TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE

Glasilo zaječarske podružnice Srpskog lekarskog društva
The Bulletin of the Zajecar branch of the Serbian Medical Association

Izlazi od 1976.
has been published since 1976.

Godina 2020 *Vol. 45 Broj 1-2*

Year 2020 *Vol. 45 No. 1-2*

YU ISSN 0350-2899

Milorad Mile Antić
Landscape Pejzaž

www.tmg.org.rs *tmglasnik@gmail.com*

TIMOČKI MEDICINSKI GLASNIK

TIMOK MEDICAL GAZETTE

Glasilo zaječarske podružnice Srpskog lekarskog društva **Izlazi od 1976.**
The Bulletin of the Zajecar branch of the Serbian Medical Association **has been published since 1976.**

VLASNIK I IZDAVAČ/OWNER AND PUBLISHER

Srpsko lekarsko društvo, podružnica Zaječar/
Serbian Medical Society, Branch of Zaječar
web adresa/web address: www.sldzajecar.org.rs

ADRESA REDAKCIJE/EDITORIAL OFFICE
Timočki medicinski glasnik
Zdravstveni centar Zaječar
Pedijatrijska služba
Rasadnička bb, 19000 Zaječar

ADRESA ELEKTRONSKE POŠTE/E-MAIL
tmglasnik@gmail.com
dusanbastac@gmail.com

WEB ADRESA/WEB ADDRESS
www.tmg.org.rs

Časopis izlazi četiri puta godišnje./The Journal is published four times per year.

TEKUĆI RAČUN/ CURRENT ACCOUNT
Srpsko lekarsko društvo, podružnica Zaječar 205-167929-22

ŠTAMPA/PRINTED BY
Spasa, Knjaževac

TIRAŽ/CIRCULATION 500 primeraka/500 copies

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд

61
TIMOČKI medicinski glasnik /
glavni i odgovorni urednik Prim Dr Sc med Dušan Bastać; - God. 1, br. 1 (1976)-
- Zaječar : Srpsko lekarsko društvo, podružnica Zaječar, 1976- (Knjaževac : Spasa). - 30 cm

Dostupno i na: http://www.tmg.org.rs. - Tromesečno
ISSN 0350-2899 = Timočki medicinski glasnik
COBISS.SR-ID 5508610

Vol 45 (2020) br. 1-2

TIMOČKI MEDICINSKI GLASNIK

REČ GLAVNOG UREDNIKA ČASOPISA TIMOČKI MEDICINSKI GLASNIK

Reč glavnog urednika o Dr Vukašinu Vuletu Antiću iz Vranja,

Ovaj dvobroj Timočkog Medicinskog Glasnika posvećujemo velikom intelektualcu, kolegi, izvrsnom doktoru, hirurgu, onkologu, istoričaru medicine, predavaču na brojnim medicinskim i istorijskim simpozijumima i kongresima, uključujući Timočke medicinske dane i Simpozijume Medicina u umetnosti, humanisti i entuzijasti Dr Vukašinu Vuletu Antiću iz Vranja.

Moj veliki prijatelj i brat od tetke Vukašin Vule Antić, još kao odličan student Medicinskog fakulteta u Beogradu, počinje da se bavi naučnim radom. Tada smo zajedno napisali dva studentska rada iz oblasti onkologije raka dojke, objavljeni u TMG i prezentirani usmeno na Studentskom kongresu u Crikvenci 1982.

Ispunjava me neizmernom tugom sećanje na njega i dane provedene sa njim, ispunjene entuzijazmom, radošću bavljenja inventivnim naučnim i stručnim radom ali i druženjem i humorom. Imao je nadasve ispunjen, kreativan i kvalitetan život u svakom pogledu, posvećen nauci, knjizi ali i filmskoj umetnosti, posebno animiranom filmu (jedan od osnivača škole animiranog filma u Vranju-ŠAF), te književnosti, muzici i likovnoj umetnosti. Njegov otac Milorad Mile Antić, koji ga je ga je uveo u svet umetnosti, bio je prvi akademski vranjski slikar i vajar (njegove slike su na prvoj i zadnjoj strani ovog dvobroja TMG). Naš dragi Vule je imao kreativan, srećan i ispunjen život. Na njega su se odnosile reči Pabla Nerude:

… lagano umire onaj koji ne putuje, onaj koji ne čita, onaj koji ne sluša muziku, onaj koji ne nalazi zadovoljstvo u sebi, onaj koji ne prihvata pomoć, onaj koji se pretvara u roba navika postavljajući svaki dan ista ograničenja, onaj koji ne menja rutinu, onaj koji ne priča sa ljudima koje ne poznaje....lagano umire onaj koji beži od strasti i njenog vrela emocija, onaj koji ne menja svoj život kad nije zadovoljan, onaj koji se ne želi odreći svoje sigurnosti ... živi danas, učini danas, rizikuj danas, ne dozvoli lagano umiranje, ne zaboravi da budeš srećan.

Vuletova smrt u punom zamahu života je velika tragedija i nenadoknadiv gubitak za njegovu porodicu, prijatelje, rođake i bolesnike koje je uspešno lečio kao vrhunski hirurg, onkolog, lekar i humanista, ne samo hirurški već i toplom reči, sa empatijom. Jedina uteha je, kao što je rekao Ivo Andrić,"da se osećamo čovekom jedino ako stvaramo i volimo" a naš Vule je bio ispunjen i radom i ljubavlju.

Slava mu!

Glavni i odgovorni urednik
Prim Dr Sc Dušan Bastać
28. maj 2020. u Zaječaru

A WORD FROM THE EDITOR-IN-CHIEF OF THE TIMOK MEDICAL GAZETTE

Editor's note on Dr. Vukasin Vule Antic from Vranje,

We dedicate this double issue of the Timok Medical Gazette to the great intellectual, colleague, excellent doctor, surgeon, oncologist, medical historian, lecturer at numerous medical and historical symposia and congresses, including the Timok Medical Days and the Symposiums of Medicine in Art, humanists and enthusiasts Dr. Vukasin Vule Antic .

My great friend and brother from aunt Vukasin Vule Antic, while still an excellent student at the Faculty of Medicine in Belgrade, began to engage in scientific work. Then we wrote together two student papers in the field of breast cancer oncology, published in TMG and presented orally at the Student Congress in Crikvenica in 1982.

I am filled with immeasurable sadness by the memory of him and the days spent with him, filled with enthusiasm, the joy of engaging in inventive scientific and professional work, but also socializing and humor. He had a very fulfilled, creative and quality life in every respect, dedicated to science, books and film art, especially animated film (one of the founders of the school of animated film in Vranje -SAF), and literature, music and fine arts. His father Milorad Mile Antic, who introduced him to the world of art, was the first academic Vranje painter and sculptor (his paintings are on the first and last page of this double issue of TMG). Our dear Vule had a creative, happy and fulfilled life. Pablo Neruda's words referred to him:

…the one who does not travel, the one who does not read, the one who does not listen to music, the one who does not find pleasure in himself, the one who does not accept help, the one who turns into a slave of habit by setting the same restrictions every day, the one who does not change routine , the one who doesn't talk to people he doesn't know .... the one who runs away from passion and its hot emotions, the one who doesn't change his life when he is not satisfied, the one who doesn't want to give up his security ... lives today , do it today, take a risk today, don't let it die easily, don't forget to be happy ….

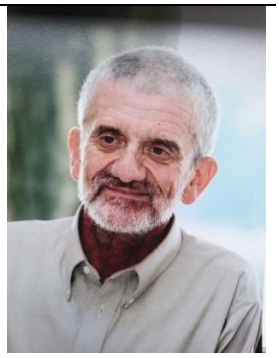
Vule's death in full swing is a great tragedy and an irreparable loss for his family, friends, relatives and patients, whom he successfully treated as a top surgeon, oncologist, doctor and humanist, not only surgically but also warmly, with empathy. The only consolation is, as Ivo Andric said, "to feel human only if we create and love" and our Vule was filled with work and love.

His glory!

Editor in chief
Prim Dr Sc Dusan Bastac
May 28, 2020 in Zajecar

Vol. 45 (2020) No. 1-2

TIMOK MEDICAL GAZETTE



IN MEMORIAM
DR VUKAŠIN M. ANTIĆ
(1958 – 2020)

In the early morning of April 1, 2020, Dr. Vukašin Antić, a well-known surgeon-oncologist from Vranje, a historian of medicine and a great humanist, lost the battle with a serious illness. A man, also known outside the Vranje area, who marked a turbulent and significant time with his work and deeds, both professionally and socially. Gone is the brave individual ready to change and fix the world for the better, committed to science and continuous learning. One extremely rich, versatile person, interested in almost all spheres of human creativity, has disappeared. He disappeared, a great connoisseur of the history of Vranje and its health life, who in this area built his whole self into the foundations of the struggle for the public health and well-being of his people.

He was a prominent expert, especially in the field of breast oncology, a good and above all humane man, full of love for his vocation, a favorite among patients, colleagues and associates, gladly seen in the manifestations of cultural life in the city.

Dr. Vukašin Antić was born in Belgrade on April 19, 1958, in a famous Vranje family, to father Milorad, a professor and painter, and mother Nadežda, a professor of French. He was brought up in a family of intellectuals in the spirit of human and social justice. In Vranje, where he spent his whole life, he received primary and high school education. He completed his medical studies in Belgrade in 1983, as well as his specialization in general surgery in 1991.

He worked as a surgeon at the Surgical Department of the Vranje Hospital, whose successful manager he was in 2000-2004. years.

As a specialist in general surgery, he showed a special affinity for breast diseases. He trained in the field of breast oncological surgery in 1998 and 2006 at the Clinic "La Conception" in Marseille with Professor Lucien Piano, where he mastered the most modern techniques in surgical treatment.

The motto of his life was to help women in the fight against breast cancer, regardless of personal sacrifices. Love for the patient was the source of his strength and energy, it was his inspiration and that was the secret of his success. He was a humane doctor who gained trust through kindness, expertise and human warmth. By nature, an optimist and eloquent person brought a cheerful mood to the environment, and he was able to alleviate the difficulties of patients, to hope for recovery and to be loyal to them until the last day.

The ambitious and tireless doctor Vukasin did not stop there. He presented his experiences with numerous speeches at numerous scientific gatherings, thus making a significant contribution to the fight against breast cancer. He also published a large number of papers in professional publications.

Surgery was not the only preoccupation of Dr. Vukasin. With the same zeal, he engaged in researching the history of medicine as an extremely active long-term member of the Section for the History of Medicine SLD. The result of his valuable and fruitful engagement in the field of the history of medicine is his rich and diverse bibliography, which includes a large number of scientific papers that have been published in journals and conference proceedings.

A number of papers were also published in electronic form on the site for the history of medicine "Rastko". He was a reviewer of several books and articles and a collaborator and co-author in publications: Chronicle of Surgery in Serbia in 2002 and Serbian Military Medical Service 1914–1915, 2009 and others.

He considered that in addition to the fight against breast cancer, his greatest contribution to the history of medicine was his book - Hospital in Vranje (chronicle), 2003. He was also proud of his other two books: New contributions to the biography of the national hero Simo Pogačarević, 2014 and Tragom dr. Tome M. Jovanović (1928–2018), 2018.

He was adorned with curiosity, an extremely sharp mind and an ultimate commitment to everything he did. That need for work was stronger than his own and his interests were numerous.

He was an active participant in the social and cultural life of the city, the initiator of numerous events. He is the founder of the Club of Film Art Lovers and the School of Animated Film, in which he was on the board for many years. He was also a member of the management boards of the Literary Community "Borisav Stanković" and the Gymnasium "Bora Stanković" in Vranje.

He initiated that the Secondary Medical School in Vranje be named after Dr. Isabel Emsley Hutton, the erection of a monument to the "America" unit of the Scottish Women's Hospital in front of the Health Center and a monument in the City Park to Dr. Franjo Kopsha, the founder of the first hospital in Vranje. He was a tireless fighter for many years to get Vranje a modern hospital under one roof.

For his rich and fruitful work, he received the award of the city of Vranje "January 31" for exceptional results and achievements in the field of oncology, prevention and fight against cancer and the St. George's Day Charter of the Section for the History of Medicine SLD in 2012. In 2020, the same Section decided to award him the "Dr Vladan Djordjevic" award for his life's work in the field of medical history.

Dr. Vukasin was an unusual phenomenon, a modest and exceptional person, with a broad education and European manners, always correct towards his interlocutors, a man with a specific sense of humor. By nature righteous, he reacted to injustices in his own way, but not rudely, regardless of possible personal consequences.

He is an unforgettable example of how he uses his profession and his people, and his work will be an inexhaustible source of inspiration for future doctors.

Dr. Vukasin, without any doubt, joined the famous, intelligent people of Vranje, with whom he enters the history of his homeland.

We will remember him as a modest, favorite doctor, humanist and selfless collaborator.

Deep sadness is a reminder of Pliny's thought: "The memory of us will last if we deserve it in life."

Without any doubt, Dr. Vukasin deserved to have the memory of him forever.

Thanks to Dr. Vukasin Antic for everything he has done for the medical profession and social progress, and may he have eternal glory.

Prim. Mr Sci. med. Marina J. Janjić, M.D.
General Hospital Vranje,
Gynecology and obstetrics department

C O N T E N T S

ORIGINAL PAPERS

REVIEW ARTICLE

CASE REPORT

HISTORY OF MEDICINE

UDK 616.895.4-056.83
613.81
COBISS.SR-ID 16466185

FACTORS AFFECTING DEVELOPMENT OF DEPRESSION IN PEOPLE WHO DRINK ALCOHOL

Jandric-Kocic Marijana

HEALTH CENTER KRUPA NA UNI, REPUBLIC OF SRPSKA

SUMMARY : Introduction: About 90% of people consume alcohol at some point in their lives. Alcohol abuse occurs in 5-10% of these, while addiction develops in 10% of men and 3-5% of women. Alcohol consumption can induce depression or contribute to its severity. Objective: The study aimed to examine the existence of statistically significant associations between patterns of drinking alcohol, duration of alcohol use, and sociodemographic factors with depression present in persons consuming alcohol. Materials and Methods: The cross-sectional study included 100 individuals, 25.0% women and 75.0% men, with an average of 53.0 ± 1.5 years consuming alcohol over a period of eight months, from 01.10.2018. to 01.06.2019. at the Krupa Health Center on the Una. In addition to the additional tests, they also used the Audit of Identity Disorders Identification Disorders (AUDIT) test and Beck's Depression Inventory (BDI). Results: Participants with harmful alcohol drinking had a statistically significant presence of depression compared to subjects with other alcohol drinking patterns ($p < 0.05$). There was no statistically significant difference in the presence of depression in relation to the duration of alcohol use ($p = 0.09$) and the gender of subjects consuming alcohol ($p = 0.07$). Participants aged 40-59 with high school diploma who consumed alcohol had statistically significant presence of depression in relation to other good groups and the level of education ($p < 0.05$).Conclusion: The study confirmed the significant role of harmful alcohol drinking, the age and level of education in the development of depression in persons consuming alcohol.

