The prognosis for CVD is determined by the activity of RA presented with DAS28 (CRP), corticosteroid treatment, and MTX combination therapy. The activity (<3.2) and the combination of a biological medicine with Methotrexate have a beneficial effect on CVD. The coefficients in front of the factors in the equation show that the significance of DAS28 (CRP) is almost twice as high.

The predicted probability of CVD in the long-term RA patients studied according to this model is 55.97% (Figure 34).

6. *Propose an algorithm to improve the clinical course of RA and reduce the risk of CVD.*

Discontinuation of corticosteroid therapy and replacement with 0 in the equation leads to a change in the predicted probability of an expected development of CVD. DAS28 (CRP) <3.2 and MTX combination therapy had a beneficial effect on the predicted probability of developing CVD (OR = 0.51). The forecast probability for CVD in this case decreases - 33.98%. (Fig. 35).

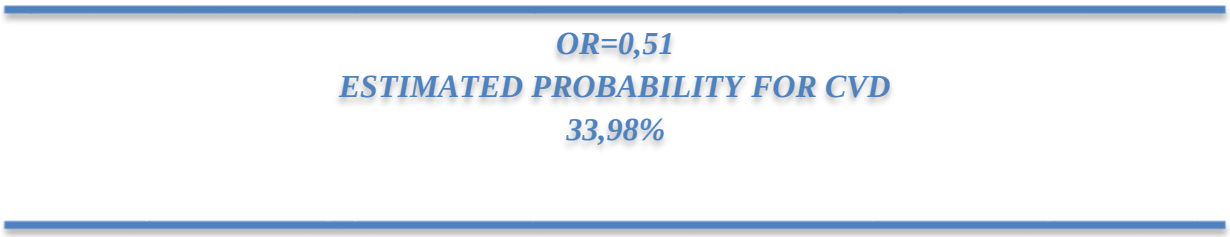


Fig. 35. Estimated probability of CVD development when corticosteroid treatment is discontinued.

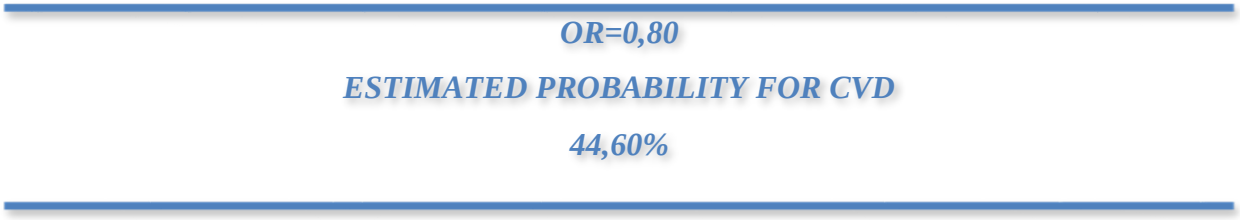
The optimized DAS28 (CRP) threshold for low activity <2.67 alters the statistically significant MODEL - 4. MODEL - 5 is obtained (χ 2 = 24.15, p <0.001). The cardiovascular risk profile in this model was determined by therapeutic behavior (corticosteroid and MTX intake) and averaged RA activity over the study period, expressed by DAS28 (CRP) at a low activity threshold of <2.67. The resulting OR in this model is presented in Table 33.

Table 33. Predictors of CVD using the optimized low disease activity threshold-DAS28 (CRP) <2.67.

Predictor	OR=	95% C.I. за EXP(B)	
		Lower	Upper
Average activity of RA [DAS28- CRP <2.67]	0.332	0.168	0.655
Corticosteroid intake	2.490	1.349	4.596
Combination therapy of biological drugs with MTX	0.498	0.261	0.950

A new formula for calculating the predicted probability of CVD was obtained with a sensitivity of 85% and a specificity of 32.4% (Fig. 35).