Keywords: alcohol, abuse, mental health, depression

INTRODUCTION

Alcohol consumption is a socially acceptable activity in Western Europe. In our region it is favoured to the level of an obligatory ritual in many social situations. It is estimated that about 90% of people consume alcohol at some point in their life. Alcohol abuse occurs in 5-10%, while addiction develops in 10% of men and 3-5% of women [1,2,3]. Alcohol consumption can induce depression or contribute to its severity through several potential mechanisms. Moderate doses of alcohol reduce the concentration of tryptophan, homovalinic acid, γ-amino butyric acid, N-methyl-D aspartate endogenous opioids. Its use has a negative impact on cognitive functions, contributes to feelings of inferiority, guilt and hopelessness, disrupts interpersonal relationships, and induces delinquency [4]. A primary depressive disorder in persons who consume alcohol precedes alcohol intoxication and/or alcohol withdrawal or occurs within four weeks after alcohol consumption has stopped. Between these two periods, there can only be alcohol-induced depression that is considered a consequence of abstinence syndrome and goes away spontaneously. Depression that persists after four weeks of abstinence is considered secondary [5].

OBJECTIVE

The aim of the study was to investigate: -1): the existence of statistically significant correlation of alcohol drinking pattern with the presence of depression in alcohol drinkers, -2): the existence of statistically significant association of the duration of alcohol use with the presence of depression in alcohol drinkers,-3) : the existence of a statistically significant association of sociodemographic factors with the presence of depression in alcohol drinkers.

MATERIAL AND METHODS

The cross-sectional study included 100 people who consumed alcohol for a period of eight months from 01.10.2018. do 01.06.2019. at the Krupa Health Center on the Una. The criteria for inclusion of the respondents in the study were: age between 20 and 79 years, completed

primary school and anamnestic data on alcohol consumption for at least twelve months. The study excluded persons: over the age of 79 and under 20 with alcohol consumption of less than twelve months, as well as all persons with malignant and advanced chronic diseases (chronic renal failure, heart decompensating, liver failure). Data were collected through the use of general and specific questionnaires. The general questionnaire collected sociodemographic data (gender and age, level of education). Beck's Depression Inventory (BDI) is used as an indicator of the existence and intensity of depressive symptoms that are in accordance with the current Diagnostic and Statistical Manual of Mental Disorders (DSM). Today, another revised version recommended by the American Psychiatric Association (APA) is in use. It consists of 21 statements (each statement is a list of four statements ranked according to the intensity of a particular symptom of depression) that we score from 0 to 3. A total score of 0 to 13 excludes the existence of depression. The results in the interval of 14 to 19 speak in favour of mild depression. There is moderate depression in the score 20-28. Severe depression is present in patients who have a score of 29-63 [6,7]. The Alcohol Use Disorders Identification Test (AUDIT) is intended for the early identification of risky and harmful drinking as well as alcohol dependence, developed and recommended by the World Health Organization (WHO). The test consists of three questions in the area of risky alcohol use (frequency of drinking, typical amount, frequency of heavy drinking), three questions covering the symptoms of addiction (diminished control over drinking, increased drinking desire, morning drinking) and four questions in the area of harmful alcohol use (guilt after drinking, amnesia, alcohol-related injuries, environmental concerns), which we score 0-4. Score 0-7 is in favour of low-risk drinking. The result in the interval 8-15 corresponds to risky drinking. Harmful drinking is present in subjects with a score of 16-19. The score 20-40 reveals alcohol abuse [1,8]. Descriptive statistical methods were used to analyse the data: abundance frequency distribution, arithmetic mean, standard deviation, and percentages. To determine statistical significance the $\chi 2$-independence test was used. The significance level was set at 95% confidence interval. The results are presented textually, in tabular form and graphically, and the complete work is processed in Microsoft Word for Windows text processor.

RESULTS

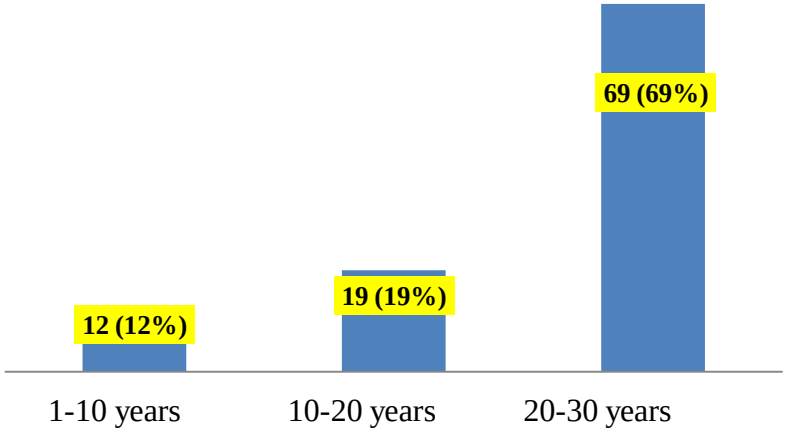
The study included 100 patients. Among them, 25.0% were women and 75.0% were men. The majority of respondents who consume alcohol (58%) are 40-59 years of age. The average age of the study population was 53.0 ± 1.5 years. Women were statistically significantly older than men. 22% of respondents had completed primary school, 2% had college education. High school graduation rate was 76%.

Table 1. Distribution of alcohol drinkers by gender, age and education level

Age (years)	MenNo (%)	WomenNo (%)	TotalNo (%)
20-39	10 (10,0%)	0 (0,0%)	10 (10,0%)
40-59	58 (58,0%)	16 (16,0%)	74 (74,0%)
60-79	7 (7,0%)	9 (9,0%)	16 (16,0%)
TotalNo (%)	75 (75,0%)	25 (25,0%)	100 (100,0%)
Level of education	MenNo (%)	WomenNo (%)	TotalNo (%)
Primary school	12 (12,0%)	10 (10.0%)	22 (22,0%)
High school	61 (61,0%)	15 (15,0%)	76 (76,0%)
College	2 (2,0%)	0 (0,0%)	2 (2,0%)
TotalNo (%)	75 (75,0%)	25 (25,0%)	100 (100,0%)

Most participants (69%) consumed alcohol for 20-30 years. The second most frequent were respondents (19%) who consumed alcohol for a period of 10-20 years. The smallest number of study participants (12%) consumed alcohol for 1-10 years.

Graph 1. Length of drinking alcohol in years of participants
N = 100



The highest number of respondents (49%) identified risky drinking. Low-risk drinking was verified in 35% of respondents, harmful drinking in 13%. The smallest number of respondents reported alcohol abuse (3%). Male respondents, 40-59 year old with high school diploma as well as alcohol drinkers for 20-30 years had a statistically significantly higher percentage of risky and harmful drinking as well as alcohol dependence.

Table 2. Distribution of gender, age and education level of alcohol drinkers by AUDIT (alcohol use disorders identification test)

Characteristics		Score 0-7**	Score 8-15***	Score 16-19****	Score ≥20*****	p value*
Gender	Men	19 (25,3%)	43 (57,4%)	10 (13,3%)	3 (4,0%)	NS, 0.07
	Women	16 (64,0%)	6 (24,0%)	3 (12,0%)	0 (0,0%)	
Age in years	20-39 years of age	1 (10,0%)	7 (70,0%)	2 (20,0%)	0 (0,0%)	< 0.05
	40-59 years of age	20 (27,0%)	40 (54,1%)	11 (14,9%)	3 (4,0%)	
	60-79 years of age	14 (87,5%)	2 (12,5%)	0 (0,0%)	0 (0,0%)	
Education level	Primary school	13 (59.1%)	6 (27,3%)	3 (13,6%)	0 (0,0%)	< 0.05
	High school	22 (28,9%)	41 (53,9%)	10 (13,2%)	3(4,0%)	
	College	0 (0,0%)	2 (100,0%)	0 (0,0%)	0 (0,0%)	
Length of drinking alcoholin years	1-10 years	1 (8,3%)	10 (83,4%)	1 (8,3%)	0 (0,0%)	< 0.05
	10-20 years	10 (52,6%)	9 (47,4%)	0 (0,0%)	0 (0,0%)	
	20-30 years	24 (34,8%)	30 (43,4%)	12 (17,4%)	3 (4,3%)	

LEGEND:*According to hi square test or Fisher test; **Low-risk drinking; ***Risky drinking; **** Harmful drinking; *****Alcohol abuse.

Depression was reported in 42 (46.0%) men and 15 (60.0%) women. 6 (8.0%) men and 8 (32.0%) women had moderate depression. Severe depressive disorders were verified in 3 (4.0%) men and 1 (4.0%) woman. The study could not detect a statistically significant difference in the presence of depression in relation to the gender of alcohol-consuming subjects (p = 0.07). Depression was present in 4 (40.0%) subjects aged 20-39 years, 49 (66.2%) subjects aged 40-59 years and 4 (25.0%) subjects aged 60-79 years. Moderate depressive disorders were experienced by 1 (10.0%) subject aged 20-39 years, 12 (16.2%) subjects aged 40-59 years and

1 (6.2%) subject aged 60-79 years. Severe depressive disorders were found in 4 (5.4%) persons aged 40-59 years. Presence of depression in subjects 40-59 years of age who consumed alcohol was statistically significantly more frequent than in subjects of other age groups (p <0.05). Depression problems were experienced by 12 (44.5%) respondents with completed primary education and 43 (46.6%) respondents with completed secondary education. Moderate depression was found in 3 (13.6%) subjects with completed primary education and 11 (14.5%) subjects with completed secondary education. Severe depressive disorders were verified in 4 (5.3%) of high school graduates. Participants in the study who consumed alcohol with high school diploma had presence of depression statistically significantly more frequent compared to respondents with other levels of education (p <0.05). Depression was found in 8 (66.7%) subjects who consumed alcohol for 1-10 years, 14 (95.0%) subjects who consumed alcohol for 10-20 years, and 35 (50.7%) subjects who consumed alcohol for 20-30 years. Moderate depressive disorders were experienced by 3 (25.0%) subjects who consumed alcohol for 1-10 years, 7 (7.0%) subjects who consumed alcohol for 10-20 years, and 4 (5.8%) subjects who consumed alcohol for 20- 30 years. Severe depressive disorders were verified in 4 (4.0%) subjects who consumed alcohol for 10-20 years. There was no statistically significant difference in the presence of depression in alcohol drinkers with respect to the duration of alcohol consumption (p = 0.09).

Depression was verified in 13 (37.1%) subjects with low-risk drinking, 28 (47.1%) subjects with risky drinking, and all (100%) subjects with harmful drinking and alcohol abuse. Moderate depression was experienced by 4 (8.2%) subjects with risky drinking and 10 (76.9%) by subjects with harmful drinking. Severe depressive disorders were identified in 1 (7.7%) subject with harmful drinking and 3 (100.0%) subjects with alcohol abuse. Respondents with harmful drinking had presence of depression statistically significantly more frequent than subjects with other drinking patterns (p <0.05).

Table 3. Distribution of sociodemographic characteristics, length of drinking alcohol and drinking patterns of alcohol drinkers by BDI (Beck's Depression Inventory)

Characteristics		Score 0-13**	Score 14-19***	Score 20-28****	Score ≥29*****	p value*
Gender	Men	33 (44,0%)	33 (44,0%)	6 (8.0%)	3 (4.0%)	NS, 0.07
	Women	10(40,0%)	6 (24,0%)	8 (32,0%)	1 (4,0%)	
Age in years	20-39 years of age	6 (60,0%)	3 (30,0%)	1 (10,0%)	0(0,0%)	< 0.05
	40-59 years of age	25 (33,8%)	33 (44,6%)	12 (16,2%)	4 (5,4%)	
	60-79 years of age	12 (75,0%)	3 (18,8%)	1 (6.2%)	0(0,0%)	
Education level	Primary school	10(45,5%)	9 (40,9%)	3 (13,6%)	0(0,0%)	< 0.05
	High school	33 (43,4%)	28 (36,8%)	11 (14,5%)	4 (5,3%)	
	College	0(0,0%)	2 (100,0%)	0(0,0%)	0(0,0%)	
Length of drinking alcoholin years	1-10 years	4 (33,3%)	5 (41,7%)	3 (25,0%)	0(0,0%)	NS, 0.09
	10-20 years	5 (5,0%)	3 (3,0%)	7 (7,0%)	4 (4,0%)	
	20-30 years	34 (49,3%)	31 (44,9%)	4 (5,8%)	0(0,0%)	
Alcohol drinking pattern	Low-risk drinking	22 (62,9%)	13 (37,1%)	0(0,0%)	0(0,0%)	< 0.05
	Risky drinking	21 (42,9%)	24 (49,0%)	4 (8,2%)	0(0,0%)	
	Harmful drinking	0(0,0%)	2 (15,4%)	10(76,9%)	1 (7,7%)	
	Alcohol abuse	0(0,0%)	0(0,0%)	0(0,0%)	3 (100,0%)	

LEGEND:*According to hi square test or Fisher test; ** Absence of depression problems; *** Mild depression problems ; **** Moderate depression problems ; ***** Severe depression problems;

DISCUSSION

The study found that depression was present in 64% of people who consumed alcohol (39% mild depression, 14% moderate depression, and 4% severe depression). In a study by a group of authors in Kenya, secondary depression was present in 68.3% of alcohol drinkers [9]. Studies conducted in England have verified the existence of moderate depression in 47% of people diagnosed with alcoholism. Severe depressive disorders were reported by 34% of people consuming alcohol [1]. A study by a group of authors in Nepal found that there was depression in 41.7% of people hospitalized for alcohol abuse [10]. The study did not verify a statistically significant difference in the presence of depression compared to the gender of alcohol drinkers. Research by a group of authors from the Netherlands has concluded that women who consume alcohol have a statistically significantly higher risk of secondary depression [11]. Research by an author group in Taiwan and the United States has found a strong correlation between alcohol use and depression in upper elementary school students. Alcohol use in the early adolescent period results in changes in the frontal and limbic cortex responsible for affective damage [12,13]. Studies conducted in Russia have found that alcohol consumption in women is associated with a faster development of depression than in men. A possible reason is that women achieve higher levels of alcohol in their blood than men after drinking equivalent amounts of alcohol per kilogram of body weight [14,15]. In addition, women are at greater risk of developing depression as a result of gender differences in roles in contemporary society [16]. The age of 40-59 years was associated with statistically significantly more frequent presence of depression in alcohol drinkers. At that age, there may be an increased alcohol consumption in an attempt to cope with growing socioeconomic problems. Research by a group of American authors indicates that people who start consuming alcohol in older adulthood have a statistically significantly bigger chance of experiencing depression than their non-drinking peers [4]. Participants in the study with high school diploma who consumed alcohol had presence of depression which was statistically significantly more frequent compared to respondents with completed primary school and university-educated persons. The more frequent presence of depression can be explained by significantly more frequent occurrence of harmful drinking and alcohol abuse in the same respondents. The duration of alcohol consumption did not statistically significantly influence the development of depression. Studies indicate that alcohol use leads to the development of depression quite early. Research in the United States indicates that over 28% of people who consume alcohol have developed depression by the age of 30 [17]. The pattern of alcohol consumption is closely related to the onset of depression in study participants. A study by a group of US authors indicates that men who drink 14-27 alcoholic beverages per week and women who drink 7-13 alcoholic beverages per week have a statistically significantly higher presence of depression than those who drink less alcohol [3]. Research conducted in Singapore has identified alcohol dependence as an independent predictive factor for the development of depressive disorders in female subjects [18]. Research conducted in Australia found a statistically significant association between alcohol abuse and the development of depression in young women [19,20]. A study conducted in China found that low-risk drinking significantly reduced the risk of depression in both sexes [21]. A study by a group of US authors found significantly fewer depression problems in the elderly with low-risk alcohol consumption (they had a statistically significantly lower C reactive protein concentration) [22]. Research by a group of authors in Spain has not found a protective effect of moderate alcohol consumption on the development of depression in the elderly [23].

CONCLUSION

Harmful drinking is a strong predictor of the presence of depression. The duration of alcohol use was not statistically significantly associated with the presence of depression. There is no statistically significant difference in the presence of depression in relation to the gender of alcohol drinkers. 40-59 years of age and secondary education were associated with the presence of depression in people consuming alcohol.

LITERATURE:

1. Republička stručna komisija za izradu i implementaciju vodiča dobre kliničke prakse. Nacionalni vodič dobre kliničke prakse Alkoholizam. Ministarstvo zdravlja Republike Srbije. 2013. Available from: http://www.batut.org.rs/download/nacionalni%20vodici/vodicZaDijagnostikovanjeILecenjeAlkoholizma.pdf.
2. Sher L. Depression and alcoholism.QJM: An International Journal of Medicine.2004; 97 (4): 237–240. Available from: https://doi.org/10.1093/qjmed/hch04
3. Toornstra A, Massar K, Hurks PPM, Timmermans MMMS, Kok G, Curfs LMG. Perceptions of Alcohol and Alcohol Use among Community Members and Young Adults in Ukraine. Substance Use & Misuse. 2020. Available from: https://www.tandfonline.com/doi/full/10.1080/10826084.2020.1735436?fbclid=IwAR2wldZ7PjI3zq2ZcSdwp5KQ2nIwijBnEodzET2pqjppr9KAocrqaY1rVyY-
4. Ramsey SE, Engler PA, Stein MD. Alcohol Use Among Depressed Patients: The Need for Assessment and Intervention. Prof Psychol Res Pr. 2005; 36(2):203-207. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874911.
5. Mandić-Gajić G. Sekundarna depresija kod alkoholičara – klinički značaj. Vojnosanit Pregl. 2005; 62(9): 671–677. Available from: http://www.doiserbia.nb.rs/img/doi/0042-8450/2005/0042-84500509671M.pdf..
6. Stanojević D, Jaredić B, Mandić S. Depresivnost kod adolescenata na Kosovu i Metohiji. Timočki medicinski glasnik.2012; 40(3): 187-220. dostupno na: http://www.tmg.org.rs/v370406.htm.
7. Jackson-Koku G. Questionnaire review. Beck Depression Inventory. Occupational Medicine 2016;66:174–175. Available from: https://watermark.silverchair.com/kqv087.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAl4wggJaBgkqhkiG9w0BBwagggJLMIICRwIBADCCAkAGCSqGSIb3.
8. Williams N. The AUDIT questionnaire. Occupational Medicine. 2014: 64 (4): 308. Available from:https://doi.org/10.1093/occmed/kqu011.
9. Kuria MW, Ndetei DM, Obot IS, Khasakhala LI, Bagaka BM, Mbugua MN, Kamau J. The Association between Alcohol Dependence and Depression before and after Treatment for Alcohol Dependence. ISRN Psychiatry. 2012:482802. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3658562/#__ffn_sectitle.
10. Khalid A, Kunwar AR, Rajbhandari KC, Sharma VD, Regmi SK. A study of prevalence and comorbidity of depression in alcohol dependence. Indian J Psychiatry. 2000;42(4):434–438. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2962747/pdf/IJPsy-42-434.pdf.
11. Boschloo L, Vogelzangs N, Smit JH, Brink W, Veltman DJ. Beekman ATFet al. Comorbidity and risk indicators for alcohol use disorders among persons with anxiety and/or depressive disorders. Findings from the Netherlands Study of Depression and Anxiety (NESDA). Journal of Affective Disorders.2011. 131 (1–3): 233-242. Available from: https://www.sciencedirect.com/science/article/pii/S0165032710007494?via%3Dihub.
12. Wichaidit W, Pruphetkaew N, Assanangkornchai S. Variations by sex and age in the association between alcohol use and depressed mood among Thai adolescents. Plos One. 2019. Available from: https://journals.plos.org/plosone/article/authors?id=10.1371/journal.pone.0225609
13. Danzo S, Connell AM, Stormshak EA. Associations between alcohol-use and depression symptoms in adolescence: Examining gender differences and pathways over time. J Adolesc. 2017;56:64-74. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5578443/
14. Zhan W, Shaboltas AV, Skochilov RV, Kozlov AP, Krasnoselskikh TV, Abdala N. Gender differences in the relationship between alcohol use and depressive symptoms in St. Petersburg, Russia. J Addict Res Ther. 2012;3(2):1000124. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3519357/.
15. Boykoff N, Schneekloth TD, Hall-Flavin D, et al. Gender differences in the relationship between depressive symptoms and cravings in alcoholism. Am J Addict. 2010;19(4):352–356. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4671371/.
16. Nazroo JY. Exploring Gender Difference in Depression. Psychiatric Times.2001; 18: (3). Available from: https://www.psychiatrictimes.com/depression/exploring-gender-difference-depression.
17. Brière FN, Rohde P, Seeley JR., Klein D, Lewinsohn PM. Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. Comprehensive psychiatry.2014; 55(3): 526–533. Dostupno na: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4131538/.
18. Subramaniam M, Valli Mahesh M, Xu Peh C, Tan J, Fauziana R, Satghare Pet al. Hazardous alcohol use among patients with schizophrenia and depression. Alcohol. 2017: 65: 63-69. Available from: https://reader.elsevier.com/reader/sd/pii/S0741832916302828?token=840872A69CF6EE320435564672CB2AF00847E78DE646B8706E11F58439EB8B6F7DBA54171ACDBBF51AE8324A7719BF38.
19. Powersa J, Duffya L, Burnsb L, Loxtona D. Binge drinking and subsequent depressive symptoms in young women in Australia. Drug and Alcohol Dependence. 2016; 161: 86-94. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0376871616000478?via%3Dihub.
20. Ying Lee Y, Wang P, Abdin E, Chang S, Shafie S, Sambasivam Ret al. Prevalence of binge drinking and its association with mental health conditions and quality of life in Singapore. Addictive Behaviors.2020; 100: 106114. Available from: https://www.sciencedirect.com/science/article/pii/S0306460319304460?fbclid=IwAR2S5_Zp04p2wuPjIg1uRtUBmI0aDrMe5PwAG_nVNh7v6YhX4Zulo6-zQ7A
21. Li J, Wang H, Li M, Shen Q, Li X, Zhang Yet al. Effect of alcohol use disorders and alcohol intake on the risk of subsequent depressive symptoms: a systematic review and meta-analysis of cohort studies. Addiction.2020. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/add.14935?fbclid=IwAR1hALiPkFt9JbwL1N_92PV7lJOsr6lOsd9gKkohttYKVXdeMHj9gHjhl7o
22. Paulson D, Shah M, Herring D, Scott R, Herrera M, Brush Det al. The relationship between moderate alcohol consumption, depressive symptomatology, and C-reactive protein: the Health and Retirement Study. Int J Geriatr Psychiatry.2018; 33: 316– 324. Available from: https://onlinelibrary.wiley.com/action/showCitFormats?doi=10.1002%2Fgps.4746
23. García-Esquinas E, Ortolá R, Galán I et al. Moderate alcohol drinking is not associated with risk of depression in older adults. Sci Rep .2018; 8: 11512 (2018). Available from: https://www.nature.com/articles/s41598-018-29985-4?fbclid=IwAR1H7j0jTuVNvYuOMaGDBkNedvVtMat-2Hw9l5ddLG8pLDbwM4KDiJMGDtU

Vol. 45 (2020) No. 1-2 TIMOK MEDICAL GAZETTE Original papers

UDK 616.97-036.22-053.9
COBISS.SR-ID 16474121

REASONS OF ATTENDANCE BY OLDER PATIENTS TO DEPARTMENT OF VENEREAL DISEASES AND THEIR KNOWLEDGE OF SEXUALLY TRANSMITTED DISEASES

Milan Bjekić (1) , Sandra Šipetić-Grujičić (2) , Hristina Vlajinac (2)

(1) CITY INSTITUTE FOR SKIN AND VENEREAL DISEASES, BELGRADE; (2) INSTITUTE OF EPIDEMIOLOGY, FACULTY OF MEDICINE, UNIVERSITY OF BELGRADE

ACKNOWLEDGMENT: This work was supported by the Ministry of Science and Technology of Serbia, through the Contract №175042 (2011-2014).

Abstract: Introduction: Several studies have shown increasing rates of many sexually transmitted diseases (STDs) in the population group aged 50 years and older, worldwide. Older persons usually know less about STDs and HIV/AIDS than younger individuals. The aim of the present study was to reveal why older patients seek venereologists' help and to assess their knowledge of STDs. Material and Methods: Data were collected from consecutive patients aged 60 and over who attended counselling for sexually transmitted diseases at the City Institute for Skin and Venereal Diseases in Belgrade from July to December 2017. One dermatologist examined and interviewed all participants by the use of a questionnaire. Results: Out of all participants (174 patients), 23.56% had some of STIs, 58.62% had some other genital disorders and 17.82 came for counselling. The most frequent viral STDs were acute and recurrent genital warts and recurrent genital herpes, while the most frequent bacterial STD was syphilis. Out of non STDs the most frequent were balanitis, in men, and lichen sclerosis in both sexes. The perceived knowledge mean scores for each STD, ranging from "0", meaning not knowledgeable at all, to "5", meaning very knowledgeable, ranged from 0.63 to 2.71. It was the best for syphilis, followed by gonorrhoea, HIV/AIDS, hepatitis B, genital warts and Chlamydia. Correct answers concerning general knowledge of STDs were given by 59% to 96% of participants. Conclusion: A considerable number of older people who sought venereologists' help had an STD. Their general knowledge of STDs as well as perceived knowledge of single STDs were unsatisfactory and did not differ between patients with and without STDs.

Key Words: sexually transmitted diseases, genital disorders, HIV, counselling, elderly, knowledge of sexually transmitted diseases

INTRODUCTION:

Sexually transmitted diseases (STDs) occur predominantly in individuals of younger age groups. Nonetheless, several studies have shown increasing rates of many STDs in the population group aged 50 years and older, worldwide [1-4]. Globally, the share of people aged ≥60 has risen from 8% (200 million people) of world population in 1950 to 11% (760 million) in 2011 and people older than 60 years are expected to reach 22% of world population (2 billion) by 2050 [5]. The situation in Serbia is similar: in the last six decades population aged 60-plus increased from 0.6 million in 1948 to 1.8 million in 2011 [6].

Sexual activity and the potential for STDs continue into late life. Several factors contribute to STD increase in older adults such as: increased longevity, better quality of life due to healthcare advancements, high divorce rates, being widowed, meeting new partners later in life, internet dating, effective pharmacotherapy for erectile dysfunction, no risk of pregnancy and lack of condom use during sex [4]. Moreover, older persons know less about STDs and HIV/AIDS than younger individuals because the elderly have been neglected by those responsible for education and prevention messages [7].

Genitourinary medicine departments predominantly target younger persons but are attended also by many older people. Epidemiological data about incidence of syphilis and gonorrhoea in Serbia in 2016 have shown

that the lowest incidence rates were in patients older than fifty years (0.35 per 100,000 for syphilis and 0.11 per 100,000 for gonorrhoea) [8]. The objectives of our study were to reveal why older patients came to the Department for Sexually Transmitted Diseases at the City Institute for Skin and Venereal Diseases in Belgrade and to assess their knowledge of sexually transmitted diseases.

METHODS:

In this cross-sectional study, the data were collected from consecutive patients, both male and female, aged 60 and over who attended the Department for Sexually Transmitted Diseases at the City Institute for Skin and Venereal Diseases in Belgrade. This is the main institution for patients with sexually transmitted diseases in Belgrade, with a counselling department. The study was conducted between 1 July and 31 December 2017 and covered 174 patients. One dermatologist examined and interviewed all participants by the use of a questionnaire. Data on demographic characteristics (age, education, marital status), reasons for attendance, as well as sexual history data (sexual orientation, steady partner, human immunodeficiency virus (HIV) status, date of last sexual intercourse and condom use during this intercourse, number of sexual partners in past 6 months, and history of sexually transmitted diseases) were also collected. Diagnoses were made by physical and/or laboratory examinations.

The participants' knowledge of sexually transmitted diseases were assessed by a list of 14 questions (7 true and false questions and 7 Likert-style questions with responses ranging from not at all knowledgeable to very knowledgeable), taken from a study conducted by Andrea Jennings [9].

Data were presented as numbers and percentages. According to diagnoses, patients were divided into three groups: patients with STDs, with non-STDs and with no diagnoses. For the analysis of data, all participants were divided into two groups, group of patients with STDs and and group of patients without STDs. Throughout the analysis of differences between these groups, chi-square test and t- test were performed. P value <0.05 was considered as significant.

The research was approved by the Ethics Committee of the City Institute for Skin and Venereal Diseases in Belgrade (the Ethics Committee approval number 3/2017).