Reducing the target value of DAS28 (CRP) by 0.53 points achieves a 11.3% reduction in the predicted CVD probability (from 55.9% to 44.6%) without correcting the other prognostic factors in the model (Fig. 36, 37).



.FIG. 36. *Estimated probability of CVD using optimized DAS28 threshold (CRP) <2.67*

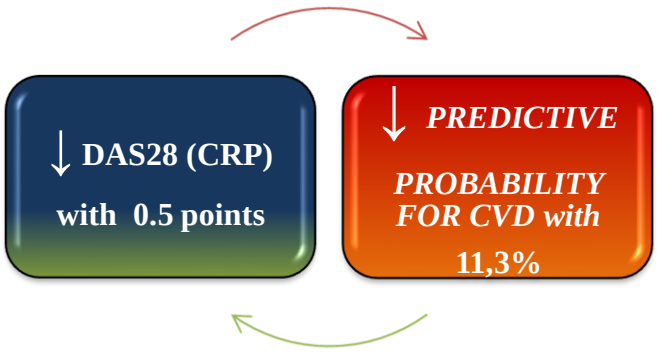


FIG. 37. Relationship between the reduction of the DAS28 target value (CRP) and the change in the predictive probability of CVD.

Optimization of the therapeutic model - combination therapy with Methotrexate and discontinuation of corticosteroid treatment

Optimizing the therapeutic model - combination therapy between biological agents and Methotrexate, discontinuing treatment with corticosteroids at the earliest opportunity and reaching and retaining RA activity below 2.67 for DAS28 (CRP) can lead to a significant reduction in the prognosis for CVD by almost 32 % (FIG. 38, 39)

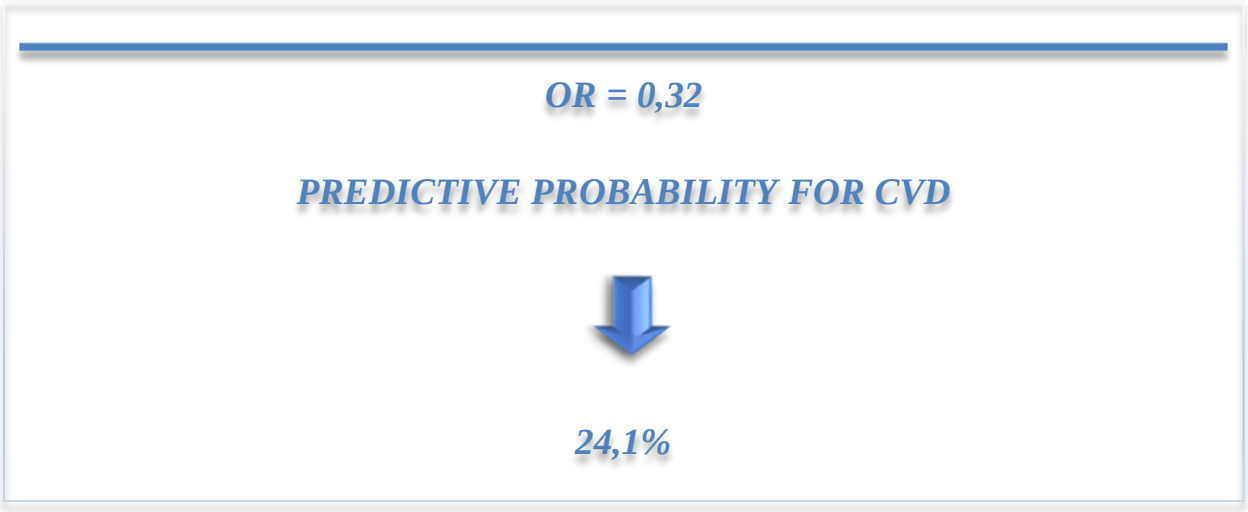


Fig. 38. Prognosis of CVD in optimizing DAS28 (CRP), combination therapy with Methotrexate, and discontinuation of corticosteroid therapy during biological treatment

The benefit to patients of this modern, targeted to specific treatment molecules, as a result of this proposed algorithm, is expected to increase. *(фиг.40)*.