RESULTS:

The study included 174 patients. Out of them 41 had an STd (26 acute STd and 15 recurrent STd), 102 patients had some other genital disorders and 31 persons visited the STD department for counselling (i.e. erectile dysfunction, drugs for erectile dysfunction, fear of STDs, lubricants) (Table 1). Among men, 23.3% had an STD, and among women 20.8%. The most frequent viral STDs were acute and recurrent genital warts and recurrent genital herpes, while the most frequent bacterial STD was syphilis. Out of non STDs the most frequent was balanitis, in men, and lichen sclerosus both in men and women.

Table 1. Reasons for attendance in the Department for Sexually Transmitted Diseases

Diagnosis	Men (n = 150) Number	Women (n = 24) Number
Acute STDs:		
Trichomoniasis	2	2
Gonorrhoea	2	-
Chlamydia	2	-
Non-specific urethritis	3	-
Early syphilis	5	-
Primary genital herpes	2	-
Genital warts	7	1
Recurrent STDs:		
Recurrent genital herpes	4	3
Recurrent genital warts	8	-
Non-STDs disease:		
Balanitis	50	-

Lichen sclerosus	13	9
Genital eczema	4	4
Candidiasis	5	1
Induratio penis plastica	4	-
Phimosis	6	-
Angiokeratoma	3	3
None/ Counselling	30	1

STD, sexually transmitted disease.

For further analysis, all participants were divided into two groups: a) group of patients with STDs (41 patients) and b) group of patients without STDs which included both patients with some genital disorders and those coming for counselling (all together 133 persons). Their demographic and some other characteristics are presented in Table 2.

Table 2. Some characteristics of the study participants

Variable	Patients with STD (n = 41) No (%)	Patients without STD (n = 133) No (%)	Total (n = 174) No (%)
Age:			
60 – 64	20 (48.8)	39 (29.3)	59 (33.9)
65 – 69	11 (26.8)	35 (26.3)	46 (26.4)
70 – 74	6 (14.6)	28 (21.1)	34 (19.5)
75 – 79	3 (7.3)	23 (17.3)	26 (14.9)
≥ 80	1 (2.4)	8 (6.0)	9 (5.2)
Gender:			
Men	35 (85.4)	115 (86.5)	150 (86.2)
Women	6 (14.6)	18 (13.5)	24 (13.8)
Marital status:			
Married	21 (51.2)	75 (56.4)	96 (55.2)
Single	5 (12.2)	8 (6.0)	13 (7.5)
Divorced	11 (26.8)	29 (21.8)	40 (23.0)
Widowed	4 (9.8)	21 (15.8)	25 (14.4)
Education (years of school:			
≤ 8	4 (9.8)	6 (4.5)	10 (5.7)
9 -12	18 (43.9)	63 (47.4)	81 (46.6)
> 12	19 (46.3)	64 (48.1)	83 (47.7)
Sexual orientation:			
Heterosexual	36 (87.8)	133 (100.0)	169 (97.1)
Homosexual	3 (7.3)	0 (0.0)	3 (1.7)
Bisexual	2 (4.9)*	0 (0.0)	2 (1.1)
HIV test:			
Positive	0 (0.0)	0 (0.0)	0 (0.0)
Negative	7 (17.1)	9 (6.8)	16 (9.2)
Unknown	34 (82.9)†	124 (93.2)	158 (90.8)
Reason for visiting STD department:			
Suspicion for STDs			
Genital symptoms	2 (4.9)	1 (0.8)	3 (1.7)
STD symptoms	18 (43.9)	101 (75.9)	119 (68.4)
Counselling	21 (51.2)	0 (0.0)	21 (12.1)
	0 (0.0)*	31 (23.3)	31 (17.8)
Permanent sexual partner:			
Yes	33 (80.5)	87 (65.4)	120 (69.0)
No	8 (19.5)	46 (34.6)	54 (31.0)
Last sexual contact:			
≤ 3 months	31 (75.6)	68 (51.1)	99 (56.9)
> 3 months	10 (24.4)‡	65 (48.9)	75 (43.1)
Number of sexual partners in the last 6 months:			
0	10(24.4)	62 (46.6)	72 (41.4)
1 – 2	23 (56.1)	69 (51.9)	92 (52.8)
≥ 3	8 (19.5)*	2 (1.5)	10 (5.7)
Condom use during last intercourse:			
Yes			
No	2 (4.9)	7 (5.3)	9 (5.2)

	39 (95.1)	126 (94.7)	165 (94.8)
STD in personal history:			
Yes	29 (70.7)	37 (27.8)	66 (37.9)
No	12 (29.3)*	96 (72.2)	108 (62.1)

HIV, human immunodeficiency virus; STD, Sexually transmitted disease; For comparison between patients with and without STD: *p<0.001 †p<0.05 ‡p < 0.01

More than half of participants (63.3%) were 60-69 years old, 34.4% were 70-79 years of age and only 5.2% were 80 and more years old. Majority of them were men (86.2%) with secondary (46.6%) or university (47.7%) education and nearly half of them (44.9%) were single, divorced or widowed. Only 5 (2.8%) patients declared as homosexual or bisexual and 90.8% of all participants were never tested for HIV. With the exception of 31 patients who visited STD department for counselling, all others came because of genital symptoms (68.4%), STD symptoms (12.1%) or suspicion of STIs (1.7%). As much as 69.0% had a regular sexual partner and 56.9% had their last sexual contact in the preceding 3 months. In the last 6 months, 41.4% had no sexual partner, 52.8% had 1-2 and only 5.7% had 3 or more sexual partners. During the last intercourse, 94.8% of participants did not use a condom. STD in personal history was reported by 37.9% of participants.

Compared groups significantly differed in several characteristics. Homosexual and bisexual orientation was reported only by patients with STD (p<0.001), and in this group higher proportion of patients have been tested for HIV (p<0.05). In comparison with patients without STD, those who had STDs more frequently came to the STD department because of their suspicion of STDs or STD symptoms than because of genital symptoms or for counselling (p<0.001), more frequently had their last sexual contact in the preceding 3 months (p<0.01), had sexual partners more frequently, and greater number of sexual partners in the last 6 months (p<0.001), and had an STD more frequently in their past history (p<0.001).

General knowledge of STDs (resulting from the true and false knowledge questions) among study participants is presented in Table 3. Almost all participants new that STDs are transmitted by sexual contact (97.7%) and that STDs if not diagnosed or treated can affect sexual and reproductive organs (99.4%). More than a half of participants new that STDs are sometimes incurable (60.3%), as well as that one can have an STD without any signs and symptoms (61.5%). However, considerable number of patients thought that STDs are only a problem for young people (59.2%), but a very small percentage of patients think that there is no need to get treated for STDs when you are older (3.4%), and that only young men can get an STD if they are exposed to an infection (8.0%). Compared groups, patients with and those without STDs, did not significantly differ in their general knowledge of STDs.

Table 3 General knowledge of sexually transmitted infections among study participant

Statement	Patients with STD (n = 41) True vs. False	Patients without STD (n = 133) True vs. False	Total (n = 174) True vs. False
Sexually transmitted disease (STD) is a disease that is transmitted by sexual contact.	97.6% vs. 2.4%	97.7% vs. 2.3%	97.7% vs. 2.3%
STDs are sometimes incurable	58.5% vs. 41.5%	60.9% vs.39.1%	60.3% vs. 39.7%
If not diagnosed or treated, STDs can affect sexual and reproductive organs.	100.0% vs. 0.0%	99.2% vs. 0.8%	99.4% vs. 0.6%
STDs are only a problem for young people.	58.5% vs. 41.5%	59.4% vs. 40.6%	59.2% vs. 40.8%
One could have a STD without any signs and symptoms.	70.7% vs. 29.3%	58.6% vs. 41.4%	61.5% vs. 38.5%
There is no need to get treated for STDs when you are older.	2.4% vs. 97.6%	3.8% vs. 96.2%	3.4% vs. 96.6%
Only young people can get an STD if they are exposed to an infection.	9.8% vs. 90.2%	7.5% vs. 92.5%	8.0% vs. 92.0%

STD, Sexually transmitted disease.

Perceived knowledge mean scores for single STD among the study participants (Table 4) ranged from 0.61 to 2.80. Perceived mean scores were the best for syphilis (2.71), gonorrhoea (2.69) and HIV/AIDS - acquired immunodeficiency syndrome (2.56), followed by hepatitis B (1.43), herpes (1.31) and genital warts (1.10), and the poorest for Chlamydia (0.63). There were no significant differences between patients with and without STDs. The only exception was perceived knowledge of genital warts which was better in patients with STDs in comparison with patients without STD (1.51 vs. 0.98, $p<0.05$).

Table 4 Perceived knowledge mean scores* for single sexually transmitted diseases among the study participants

Disease	Patients with STD (n = 41) Mean (SD)	Patients without STD (n = 133) Mean (SD)	Total (n = 174) Mean (SD)
Gonorrhoea	2.75 (1.68)	2.67 (1.59)	2.69 (1.61)
Syphilis	2.80 (1.63)	2.68 (1.62)	2.71 (1.62)
Genital Warts	1.51 (1.61)†	0.98 (1.46)	1.10 (1.61)
Herpes	1.32 (1.52)	1.31 (1.45)	1.31 (1.46)
Hepatitis B	1.34 (1.59)	1.46 (1.62)	1.43 (1.61)
HIV/AIDS	2.54 (1.70)	2.57 (1.70)	2.56 (1.69)
Chlamydia	0.68 (1.17)	0.61 (1.19)	0.63 (1.18)

SD, standard deviation; STD, Sexually transmitted disease;
* Perceived knowledge was ranged from"0" meaning not knowledgeable at all to "5" meaning very knowledgeable; †$p<0.05$ for comparison between patients with and without STD.

DISCUSSION:

Out of patients 60 and more years old who came to the Department for Sexually Transmitted Diseases at the City Institute for Skin and Venereal Diseases, 23.6% had STD, 59.2% had some genital disorders, and 17.2% came for counselling. Their general knowledge of STDs as well as perceived knowledge of single STDs were unsatisfactory and did not differ between patients with and without STDs.

Similar to young people, elders express sexual desire, while sexual activity for them is a means of affirming their physical functioning, establishing self-confidence, as well as a mode of pure physical pleasure [10]. However, sexuality in the elder is particularly affected by different problems that are common in this age group such as medical disorders, depression or death of a partner [11].

Unprotected sexual intercourse is a risk factor for contracting STDs and literature data have shown increasing rates of many STDs in older people which correlates with knowledge deficit about venereal diseases and risky sexual behaviour among elderly [4, 9]. Although the majority of our patients visited the Department for some genital disorders or counselling, venereal diseases were diagnosed in ¼ of participants which is in line with other studies [12, 13]. Genital herpes, genital warts and syphilis were the most prevalent diseases among our patients. Griffiths & David reported that 23% of older people who attended genitourinary medicine service had some STDs, predominantly genital herpes [12]. In the study of Tobin et al. 18% of men and 2% of women older than 50 years attended genitourinary medicine departments with an STD [13].

In comparison with non-STDs patients our STDs patients were significantly more frequently men who have sex with men. All early syphilis cases in our sample were diagnosed among homosexual men. Moreover, homosexual men accounted for the most cases of syphilis during an early syphilis outbreak in Belgrade in 2014, and 5% of them were older than 50 years [14]. Matched to heterosexuals, older homosexual men are at higher risk of getting HIV and some other STDs [15]. Our STD cases also had greater number of sexual partners in the past 6 months, last sexual contact in the preceding 3 months, have been tested for HIV and had some venereal diseases in their personal history.

Although STD cases were more sexually active, their general knowledge of STD did not differ from non-STD patients. There was lack of knowledge regarding the following statements: STDs are sometimes incurable, STDs are only a problem for young people, and one could have a

STD without any signs and symptoms. Our results are in line with study conducted among older veterans in Ohio [9]. Taking into account the results from the true and false knowledge statements, we suppose that the statement "STDs are only a problem for young people" was misunderstood by some participants as a statement that STDs are more frequent in younger compared with older and consequently present problem for them only. The perceived knowledge mean scores for each STD were particularly low and warrants concern. The best mean scores were for syphilis, gonorrhoea and HIV/AIDS and the worst was for Chlamydia. It may be explained by the fact that syphilis and gonorrhoea are "old STDs", while Chlamydia is a "new" one, and HIV/AIDS is the most dangerous followed by stigma and fear. Patients with STDs had significantly better knowledge about genital warts, moreover 40% of them had warts and received education from physicians during the treatment.

The limitation of this study is that it was not performed in a representative population sample, but it was restricted to older patients who attended Department for STD. Because of that, it is questionable whether the study results could be generalized.

CONCLUSION

The findings of our study show that a considerable number of older people who attended Department for STD (23.56%) had some venereal diseases. The perceived knowledge mean scores for each STD ranging from "0", meaning not knowledgeable at all, to "5", meaning very knowledgeable, ranged from 0.63 to 2.71. Correct answers concerning general knowledge of STDs were given by 59% to 96% of participants. The knowledge deficit about sexually transmitted infections in older people and low rate of condom use in this group highlight the need for targeted public health campaigns. Healthcare providers should offer adequate, age appropriate education about sexually transmitted infections to older adults in order to improve their knowledge and diminish risks of contracting sexually transmitted infections and their consequences. Health workers should take sexual history of the elderly and offer them tests for STDs.

REFERENCES:

1. Bodley-Tickell AT, Olowokure B, Bhaduri S, White DJ, Ward D, Ross J, et al. Trends in sexually transmitted infections (other than HIV) in older people: Analysis of data from an enhanced surveillance system. Sex Transm Infect 2008; 84 (4): 312-7.
2. Choe HS, Lee SJ, Kim CS, Cho YH. Prevalence of sexually transmitted infections and the sexual behavior of elderly people presenting to health examination centers in Korea. J Infect Chemotherapy 2011; 17 (4): 456-61.
3. Pearline RV, Tucker JD, Yuam LF, Bu J, Yin YP, Chen XS, et al. Sexually transmitted infections over fifty years of age in China. AIDS Patient care and STDs 2010; 24 (6): 345-7.
4. Minichiello V, Rahman S, Hawkes G, Pitts M. STI epidemiology in the global older population: emerging challenges. Perspect Public Health 2012; 132 (4): 178-81.
5. Beard JR, Biggs S, Bloom DE, Fried LP, Fried LP, Hogan P, et al. Global population ageing: peril or promise. Geneva: World Economic Forum 2011: 4-6.
6. Statistical Office of the Republic of Serbia:. 2011 Census of Population, Households and Dwellings in the Republic of Serbia. Belgrade: Statistical Office of the Republic of Serbia; 2014.
7. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med 2007; 357 (8): 762-74.
8. Institute of Public Health of Serbia "Dr Milan Jovanovic Batut": Center for Disease Control and Prevention: Report of infectious diseases in the Republic of Serbia in 2016. Belgrade: Institute of Public Health of Serbia "Dr Milan Jovanovic Batut"; 2017.
9. Jennings A. Knowledge of sexually transmitted infections among older veterans. J Gerontol Geriatr Res 2015; 4 (2): 203.
10. Kalra G, Subramanyam A, Pinto C. Sexuality: Desire, activity and intimacy in the elderly. Indian J Psychiatry 2011; 53 (4): 300-6.
11. Pfeiffer E, Verwoerdt A, Davis GC. Sexual behavior in middle life. Am J Psychiatry 1972; 128 (10): 1262-7.
12. Griffiths M, David N. Sexually transmitted infections in older people. Int J STD AIDS 2013; 24 (9): 756-7.
13. Tobin JM, Harindra V. Attendance by older patients at a genitourinary medicine clinic. Sex Transm Infect 2001; 77 (4): 289-91.
14. Bjekić M, Šipetić-Grujičić S, Begović-Vuksanović B, Rafailović N, Vlajinac H. Syphilis resurgence in Belgrade, Serbia in the new millennium - an outbreak in 2014. Cent Eur J Public Health 2017; 25 (4): 171-6.
15. Poynten IM, Grulich AE, Templeton DJ. Sexually transmitted infections in older populations. Curr Opin Infect Dis 2013; 26 (1): 80-5.

TIMOK MEDICAL GAZETTE

Vol. 45 (2020) No. 1-2 Original papers

UDK 616-001:796.071"2018/2019"
COBISS.SR-ID 16478729

OVERUSE INJURIES IN YOUNG ATHLETES

Danilo Višnjevac (1), Vesna Petrović (1), Tanja Rožek Mitrović (1), Slavica Višnjevac (2)

(1) COMMUNITY HEALTH CENTRE "DR MILORAD MIKA PAVLOVIĆ" INĐIJA; (2) POLYCLINIC "DR VIŠNJEVAC" INĐIJA

Summary: In overuse injuries, there is no clear single event that can be associated with the injury. They are thought to arise as a result of repeated submaximal loading of the musculoskeletal system that is not followed by adequate rest. The aim of the study is to determine the incidence of overuse injuries in young athletes, their gender structure and anatomical localization, as well as their impact on the level of training and competition in the previous season. The study is based on the analysis of questionnaires completed by athletes at the end of the 2018/2019 season. The Oslo Sports Trauma Research Center Overuse Injury Questioner questionnaire was translated into Serbian and modified to reflect the previous season. A total of 171 athletes participated, of which 99 (58.1%) were men and 72 (41.9%) were women. The research involved athletes aged 15 to 30 who competed in 5 sports disciplines: basketball, football, volleyball, handball and karate. Of the 171 athletes who participated in the trial, 48.5% registered at least one in the group of overweight injuries. Of the 99 male athletes, 44.4% reported injuries. In women, 54.8% of the total were registered in 72. According to anatomical localization, in men, knee injuries were registered in 4o, 9%, back injuries in 31.8%, injuries in multiple anatomic locations in 15.9% and shoulder injuries in 11.4%. In women, knee injuries were reported in 47.1%, shoulder injuries in 23%, back injuries 17.6% and more localization11.8%. Of the men who reported a knee injury, 61.1% reported having had a lot of involvement but with knee problems, as well as reduced training. A little more than half reported that they did not affect performance during the last season and reported mild knee pain. In the majority of respondents, they reported full participation without knee problems and did not reduce the amount of training and that their knee problems did not affect performance. The highest percentage reported mild pain. In male subjects with lower back injury, the highest percentage, 64.3%, reported full participation, but with problems, half reduced training. In the largest percentage, 64.4% had no effect on performance during the previous season and all subjects reported mild pain. All the respondents answered that they had full participation but with problems in the lower back. The largest 71.4% reduced training volume to a lesser extent, while 42.8% said the lower back problem did not affect performance during the previous season and all reported mild pain. Questions about shoulder problems the majority of male respondents, 60%, said they had reduced participation due to shoulder problems. An equal percentage of 40% reported that they had reduced their training volume to a lesser extent and generally decreased it. More than half, 60% reported having a shoulder problem that affected performance, and all respondents reported some level of shoulder pain. Also, the largest number of female respondents, 77.8%, reported full participation but with shoulder problems, decreased training and affected performance during last season. The highest percentage reported some level of pain.
In our research, some of the injuries caused by overstress were registered in almost half of the respondents, 48.5%. Injuries are more commonly reported in female subjects. In both groups of subjects, knee was the most common anatomical localization

Keywords: sport's overuse, sport's injuries, young athletes

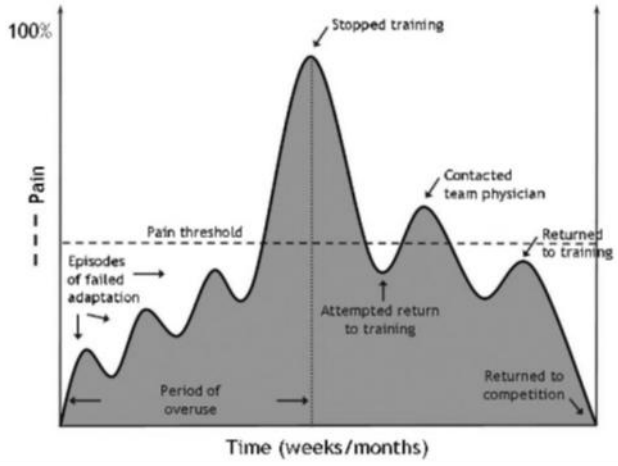
INTRODUCTION:

The participation of young people in sports and regular physical activity offers many benefits: improving general health, socializing with peers, increasing self-esteem. Regular physical activity and sports have been widely promoted due to its many positive effects. Contributes to improving the function of the cardiovascular system, has a positive effect on the development of the nervous and muscular systems, reduces anxiety [1,2,3,4,5]. Although children and young people should be encouraged to participate in a number of different sports activities and develop different skills, it is increasingly common today

for young athletes to participate in only one sport and the so-called "early specialization" in sports, which often ends before the end of primary school. Young people, like their parents, start with high intensity training from the desire to participate in elite leagues, get scholarships and the like. All this leads to more frequent injuries in sports. A large number of participants in sports activities have led to sports being the primary cause of injury in young people [1,6,7].

Today, sports injuries are most often divided into acute (traumatic) and overuse injuries. Traumatic injuries are the result of a specific event, which can be identified. In overuse injuries, there is no single individual event that can be associated with the injury. Overuse injuries are thought to result from repeated submaximal loading of the musculoskeletal system that is not followed by adequate rest. These are repetitive microtrauma resulting from repeated exposure to force or a large number of repetitions. In most cases, the tissue recovers at the beginning of the process without visible signs and symptoms, however as the process continues the possibility of adaptation is depleted and results in clinically clear symptoms [1,4,8,9,10,11,12,13]. Figure 1

Figure 1. Hypothetical overview of the onset of tissue injury and pain in a typical overuse injury. Adopted from R. Bahra. No injuries, but plenty of pain?On the methodology for recording overuse symptoms in sports. Br J Sports Med 2009;43:966–972. doi:10.1136/bjsm.2009.066936



Overuse injuries are considered to be one of the most common etiological factors leading to injuries in young athletes, and that almost half of sports injuries in children and young people belong to overuse injuries. Overuse injuries can affect: bones, muscles, tendons, ligament. There are several risk factors for the occurrence of an overuse injuries as: previous injury, adolescent age, higher training intensity, etc. Overuse injuries are considered to be underestimated in the literature because the majority of studies define injuries based on time off from competition. While more recent studies have cited the term "presence of any physical discomfort", and above all pain, which has led to a significantly higher number of reported overuse injuries [1,8,9,12,13]. However, there are also works that indicate that the term overuse injuriesis used too often and advise that it should be avoided until there is definitive evidence of a cause of injury. Overuse injuries most commonly affect the knee, shoulder, and lower back [10,11,13,14,15,16] . The importance of regular monitoring and protection of the health of athletes is increasingly recognized. For this reason, several systems for reporting and monitoring illnesses and injuries in athletes have been developed. Since 2008, the International Olympic Committee has also developed an injury monitoring system. The first official guidelines were for reporting and monitoring injuries in football, and later they formed the basis for other sports. Nowadays, a questionnaire developed in 2013 to register overuse injuries is increasingly used. The Oslo Sports Trauma Research Center Overuse Injury Questioner has 4 key questions and a response and scoring system. The questionnaire collected

data based on whether the athletes experienced / felt pain, limited participation in training or competition, and reduced training or competition volume [2,8,10,15,16,17,].

The goal. The aim of the study is to determine the frequency of overuse injuries in young athletes, their gender structure and anatomical localization, as well as their impact on the level of training and competition in the previous season.

METHOD

The research is based on the analysis of questionnaires completed by athletes at the end of the 2018/2019 season. The study involved 171 athletes, ages 15 to 30. The tested athletes competed in 5 sports disciplines: basketball, football, handball, volleyball and karate. We used the Oslo Sports Trauma Research Center questionnaire Overuse Injury Questioner translated into Serbian and modified so that the questions relate to the past season.

RESULTS

A total of 171 athletes participated, of which 99 (58.1%) were men and 72 (41.9%) were women. The study involved athletes aged 15 to 30 years competing in 5 sports disciplines: basketball, football, volleyball, handball and karate. Athletes aged 15 years were 29.7% (51), 16 years 18.8% (32), 17 years 5.45 (9), 18 years 10.8% (19), 19 years 2.8% (5), 20 years 5.45 (9), 21 years 2.8% (5), 22 years 5.4% (9), 23 years 5.4% (9), 24 years 4% (7), 25 years 2.8% (5), 27 years 1.3% (2), 28 years 2.8% (5), 29 years 1.3% (2) And 30 years 1.35 (2). Of the 171 athletes who participated in the test, 48.5% (83) registered at least one overuse injuries. Of the 99 male athletes, 44.4% registered overuse injury (44). In women, overuse injury were registered in 54.8% (39) of the total 72. According to anatomical localization, in men, knee injuries were registered in 40,9% (18), back injuries in 31.8% (14), injuries at multiple anatomical locations at 15.9% (7) and shoulder injury at 11.4% (5). In women, knee injuries were reported in 47.1% (18), shoulder injuries in 23% (9), back injuries 17.6% (7) and multiple localizations 11.8% (5) .

Among men who reported knee injury, 61.1% (11) reported having had full participation in training and competition but with knee problems, 27.8% (5) had full participation without knee problems, 11.1% (2) decreased participation due to knee problems And no one reported being unable to participate. 72.2% (13) did not reduce the amount of training due to knee problems, 11.1% (2) reported that they decreased the volume of training due to knee problems, 11.1% (2) moderately decreased, 5.6% (1) decreased to a greater extent. When asked how much your knee problem affected your performance over the past season, 55.5% (10) said they had no influence, 16.7% (3) responded to a lesser extent, 5.6 %% (1) they were moderately influenced, while 22.2% (4) responded that they were mostly influenced. Mild sports-related knee pain reported 55.5% (10), 33.4% (6) reported moderate pain, and 11.1% (2) reported severe pain. Of women, 55.5% (10) reported full participation without knee problems, 44.5% (8) reported full participation but with knee problems, no cases of reduced participation were reported. A total of 83.3% (15) did not reduce training volume, 16.7% (3) reported that they reduced training volume to a lesser extent, none reported a larger reduction volume. A total of 61.1% (11) reported that knee problems did not affect performance during the past season, while 38.9% (7) reported that they had less impact on performance, there was no response that they were moderately or mainly affected. 22.2% (4) did not report knee pain, 38.9% (7) reported mild pain, 27.8% (5) moderate pain, and 11.1% (2) severe sports-related knee pain. (Table 1.)

In men with lower back injury, 35.7% (5) reported full participation in training or competition with no problems in the lower back, 64.3% (9) reported full participation but with problems in the lower back. until reduced participation was reported. 50% (7) did not reduce the volume of training due to lower back problems, 50% (7) reduced it to a lesser extent, no moderate or major response. Respondents in 64.4% (9) answered that lower back problems did not affect performance during the last season, 35.7% (5) responded that they were less affected while there was no response that they were more affected. Subjects who had a problem in the lower back reported mild pain. In women, all respondents said that they had full participation in training or competition but with problems in the lower back. Of these, 14.3% (1) replied that the problem in the lower back did

not affect the decrease in training volume, 71.4% (5) reduced it to a lesser extent, 14.3% (1) moderately decreased until it was more extensive. When asked about the extent to which lower back problems affected their performance, over the past season, 42.8% (3) answered that it was unaffected, 28.6% (2) to a lesser extent and 28.6% (2) to a moderate extent while there was no greater response. All respondents answered that they experienced mild lower back pain related to sports. (Table 2.)

To questions about shoulder problems, during last season, of the total number of male respondents, 20% (1) answered that they had a full participation in training or competition without shoulder problems, 20% (1) a full participation but with problems with shoulder and 60% (3) responded that he had reduced involvement due to shoulder problems. None of the respondents answered that they did not reduce the volume of training due to shoulder problems. 40% (2) of the respondents reported that they reduced the training volume to a lesser extent, 20% (1) moderately and 40% (2) mostly reduced the training volume. 40% (2) of the respondents answered that the shoulder problem did not affect the performance during the last season, there was no answer to a lesser extent, 20% (1) and mostly 40% (2) answered moderately. None of the respondents answered that they did not have shoulder pain, 20% (1) reported mild pain, while moderate sport-related shoulder pain was reported in 60% (3) of the subjects and 20% (1) severe pain.

Of the total number of femal respondents who had a shoulder problem, 22.2% (2) had full participation without shoulder problems and 77.8 (7) full participation but with shoulder problems. The volume of training due to shoulder problems did not decrease 33.3% (3) of the examinee, to a lesser extent reduced 55.6% (5) of the respondents 11.1% (1) moderately. In 22.2% (2) the shoulder problem did not affect performance during the previous season, 55.6% (5) responded that it had less impact on performance and 22.2 (2) moderately. 55.6% (5) women had mild shoulder pain related to sports during the last season, while 22.2% (2) women had moderate pain and the same percentage 22.2% (2) did not report pain in the last season. (Table 3.)