The achievement and retention of low RA activity is expected to further delay the progression of RA. In everyday clinical practice, this would improve the quality of life in these patients. On the other hand, low RA activity, MTX intake and lack of corticosteroid in therapy are expected to have a beneficial effect on accelerated, early atherosclerosis, a major cause of CVD among this group of patients, and an early death factor for them.

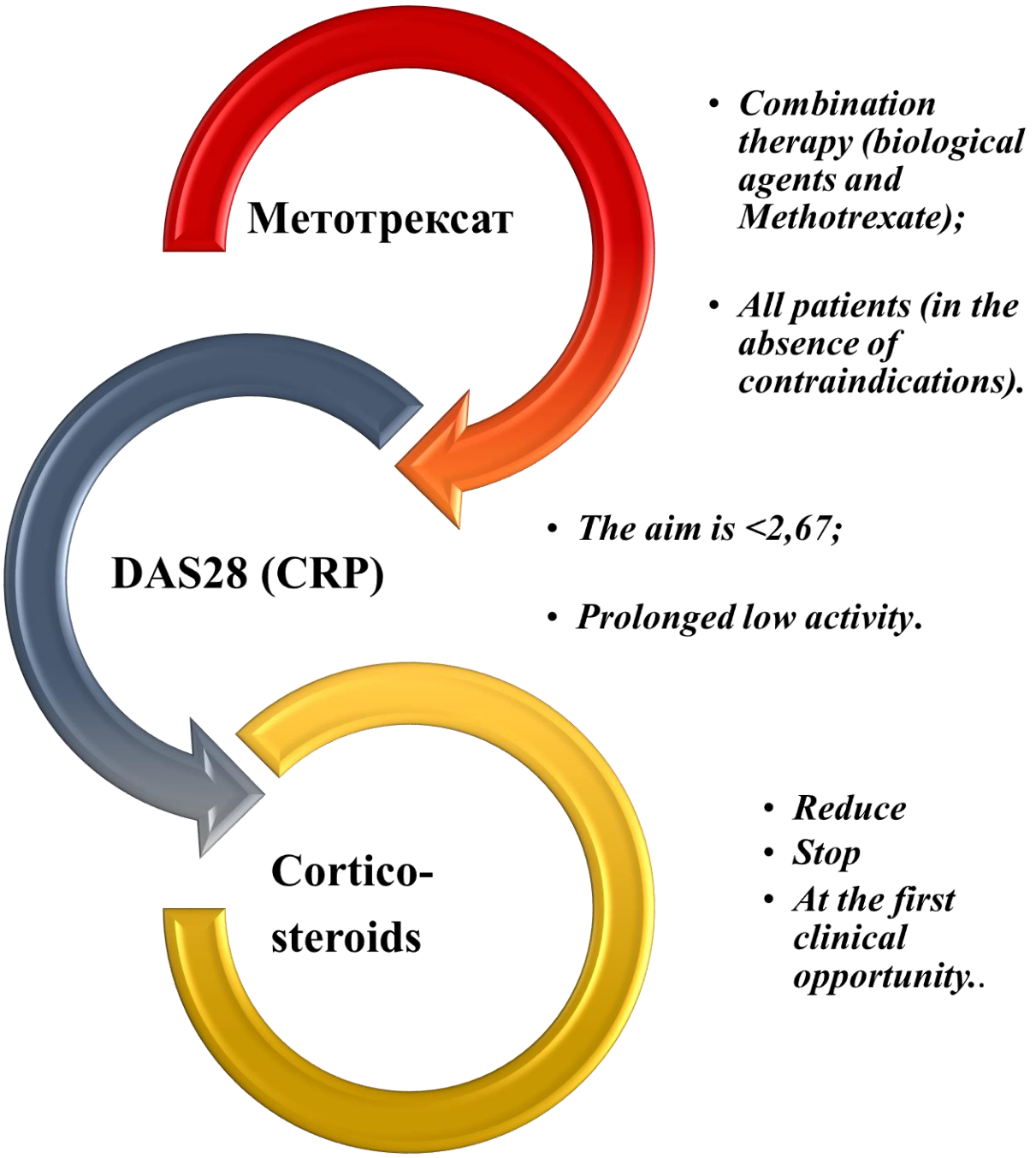


Fig. 39. Algorithm for therapeutic behavior and goal in biological treatment of RA patients with a view to a better clinical course of the disease and a better long-term prognosis for CVD risk

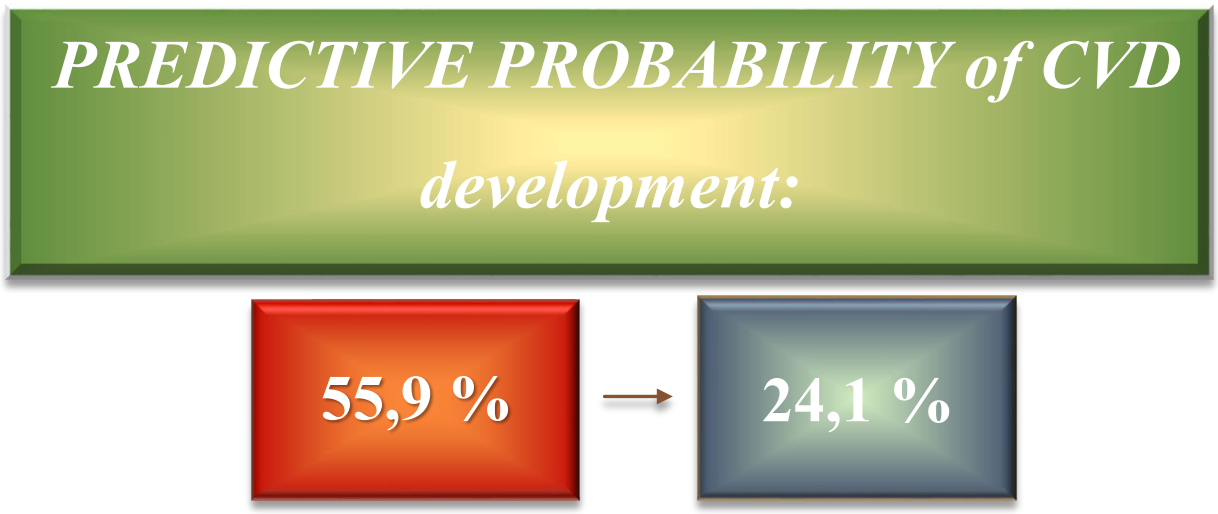


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Fig.40. Change in the predictive probability of CVD as a result of this study.

V. CONCLUSIONS

1. Patients treated with biological agents have a median duration of RA over 10 years, with erosive disease in more than 65% of cases, but with a relatively low proportion of severe functional disability leading to a limitation in daily activity.

2. The highest relative share (61.3%) of concomitant pathology in patients with RA has CVD, the most common of these being arterial hypertension followed by ischemic heart disease.

3. The combination of PA and CVD is characterized by:

- more frequent use of KS therapy (70%)
- less frequent use of MTX
- more painful joints
- higher VAS values
- higher values of DAS28 (ESR and CRP) which despite favorable biological effects remain higher over the entire tracking period

- higher average RA activity over the entire study period presented synchronously with the two variants of DAS28 (ESR) and DAS28 (CRP)

4. In determining the activity of RA during tracking, it is established that:

- average DAS28 activity (ESR) is higher than average DAS28 activity (CRP)

- significant differences in categorization of patients by groups according to activity on the two scales