Table 1. Replies regarding overuse knee injuries

	Have you had any difficulties participating in normal training and competition due to knee problems during the past season?				To what extent have you reduced you training volume due to knee problems during the past season?				
Answers	Full participation without knee problems	Reduced participation due to knee problems	Full participation but with knee problems	Cannot participate due to knee problem	No reduction	To a minor extent	To a moderate extent	To a major extent	Cannot participate at all
Men	27.8%	11,1%	61.1%	0%	72.2%	11.1%	11.1%	5.6%	0%
Women	55.6%	0%	44.4%	0%	83.3%	16.7%	0%	0%	0%
	To what extent have knee problems affected your performance during the past season?					To what extent have you experienced knee pain related to your sport during the past season?			
Answers	No effect	To a minor extent	To a moderate extent	To a major extent	Cannot participate at all	No pain	Mild pain	Moderate pain	Severe pain
Men	55.5%	16.7%	5.6%	22.2%	0%	0%	55.5%	33.4%	11.1%
Women	61.1%	38.9%	0%	0%	0%	22.2%	38.9%	27.8%	11.1%

Table 2. Replies regarding overuse lower back overuse injuries

	Have you had any difficulties participating in normal training and competition due to lower back problems during the past season?				To what extent have you reduced you training volume due to lower back problems during the past season?				
Answers	Full participation without lower back problems	Reduced participation due to lower back problems	Full participation but with lower back problems	Cannot participate due to lower back problem	No reduction	To a minor extent	To a moderate extent	To a major extent	Cannot participate at all
Men	35.7%	0%	64.3%	0%	50%	50%	0%	0%	0%
Women	0%	0%	100%	0%	14.3%	71.4%	14.5%	0%	0%

	To what extent have lower back problems affected your performance during the past season?					To what extent have you experienced lower back pain related to your sport during the past season?			
Answers	No effect	To a minor extent	To a moderate extent	To a major extent	Cannot participate at all	No pain	Mild pain	Moderate pain	Severe pain
Men	64.3%	35.7%	0%	0%	0%	0%	100%	0%	0%
Women	42.8%	28.6%	28.6%	0%	0%	0%	100%	0%	0%

Table 3. Replies regarding overuse shoulder overuse injuries

	Have you had any difficulties participating in normal training and competition due to shoulder problems during the past season?				To what extent have you reduced you training volume due to shoulder problems during the past season?				
Answers	Full participation without shoulders problems	Reduced participation due to shoulders problems	Full participation but with shoulders problems	Cannot participate due to shoulderspro blem	No reduction	To a minor extent	To a moderate extent	To a major extent	Cannot participate at all
Men	20%	60%	20%	0%	0%	40%	20%	40%	0%
Women	22.2%	0%	77.8%	0%	33.3%	55.6%	11.1%	0%	0%

	To what extent have shoulder problems affected your performance during the past season?					To what extent have you experienced shoulder pain related to your sport during the past season?			
Answers	No effect	To a minor extent	To a moderate extent	To a major extent	Cannot participate at all	No pain	Mild pain	Moderate pain	Severe pain
Men	40%	0%	20%	40%	0%	0%	20%	60%	20%
Women	22.2%	55.6%	22.2%	0%	0%	22.2%	55.6%	22.2%	0%

Discussion. It is estimated that 50% of sports injuries in children and young people are related to overuse injuries. However, detailed analysis and data on overuse injuries in children and young athletes are lacking, but in the opinion of athletes and coaches overuse injuries are very common. Young athletes are more at risk of developing overuse injuries than older athletes. There are several reasons for this: bone mineralization, cartilage development, immaturity of the musculoskeletal system, a sudden increase in training efforts, but also a lack of awareness of overuse injuries in young athletes [1,4,11,13,16]. In our study, 171 subjects participated, most of them men. Respondents are of different age groups, including sports experience, and have participated in 5 sports disciplines. This is important since it is known that overuse injuries may differ depending on the age and type of sport [1]. Of the total number of respondents, 48.5% reported at least one in the overuse injuries group. The literature data differ in part from the fact that the average prevalence of all overuse injuries is 39% to 46.2% of those who reported an injury [7,16]. A higher number of overuse injuries was registered in women than in men, 54.8% compared to 44.4%. This is

consistent with literature data that overuse injuries are more common in female than male. It is also stated that not only are overuse injuries more common but also occur earlier [11,13]. In men and women, the most common overuse injuries were knee injuries, which, like the total number of overuse injuries, were more common in women with 47.1%. This corresponds to literature data that indicate that the lower extremities are more commonly injured. Most overuse injuries are considered to include the knee, and this percentage ranges from 35% to 52%. It is also stated that overuse injuries knees are common in many different sports [3,10,13].

Lower back pain in young athletes is of particular concern because the developing skeletal system is particularly sensitive. Athletes who have had a lower back problem earlier are 3-6x more likely to have a lower back problem again [13]. The percentage of athletes who report a problem in the lower back varies between men and women. Among men out of the total who reported overuse injuries, 31.8% reported a problem in the lower back. This is slightly higher than the percentage reported in the literature of 21%, although there is data that even 40% [10.13]. In women, this percentage is lower and is 17.6%. In contrast, the proportion of athletes who reported having a shoulder problem was higher in women by 23% compared to men by 11.4%. An even higher percentage reported by the respondents is far less than some of the data that can be found in the literature I, citing 43%. [10]. The percentage of subjects who reported a problem at two or more anatomical sites was slightly higher in males 15.9% compared to females 11.8%. In our study, no anatomical localization of the injury was registered in relation to the type of sportso additional testing is needed to determine if the difference in the percentage of reported injuries, by anatomical localization, is directly related to sports discipline

The impact of overuse injuries on the level of training and competition differed in part depending on the anatomical localization of overuse injuries. In both men and women, the knee was most commonly affected. If we consider the knee as an anatomic localization of overuse injuries a higher percentage of men reported having had a full participation in training and competition but with knee problems, 61.1% of them compared to 44.4% of women. The impact on participation in training and competition was reported by respondents of both sexes. In men, an equal number, 11.1%, reported a smaller and moderate decrease in participation. Among women, 16.7% had a smaller decrease in participation rates, while there were no women who reported a moderate decrease. In both cases, this percentage is close to that found in the literature, and they state that 14% of athletes reported that overuse injuries influenced their current participation [16]. Respondents registered 16.7% of those who had a lesser impact on performance in the competition, 6.7% had a moderate effect on performance, and as many as 22.2% reported that it mainly affected performance during the competitions. The percentage of respondents who reported that their knee problem had a lesser impact on performance in the competition was slightly higher and amounted to 38.9%, but no cases were reported that had a moderate or major impact on performance. Respondents reported mild pain due to knee problems in 55.6%, moderate pain in 33.3%, and severe pain in 11.1% of cases. The subjects had mild pain in 38.9%, moderate pain 27.8% and severe pain in 11.1% of cases. Given the above percentages, it could be concluded that knee injuries had a slightly greater impact on male subjects than in female subjects

If we consider the lower back as an anatomic localization of the overuse injuries, they had a somewhat greater impact in the female subjects. While 64.3% of men reported full participation in training or competition but with problems in the lower back, 100% reported having a problem in the lower back. 71.4% reported that they had reduced training to a lesser extent, while in men it was 50%. Among respondents, 35.7% reported that lower back problems had less impact on performance in the competition, while in respondents, this percentage was 28.6%. However, the same number of 28.6% reported that it moderately influenced the performance in the competition, whereas in the male subjects this response was not registered. In men, 20% reported full participation but with shoulder problems, while as many as 60% reported reduced participation. In women, 77.8% reported full participation but with shoulder problems. The volume of training due to shoulder problems was reduced to a lesser

extent by 40% of respondents and 55.6% of respondents, while 20% of respondents moderately reduced the volume of training. Overuse injuries in the shoulder area also had quite a big impact on performance in the competition. Thus, 40% of respondents reported that shoulder injuries mainly affected performance, while 55.6% of respondents reported that shoulder injuries had less impact on performance. In both sexes, the presence of pain was high.

Our testing has several limitations. First of all, retrospective data collection that requires the athlete to remember the injury. But prospective collection, while recommended, does not ? it must also be more complete. Some studies have also shown that these results are similar, explaining that athletes report injuries more easily at the end of the season [8,13]. Overuse injuries was registered on the basis of the athlete's application and did not require clinical confirmation, which may have led to the fact that the "usual pain" associated with training was registered as overuse injuries.

Conclusion. In our study, some of the overuse injuries group was registered in almost half of the respondents, 48.5%. Injuries are more commonly reported in female subjects. In both groups of subjects, knee was the most common anatomic localization of overuse injuries. In comparison to the level of training and competition of the knee injury, the male respondents had a somewhat greater influence. Injuries localized in the lower back had a greater impact on the level of training and competitions, on the female subjects. The greatest impact on the level of training and competition in the subjects of both sexes had shoulder injuries.

REFERENCES:

1. John P. DiFiori, Holly J. Benjamin, Joel Brenner, Andrew Gregory, Neeru Jayanthi et al. Overuse Injuries and Burnout in Youth Sports: A Position Statement from the American Medical Society fot Sports Medicine. Clin J Sport Med 2014:24(1):3-20. doi: 10.1097/JSM.0000000000000060.
2. Soligard T, Steffen K, Palmer D, Alonso JM, Bahr R. Et al. Sports injury and illness incidence in the Rio de Janeiro 2016 Olympic Summer Games: A prospective study of 11274 athlets from 207 countries. Br J Sports Med 2017;0:1-8.DOI:10.1136/bjsports-2017-097956
3. Cheron C, Le Scanff C, Leboeuf-Yde C. Association between sports type and overuse injuries of extremities in adults: a systematic review. Chiropractic and Manual Therapies 2017 25:4. DOI 10.1186/s12998-017-0135-1
4. C.P. van Wilgen, E.A.L.M. Verhagen. A qualitative study on overuse injuries: The belifs od athletes and coaches. Journal of Science and Medicine in Sport 2012;15:116-121.
5. Danilo Višnjevac, Slavica Višnjevac. ECG in preparticipation screening of young athletes. Opšta medicina 2015;21(1-2):41-48.DOI. 10.5937/opmed1501041V
6. Committee on Sports Medicine and Fitness.Intensive Training and Sports Specialization in Young Athletes. Pediatrics 2000;106;154. DOI. 10.1542/peds.106.1.154
7. Philip Von Rosen, Anders Kottorp, Cecilia Friden, Anna Frohm, Annette Heijne. Young, talented and injured: Injury perceptions, experiences and consequences in adolescent elite athletes. European Journal of Sport Science 2018;18(5):731-740. DOI.10.1080/17461391.2018.1440009
8. R Bahr. No injuries, but plenty of pain? On the methodology for recording overuse symptoms in sports.Br J Sports Med 2009;43:966-972. DOI. 10.1136/bjsm.2009.066936
9. Joel S. Brenner. Overuse Injuries, Overtraining, and Burnout in Child and Adolescent Athletes. Pediatrics 2007;119;1242. DOI: 10.1542/peds.2007-0887
10. Clarens B, Myklebust G, Bahr R. Development and validation of a new method for registration of overuse injuries in sports injury epidemiology: the Oslo Sports Trauma Research Center (OSTRC) Overuse Injury Questionnair. Br J Sports Med 2013; 47:495-502
11. Allison N. Schroeder, Dawn Comstock, Christy L. Collins, Joshua Everhart, David Flaningan et al. Epidemiology of Overuse Injuries among High-School Athletes In the United States. J Pediatr 2015;166:600-6.
12. Aicale R., Tarantino D., Maffulli N. Overuse injuries in sport: a comprehensive overview. Journal of Orthopaedic Surgery and Research 2018;13:309
13. Mari Lappanen, Kati Pasanen, Pekka Kannus, Tommi Vasankari, Urho M. Kujala et al. Epidemiology of Overuse Injuries in Youth Team Sports: A 3-year Prospectiv Studey.Int J Sports Med 2017. DOI.10.1055/s-0043-114864
14. P L Gregora. „Overuse"-an overused term?Br J Sports Med 2002;36:82-83.
15. Nagano Y, Kobayashi-Yamakawa K, Higashihara A, Yako-Suketomom H. Japanese translation and modification of the Oslo Sports Trauma Research Center overuse injury questionnair to evaluate overuse injuries in female college swimmers. PloS ONE 2019;14(4):e0215352
16. Aasheim C, Stavenes H, Andersson SH, Engbretsen L, Clarens B. Prevalence and burden of overuse injuries in elit junior handball. BMJ Open Sport Exerc Med 2018;4:e000391.doi:10.1136/bmjsem-2018-000391
17. Clarens B, Ronsen O, Myklebust G, Florens TW, Bahr R. The Oslo Sports Trauma Research Center questionnaire on health problems: a new approach to prospective monitoring of illness and injury in elite athletes. Br J Sprts Med 2013;0:1-8.DOI. 10.1136/bjsports-2012-092087

TIMOK MEDICAL GAZETTE

Vol. 45 (2020) No. 1-2 Original papers

UDK 613-056.24:616-006
616.22-089.85
COBISS.SR-ID 16485129

SUBJECTIVE ASSESSMENT OF THE QUALITY OF LIFE OF LARYNGECTOMIZED PATIENTS BEFORE AND AFTER SPEECH REHABILITATION

Mila Bunijevac (1,2), Neda Milošević (1, 3), Gordana Čolić (1), Dragan Čauševac (1,3), Ivana Ristić (4)

(1)HIGH SCHOOL OF SOCIAL WORK, DEPARTMENT OF SPEECH THERAPY, BELGRADE, SERBIA; (2) PHI HOSPITAL "SVETI VRAČEVI", REPUBLIC OF SRPSKA, BIH; (3) CENTER FOR SPEECH PATHOLOGY - LOGOMEDIC, BELGRADE, SERBIA; (4) HIGH SCHOOL OF SOCIAL WORK, OCCUPATION THERAPY DEPARTMENT, BELGRADE, SERBIA

Abstract: Introduction: Total laryngectomy exposes the patient to a great deal of psychological stress, both because of the underlying disease and the loss of a very important organ in the overall functioning of the organism and organs, which enables an adequate communication process. Objective: The aim of this study is to conduct a subjective assessment of the quality of life of laryngectomized patients before and after vocal rehabilitation. Methods: The study involved 50 patients after total laryngectomy, ranging in age from 51 years to 83 years. A subjective assessment of speech and voice was conducted with the University of Michigan Quality of Life Instrument — HNQOL and Voice Handicap Index — VHI. These instruments provide information from the patient about the treatment or treatment applied, as well as the impact that vocal rehabilitation has on the quality of his or her life before and after treatment. Results: Prior to vocal rehabilitation of the HNQOL scale, patients experienced pronounced difficulties on all subscales, especially when it came to communication ($\bar{X}$ = 5.75 ± 8.64) and emotions ($\bar{X}$ = 16.66 ± 15.17); expressed, while chewing/food ingestion ($\bar{X}$ = 53.91 ± 26.45) and pain ($\bar{X}$ = 50.50 ± 17.71) had mean values. VHI scale (physical subscale $\bar{X}$ = 36.6 ± 2.93; emotional subscale $\bar{X}$ = 34.96 ± 3.79; functional subscale $\bar{X}$ = 35.64 ± 3.37) before vocal rehabilitation, all subjects (100%) belonged to the third category (severe handicap), which was a problem when it came to psychosocial functioning. After vocal rehabilitation, the mean values on the HNQOL scale were very highly expressed and statistically highly significantly improved (communication $\bar{X}$ = 93.37 ± 10.28; emotions $\bar{X}$ = 90.58 ± 8.23; chewing/swallowing food $\bar{X}$ = 96.66 ± 5.77; pain $\bar{X}$ = 92.25 ± 6.98) which indicated a good quality of life. On the VHI scale of low value (physical subscale $\bar{X}$ = 10.84 ± 4.41; emotional subscale $\bar{X}$ = 4.42 ± 4.63; functional subscale $\bar{X}$ = 21.32 ± 13.29) shows a statistically high significant improvement, ie good psychophysical and functional condition patient. Conclusion: Subjective assessment after vocal rehabilitation resulted in improvement of all parameters tested, especially in the domain of communications and emotions.Vocal rehabilitation has had a positive effect on improving the quality of life of these patients, integrating them into the family and the environment, as well as performing daily activities that we observe through their physical, emotional and functional state.