5. The risk profile for elevated cardiovascular morbidity and mortality in patients with biologically active therapy is dependent on:

- disease activity as determined by DAS28 (CRP) (values <3.2 - more favorable risk profile)

- combination with synthetic agents (MTX) (more favorable risk profile)

- concomitant corticosteroid therapy (worse risk profile)

6. A significant reduction in the estimated probability of CVD development can be achieved by:

  - reduction of the border, categorizing patients in low activity status through DAS28 (CRP) <2.67 (11.3 % reduction in predicted probability)

  - use of average values of the indicator to express background inflammatory activity

  - introduction of MTX into the therapeutic model

  - discontinuation of corticosteroid treatment at the earliest opportunity

VI. CONTRIBUTIONS

CONTRIBUTIONS WITH THEORETICAL CHARACTER:

1. For the first time in Bulgaria, a complete and detailed picture of the activity of Rheumatoid arthritis, in the background of treatment with biological agents, in real clinical practice, in different therapeutic models and according to the presence of CVD is described.

2. An accurate and detailed description of the current state of the problem of premature mortality of RA patients, the causes of death in them, the traditional risk factors, and the factors originating from the nature of RA and its treatment related to this excessive overall mortality have been made.

3. An analysis of the traditional CVD risk factors has been made, combining factors derived from the inflammatory nature of RA and its treatment in real clinical practice.

4. The activity of RA in patients with and without CVD was analyzed and presented in synchrony with two variants of the combined DAS28 indicator. An in-depth, comprehensive and dynamic analysis of the relationships between the assessments of the two DAS28 variants and the impact of CVD on them has been carried out.

CONTRIBUTIONS WITH PRACTICAL APPLIED CHARACTER

1. Available introduction into daily clinical practice of an indicator representing the average activity of RA over a time period:
   - more accurately represent the activity of RA at the time of treatment;
   - better information on the prognosis of patients;
   - momentary effects on laboratory parameters are avoided.
2. Optimized DAS28 (CRP) values are available that can be incorporated into daily clinical practice, with purpose:
   - a more accurate assessment of the residual activity of RA during biological and synthetic treatments;
   -improving the long-term prognosis of patients, taking into account the added cardiovascular risk
3. An algorithm for individual care in RA patients is proposed, with the ultimate goal of improving patient prognosis in two respects:
   - Improved quality of life;
   - Improved life expectancy.

CONTRIBUTIONS WITH ORIGINAL CHARACTER

1. The level of averaged annual activity of RA in patients undergoing biological treatment was investigated as a predictor of CVD probability.

2. Optimized scale for evaluating the activity of RA with DAS28 (CRP).

3. The prognosis of CVD in patients undergoing biological treatment is calculated and an algorithm for its reduction is proposed.

LIMITATIONS OF THE STUDY SHOWING OUTLOOK FOR FUTURE RESEARCH

1. Retrospective study;
2. Incomplete reporting of cardiovascular risk characteristics;
3. Lack of prospective registration of CV incidents;
4. Lack of clinical verification of the proposed prognostic model.

THE CURRENT SCIENTIFIC DEVELOPMENT MAY BE THE BASIS FOR PROSPECTIVE VERIFICATION OF THE PROPOSED MODEL PROPOSED.

VII. PUBLICATIONS RELATING TO DISSERTATION WORK

1. *Dimitrov, Sv., T.Shivacheva, Vl. Kadinov, Our experience with adalimumab in patient with inflammatory joint diseases, Revmatologiia (Bulgaria), 2011 19, 4,53-58*
2. S. Bogdanova, Sv. Dimitrov, S. Hristova, T. Shivacheva, V. Kadinov, AB0860 Impact of treatment with adalimumab on disease activity, work productivity and workday loss in patients with ankylosing spondylitis Annals of the Rheumatic Diseases Jun 2013, 71 (Suppl 3) 687; DOI: 10.1136/annrheumdis-2012-eular.