Keywords: Larynx tumor, Total laryngectomy, Quality of life, HNQOL scale, VHI scale.

INTRODUCTION

Total laryngectomy is a radical procedure that results in the permanent loss of the generator and part of the resonator of the voice, the larynx in which the underlying laryngeal tone is created [1]. Total laryngectomy is performed in advanced cases of laryngeal cancer with signs of deep laryngeal infiltration (T3) or in tumors that have spread to adjacent organs (T4), ie when all the potential for partial surgery is exhausted (2, 3). The patient is exposed to a great deal of psychological stress, both because of the underlying illness and the loss of a very important organ in the overall functioning of the organism and the organ participating in the exercise of communication [4]. Total laryngectomy leads to physical and functional changes that can affect the emotional state and

some of the most basic life functions, including breathing, swallowing and communication [5].
Speech rehabilitation is a complex and active process that requires the involvement and cooperation of a laryngectomized person and speech therapist. Speech is an expression of social activity because it is realized in communication with other people. Rehabilitation of laryngeomized patients modifies the anatomy of the upper aerodigestive pathways, creating new anatomical conditions on which breathing, swallowing and phonation functions will have to be organized [3]. It is a very important form of rehabilitation, which in addition to successfully mastering one of the methods of speech increases confidence, creates a better sense of security and improves quality of life [6],
The basic possibilities of speech rehabilitation after total laryngectomy are the development of esophageal speech skills, treoesophageal puncture with the use of a vocal prosthesis, and the use of electrolarynx.
Quality of life has been conceptualized as a multidimensional concept in which health, well-being, health comprehension, functional status and life choices overlap [7, 8]. Some define quality of life in cancer patients as the difference between patient expectations and low achievement that affect quality of life improvement [9]. Quality of life is a general well-being that encompasses objective factors and a subjective evaluation of physical, material, emotional and social well-being, including personal development and purposeful activities [10].

Basic aspects of quality of life are health, functional ability, life satisfaction and independence [11]. It can be measured using a variety of questionnaires, which are mostly completed by patients and thus gives an opinion on the experience of their speech and voice when it comes to physical, emotional and functional state. The quality of life of patients after total laryngectomy is studied within the oncology of head and neck tumors, because of all malignant tumors of the head and neck, laryngeal cancer is the most common cause of oral cancer and oropharynx.
The aim of this study is to examine the quality of life of laryngectomized patients before and after vocal rehabilitation.

METHODS

The study involved 50 patients after total laryngectomy, ranging in age from 51 years to 83 years. The research was conducted at SWU "SvetiVračevi" Hospital in Bijeljina and the Military Medical Academy in Belgrade from April 2014 to November 2015. Data on gender, age, education, smoking experience, time when rehabilitation was initiated, vocal rehabilitation model, and length of treatment were collected through a questionnaire and interview with a patient.
A subjective voice assessment was conducted with University of Michigan Quality of Life Instrument instruments — HNQOL, Terrell et al. [12] and the Voice Handicap Index — VHI, Jacobson et al. [13]. University of Michigan Quality of Life Instrument —HNQOL scale is used to evaluate the quality of life of patients with head and neck cancer. It has been translated into many languages and adapted to different cultures. It was adapted for our speech area by Petrovic-Lazic, Bunijevac in 2014. The scale contains 30 questions, 20 of which are used to score four domains of quality of life assessment: communication (4 points), chewing/swallowing food (6 points), pain (4 points) and emotions (6 points). Respondents were tasked with selecting the answer given for each of these questions, expressing their feelings and opinions about the possibility or success of communication, the possibility of chewing / swallowing food, pain and emotional state. The HNQOL scale can also be used to assess a patient's satisfaction with treatment or treatment, as well as the impact of speech rehabilitation on the quality of his or her life before and after treatment.
Voice Handicap Index — The VHI scale is used to measure the therapeutic outcome of vocal rehabilitation as well as to evaluate the severity of a voice problem. The VHI scale covers three areas, namely: P — physical, E — emotional, F — functional. Each area contains 10 questions. Respondents were tasked with selecting the answer given for each question: "never", "almost never", "sometimes", "almost always", "always". In this way, they expressed their opinions about the experience of their voice and speech when it comes to physical, emotional and functional state. The VHI scale can provide information about the degree of speech disability experienced by the patient himself and the impact that vocal rehabilitation has on the

quality of his or her life before and after treatment. Data were collected on two occasions. Patients completed the questionnaire the first time they came to the speech therapist, before starting treatment and the second time after completing the treatment.

Descriptive measures, arithmetic mean with associated standard deviation, as well as minimum and maximum were used in the statistical data processing. Frequency and percentages, and t-test for dependent samples were used. Statistical analysis and analysis were done in the SPSS version 20 (Statistical Package for the Social Sciences) computer program.

RESULTS

The study involved 50 patients after total laryngectomy, 47 male subjects and three female subjects, as shown in Table 1. All subjects in this study were smokers. The most frequently represented respondents were pensioners, slightly fewer were persons in employment, and these were mostly persons with secondary education. The examiners came from both urban and rural areas.

Table 1.Structure of the sample by gender, smoking status, education and place of residence

		Frequency	Percentage
Gender	Male	47	94.0
	Female	3	6.0
Smoking status	Smoker	50	100
	Non-smoker	—	—
Education	Primary school	4	8.0
	High School	31	62.0
	VS more	15	30.0
Employee	Employment	13	26
	Pensioners	26	52
	Farmere	11	22
City life	The countryside	17	34.0
	City	33	66.0

f - frequency, % - percentage.

The age of the respondents ranged from 51 to 83 years (Table 2). The length of smoking experience ranges from 20 to 55 years, and the length of treatment ranges from one month to 12 months.

Table 2.Structure of the sample by age of the respondent, length of smokers' time and length of treatment

	N	Min	Max	M	SD
Age	50	51.00	83.00	62.6	7.32
Smoking duration (years)	50	20	55	35.82	6.16
Duration of treatment (months)	50	.00	12.00	3.29	1.79

N - number of subjects, Min. - minimum, Max. - maximum, $\bar{x}$ - arithmetic mean (mean), SD – standard deviation.

Patients mastered two models of speech, namely esophageal and electro-laryngeal speech (Table 3).

Table 3. Structure of the sample according to vocal rehabilitation model

		N	%
	Patients that managed esophageal speech	44	88,0
	Patients that are using electrolarynx	6	12,0
	Total	50	100,0

N - number of subjects, % - percentage.

Prior to vocal rehabilitation, the HNQOL subscales had low levels of expression on the HNQOL subscale, especially with regard to communication and emotion subscales, whereas the subscales related to food ingestion and chewing and pain had medium levels. Using the t-test for dependent samples after vocal rehabilitation, statistically significant improvement was found on all subscales of the HNQOL scale (Table 4). A statistically significant difference on the HNQOL scale also exists in the total score before and after treatment, which means that better overall functioning of patients in all examined domains after treatment compared to the pre-treatment period, which also indicated a better quality of life.

Table 4.HNQOL scale — before and after vocal rehabilitation

HNQOL	Application Time	$\bar{x}$	SD	t	p
Chewing/swallowing food	Before treatment	53.91	26.45	-12.07	0.00
	After treatment	96.66	5.77		
Communication	Before treatment	5.75	8.64	-43.28	0.00
	After treatment	93.37	10.28		
Emotion	Before treatment	16.66	15.17	-31.94	0.00
	After treatment	90.58	8.23		
Pain	Before treatment	50.50	17.71	-15.96	0.00
	After treatment	92.25	6.98		
Total	Before treatment	52.50	17.71	-16.06	0.00
	After treatment	93.57	6.36		

$\bar{x}$ - arithmetic mean, SD - standard deviation, t - t-test, p - statistical significance
Statistically significant values are highlighted (bold)

Prior to vocal rehabilitation on all subscales of the VHI scale, subjects had high mean values, which negatively affected their quality of life. Using the t-test for dependent samples after vocal rehabilitation, statistically significant improvement was found on all subscales of the VHI scale, that is, the patients' physical, emotional and functional condition improved after treatment (Table 5).

A statistically significant difference on the VHI scale also exists in the total score before and after treatment, which means that the overall functioning of patients after treatment is better compared to the pre-treatment period.

Table 5.VHI scale — before and after vocal rehabilitation

VHI	Time of using	$\bar{x}$	SD	t	p
Physical subscale	Before treatment	36.6	2.93	32.7	0.00
	After treatment	10.84	4.41		
Emotional subscale	Before treatment	34.96	3.79	39.9	0.00
	After treatment	4.42	4.63		
Funcional subscale	Before treatment	35.64	3.37	35.4	0.00
	After treatment	6.06	5.25		
Total	Before treatment	107.2	8.46	39.10	0.00
	After treatment	21.32	13.29		

$\bar{x}$ - arithmetic mean, SD - standard deviation, t - t-test, p - statistical significance
Statistically significant values are highlighted (bold)

DISCUSSION

Laryngeal cancer accounts for 1-3% of all malignant tumors and has increased significantly in recent years. About 20% are present in head and neck tumors. They occur more frequently in males (94%) than in females (6%), which has been reported in studies by other authors [14, 15].It has been observed that men consume more alcohol and cigarettes than women.

The age structure influences its frequency, so a sharp increase is observed after the age of 40. The age of the respondents in our study ranged from 51 to 83 years ($\bar{X}$ = 62.6 ± 7.32). The results in this study are comparative with the results of a number of studies that state that laryngeal cancer occurs from 4 to 7 decades, with most cases occurring in the sixth decade of life [16, 17].

One of the leading causes of laryngeal cancer is smoking. In our study, all subjects were active smokers with an average length of smoking time of 35.8 ± 6.16. years. Other authors also highlight the negative effects of smoking when it comes to the occurrence of laryngeal cancer [18, 19, 15], as well as the combined effect of smoking and alcohol consumption [20].

The length of vocal rehabilitation ranged from one month to one year. In patients who successfully mastered esophageal speech, vocal rehabilitation lasted longer, while patients who successfully mastered electro-laryngeal speech had three to five treatments. According to other researchers, continuous speech rehabilitation lasted from three to eight months [21], and mastering esophageal speech from six to twelve months [15]. Vocal rehabilitation should take as long as necessary to achieve optimal results.

Before vocal rehabilitation based on the results obtained on the HNQOL scale, patients had impaired quality of life in all domains. Neilson et al. [17] state that in patients after total laryngectomy there is a generalized sense of diminished quality of life.

Inability to speak in our study adversely affected the quality of life of patients after total laryngectomy, which is consistent with other studies [22, 23, 24, 15, 25].

Prior to vocal rehabilitation, laryngectomized patients exhibited emotional distress related to their condition. Other authors 'research findings [22, 26, 15] also highlight the negative impact of physical appearance on patients' emotional state, leading to a decline in quality of life.

On the subscale, chewing/ingesting food prior to vocal rehabilitation, subjects experienced moderate interference with taste loss and chewing / ingestion of food, which negatively affected their quality of life, consistent with other studies [27, 28].

Pain is one of the most common symptoms in cancer patients and is a common cause of depression, fear, hopelessness and declining quality of life [29]. In our study, the presence of pain in the subjects was of moderate intensity. They mostly had shoulder pain, which negatively affected their quality of life.

Based on the results obtained on the VHI scale, all subjects belonged to the group of severe speech handicap prior to vocal rehabilitation, which is understandable because laryngeal cancer is a chronic disease that causes emotional and psychological problems in the patient [30]. Multiple studies have shown that total laryngectomy has a negative impact on the physical, emotional and functional state of the patient leading to a decline in quality of life [31, 32]. The physical consequences of total laryngectomy limit the patient in social activities as well [6]. In patients after total laryngectomy, social functions and roles in the environment in which they live are impaired, the disease prevents them from performing family, social and professional activities [6]. Inclusion in different types of treatment has a positive impact on reducing these problems, with vocal rehabilitation being the primary one, as shown in our study.

After completing vocal rehabilitation, mastering one of the methods of speech had the positive effect of neglecting physical appearance, enhancing self-confidence and a sense of security, and thus improving the quality of life. Vocal rehabilitation in patients after total laryngectomy affects their emotional, social and psychological functioning, as well as a better quality of life [33, 26, 15].

Involvement of patients after total laryngectomy in the process of vocal rehabilitation and speech control is one of the important factors for improving quality of life, facilitating return to normal life activities and positively influencing the improvement of emotional state of these patients [34]. Which method will be used in the vocal rehabilitation process varies from patient to patient. Tracheoesophageal speech is one of

the most preferred methods [35], with electro-laryngeal speech the most commonly adopted allaringeal phonation [36], while esophageal speech is the best and most natural way of establishing speech function.

The goal of vocal rehabilitation is to enable patients to successfully communicate with the environment using some of the models of alaringeal speech, and thus improve their quality of life. The success of vocal rehabilitation is judged by the patient's subjective experience, that is, his / her self-assessment of how successful he / she is in daily activities and how satisfied he / she is with his/her quality of life.

CONCLUSION

Subjective assessment after vocal rehabilitation led to an improvement in all parameters examined, especially in the domain of communication and emotions.Vocal rehabilitation is of great importance in patients after total laryngectomy and is aimed at successfully mastering one of the speech methods, which is strongly associated with improving quality of life.It allows the return to normal life activities and improves the emotional state of these patients, thus reducing the consequences of total laryngectomy. The positive effect of vocal rehabilitation is achieved by strengthening self-confidence and creating a sense of security. The success of vocal rehabilitation is judged by the patient's subjective experience, that is, their self-assessment of how successful they are in their daily activities and how satisfied they are with their quality of life. In the future, improving the quality of life of laryngectomized patients should be one of the main goals that can be achieved through a multidisciplinary treatment approach and vocal rehabilitation, enabling them to return to the social and work environments more quickly.

Gratitude. The authors thank Prof. Jeffrey Terrel, PhD, an otolaryngologist in Ann Arbor, Michigan, who allowed us to use his scale University of Michigan Head & Neck Quality of Life Instrument (HNQOL).

Conflict of interest: The authors declare that they have no conflict of interest.

REFERENCES

1. Mitrović S. Komunikacijabezlarinksa. Med pregl 2008-LXI (3-4)-121-2.
2. Ђukić V, Nešić V. Hirurškaanatomija i fiziologijalarinksa. ActaClin 2008-8(3)-21-47.
3. Bunijevac M. Uticajvokalnerehabilitacijenakvalitetživotalaringektomiranihpacijenata.Beograd: Visokaškolasocijalnograda; 2019. ISBN 978-86-81394-10-6
4. Petrović-Lazić M, Kosanović R, Vasić M. Rehabilitacijalaringektomiranihbolesnika. Beograd: Nova naučna; 2010 (pp. 87-88)
5. Attieh AY, Searl J, Shahaltough NH, Wreikat MM, Lundy DS. Voice restoration followingtotallaryngectomy by tracheoesophageal prosthesis: Effect on patients' quality of life and voice handicap in Jordan. Health Qual Life Outcomes2008, 26.
6. Bunijevac M, Petrović-Lazić M, Maksimović S. Quality of life of patients after total laryngectomy. Saarbrücken, Germany:Lambert Academic Publishing; 2017. (pp. 36).
7. Berzon R, Hays RD, Shumaker SA. International use, application and performance of health -related quality of life instruments. Qual Life Res 1993-2(6)-367-8.
8. Dolan P. Valuing health-related quality of life. Pharmacoeconomies 1998-15(2)-119-127.
9. Calman KC. Quality of life in cancer patients--an hypothesis. J Med Ethics 1984-10(3)-124-127.
10. Felce D, Perry J. Quality of life: its definition and measurement. Res DevDisabil 1995-16(1)-51-74.
11. Đukić V, Milovanović J, Folić M, Pavlović B, Jotić A, Trivić A, et al. Karcinomlarinksa. Beograd: Paratenton; 2017. (pp. 236)
12. Terrell JE, Nanavati KA, Esclamado RM, Bishop JK, Bradford CR, Wolf GT. Head and Neck cancer-specific quality of life: Instrument validation. Arch Otolaryngol Head Neck Surg1997-123-1125-1132.
13. Jacobson BH, Johnson A, Grywalski C, Silbergleit A, Jacobson G, Benninger MS, et al.. The Voice Handicap Index (VHI): development and validation. Ame J Speech Lange Pathol1997-6-66-70.
14. Rosso M, Kraljik N, Mihaljević I, Sirić L, Sos D, Vranjes Z. Epidemiology of laryngeal cancer in Osijek-Baranja County (eastern Croatia). CollAntropol2012-36(2)-107-110.
15. Bunijevac M, Petrović-Lazić M. Značajranevokalnerehabilitacije i kvalitetživotalaringektomiranihpacijenata. Spec edukacrehabilitac 2016-15(4)-379-393.
16. Woodward TD, Oplatek A, Petruzzelli GJ. Life after total laryngectomy. A measzreod long-term survival, function and quality of life. Arch Otolaryngol Head Neck Surg 2007-133(4)-526-532.
17. Neilson K, Pollard A, Boonzaier A, Corry J, Castle JD, Smith D, et al. A longitudinal study of distress (depression and anxiety) up to 18 months after radiotherapy for head and neck cancer. Psychooncology 2013-22(8)-1843-8.
18. Duffy SA, Terrel JA, Valenstein M, Ronis DL, Copeland LA, Connors M. Effect of smoking, alcohol and depression on the quality of life of head and neck cancers patients. Gen HospPsychiatry 2002-24(3)-140-147.
19. Laccourreye O, Ishoo E, de Mones E, Garcia D, Kania R, Hans S. Supracricoidhemilaryngopharyngectomy in

patients with invasive squamous cell carcinoma of the pyriform sinus. Part I: Technique, complications, and long-zerm functional outcome. Ann OtolRhynolLaryngol2005-114-25-32.
21. Vartanian JG, Carvahlo AL, Toyota J, Kowalski IS, Kowalski LP. Socioeconomic effect of and risk factors for disability in long-term survivors of head and neck cancer. Arch OtolaryngolHead Neck Surg 2006-132(1)-32-35.
22. Sokal W, Kordylewska M, Golusiński W. An influence of some factors on the logopedic rehabilitation of patients after total laryngectomy.Otolaryngol Pol 2011-65(1)-20-5.
23. Doyle PC, Keith RL. Contemporary considerations in the treatment and rehabilitation of head and neck cancer: Voice, speech and swallowing. Austin, TX: Pro-Ed; pp. 2005-76-77.
24. Palmer AD, Graham MS. The Relationship Between Communication and Quality of Life in Alaryngeal Speakers. J Speech Long PatholAudiol2004-28(1)-6-24.
25. Saki N, Nikakhlagh S, Araghi S, Khanifer Z. The quality of life of patients after total laryngectomy. Biosci Biotech Res Asia 2015-12-103-108.
26. Mertl J, Žáčková E, Řepová B. Quality of life of patients after total laryngectomy: the struggle against stigmatization and social exclusion using speech synthesis. DisabilRehabil Assist Teechnol 2017-27-1-11.
27. Nemr K, Raquel ACS, Takeshita-Monaretti TK, Pires-Buzanelli E,Simões-Zenari M, Aguiar-Ricz LA. Scientific Evidence Regarding the Quality of Life of Total Laryngectomees. Arch OtolaryngolRhinol2015-1(2)-034-044.
28. PernambucoLdeA, Oliveira JHP, Régis RMFL, Lima LM, Araújo AMB, Balata PMM, et al. Quality of life and deglutition after total laryngectomy. Int Arch Otorhinolaryngol 2012-16(4)-460-465.
29. Bunijevac M, Petrović-Lazić M, Jovanović-Simić N, Maksimović S. Uticajradioterapijenakvalitetživotalaringektomiranihpacijenata pre i poslevokalnerehabilitacije. Tim med glas2018-43(2)-41-48.
30. Simone CB 2nd, Vapiwalo N, Hampshire MK, Metz JM. Palliative care in the management of lung cancer: analgesic utilization and barries to optimal pain management. J Opioid Manag2012-8(1)-9-16.
31. Ateşci FÇ, Oğuzhanoğlu NK, Baltalarli B, Karadağ F, Özdel O, Karagöz N. Kanserhastalarindapsikiyatrikbozukluklarveilişkilietmenler. TürkPsikiyatriDergisi 2003-14(2)-145-152.
32. Elmiyeh B, Dwivedi RC, Jallali N, Chisholm EJ, Kazi R, Clarke PM, et al. Surgical voice restoration after total laryngectomy: an overview. Indian J Cancer 2010-47(3)-239-247.
33. Schindler A, Mozzanica F, Ginocchio D, Invernizzi A, Peri A, Ottaviani F. Voice-related quality of life in patients after total and partial laryngectomy. AurisNasus Larynx 2012- 39(1)-77-83.
34. Rossi VC, Fernandes FL, Ferreira MA, Bento LR, Pereira PS, Chone CT. Larynx cancer: Quality of life and voice after treatment. Braz J Otorhinolaryngol 2014-80-403-408.
35. Bunijevac M, Petrović-Lazić M, Jovanović-Simić N, Maksimović S. Quality of life of patients after total laryngectomy – SF-36. Early Intervent Spec EducatRehabilit2016-587-598. (pp. 596)
36. El-Sharnobya MK, Behairya EA, Abdel-Fettah AA, Al-Belkasy MA. Voice rehabilitation after total laryngectomy. Menoufia Med J 2015-28(4)-800-806.
37. Hanjun L, ManwaLNg. Electrolarynx in voice rehabilitation. AurisNasus Larynx 2007-34(3)-327-332.

UDK 616.12-073"2019"
COBISS.SR-ID 16541449

PARADIGM CHANGE FOR STABLE CORONARY DISEASE IN CHRONIC CORONARY SYNDROME. NOVELTIES IN THE GUIDELINES OF THE EUROPEAN SOCIETY OF CARDIOLOGISTS FROM 2019

Dušan Bastać (1), Zorica Mladenović (2), Vojkan Čvorović (3), Zoran Joksimović (4) Snežana Pavlović (5) Biserka Tirmenštajn-Janković (6), Bratimirka Jelenković (7), Brankica Vasić (7), Dragana Adamović (8), Aleksandar Jolić (8), Mila Bastać (1), Anastasija Raščanin (1).

(1) INTERNAL MEDICINE CLINIC "DR BASTAĆ", ZAJEČAR; (2) CLINIC OF CARDIOLOGY, MILITARY MEDICAL ACADEMY, BELGRADE; (3) POLYCLINIC BELMEDIC, BELGRADE.; (4) INTERNAL MEDICINE CLINIC "JOKSIMOVIĆ", BOR; (5) SPECIALIST PRACTICE FOR INTERNAL MEDICINE "DR PAVLOVIĆ-CARDIOLOGY", BELGRADE; (6) DEPARTMENT OF NEPHROLOGY, INTERNAL MEDICINE SERVICE, HEALTH CENTER ZAJECAR; (7) PEDIATRIC SERVICE, HEALTH CENTER ZAJECAR; (8)DEPARTMENT OF INVASIVE CARDIOLOGY, INTERNAL MEDICINE SERVICE, HEALTH CENTER ZAJECAR

SUMMARY: Although the English physician Heberden described angina pectoris (AP) two and a half centuries ago, our understanding of this syndrome, as a cause, an optimal diagnostic approach and treatment, continues to develop. The new guidelines of the European Society of Cardiology(ESC) from year 2019 brings, first of all, a paradigm shift for stable coronary artery disease (SCAD) to the comprehensive term chronic coronary syndromes (CCS), which essentially means that chronic coronary artery disease (CAD) has complex clinical scenarios and may have periods of instability, at any evolutionary stage. The results of the essential COURAGE study and the latest studies: ISCHEMIA, ORBITA and metha-analysis on CCS as well as the key messages of the European Guidelines for Diagnosis and Treatment of Chronic Coronary Syndromes (CCS) shed light on the issue of coronary heart disease. Chronic coronary artery disease (CCAD) has long stable periods but due to acute atherothrombotic events, erosion or rupture of atherosclerotic plaque can progress to some of the acute coronary syndromes (ACS). The disease is chronic, usually progressive and therefore serious even in asymptomatic stages. The dynamic nature of CAD is manifested in various clinical presentations, which we categorize into either acute or chronic coronary syndromes. The paradigm shift emphasizes the fact that the dynamic processes of accumulation in atherosclerotic plaques and functional alterations of the coronary circulation can be modified by lifestyle changes, pharmacological therapy and myocardial revascularization (MR), which lead to stabilization or regression of the disease but unfortunately not complete cure. Careful evaluation of the anamnesis, characterization of anginal and other symptoms and evaluation of risk factors and manifestations of previous cardiovascular diseases (CVD), as well as assessment of the adequacy of physical activity and exercise tolerance, are of cardinal importance. The current guide to CCS identifies 6 leading and most common clinical syndromes: 1. Patients with suspected CCS and stable angina pectoris and / or dyspnea on exertion; 2. Patients with newly developed heart failure (HF) or left ventricular dysfunction (LVD) and suspected CAD; 3. Asymptomatic and symptomatic patients with stabilized symptoms lasting less than one 1 year after ACS or recent myocardial revascularization (MR); 4. Asymptomatic and symptomatic patients more than 1 year after ACS or MR; 5. Patients with AP and suspected vasospastic or microvascular disease; 6. Asymptomatic individuals in whom CAD was detected at screening. Each of these scenarios is classified as CCS and is a consequence of different evolutionary phases of chronic CAD, and has a different risk for future adverse cardiovascular (CV) events. Pre-test probability (PTP) of CAD, based on age, sex and quality of symptoms, has been revised and changed from the previous guide from year 2013. A new term has been introduced: Clinical probability of obstructive coronary artery disease (CPCAD) which includes both PTP and various risks factors of atherosclerotic CAD and serves to exclude or confirm the suspicion of CAD. The general methodological approach for initial diagnosis for patients with AP and suspected obstructive CAD involves 6 steps. STEP 1-Assessment of symptoms and signs to identify patients with possible unstable AP and other forms of ACS; STEP 2 is an assessment of the general condition and quality of life that decide on treatment planning; STEP 3 includes basic diagnostic procedures and assessment of left ventricular (LV) function of the heart; STEP 4 makes the determination of Pre-test and Clinical probability of obstructive CAD; STEP 5 is the selection of a

Vol. 45 (2020) No. 1-2 TIMOK MEDICAL GAZETTE Review article

diagnostic test by physical or pharmacological stress via ECG and imaging methods including MSCT coronary angiography (CTA) to establish the diagnosis of CAD. Finally, STEP 6 is the assessment of the risk of adverse CV events, especially mortality, and based on that, make definitive therapeutic decisions with invasive coronary angiography (ICA) and possible MR. If obstructive CAD cannot be ruled out by clinical evaluation, either a noninvasive functional imaging test or anatomical imaging by CTA is performed as an initial test to exclude or confirm the diagnosis of CAD. Anatomical and functional assessment should be considered for a decision on RM, except in severe coronary stenosis> 90%. A high risk of adverse CV events identifies patients who would have great prognostic benefit from MR, even if asymptomatic. The role of myocardial revascularization (MR) has been placed in the context of recent evidence relating to the prognostic role of percutaneous coronary interventions (PCI) or coronary artery bypass graft (CABG) in this low-risk population. MR is reserved for patients where there is strong evidence to improve prognosis based on evidence of regional ischemia by perfusion imaging. Patients at high risk of mortality of 3% per year or more undergo coronary flow fractional reserve (FFR) or coronary flow reserve (CFR) due to perform MR even if they have no symptoms. The application of a healthy lifestyle reduces the risk of subsequent adverse CV events and is part of adequate secondary prevention therapy. Regular vaccination against influenza is necessary for everyone with CCS. Optimal medical therapy (OMT): non-pharmacological and pharmacological therapy of CCS is given great attention as the main type of treatment of CCS, not MR. The modern role of anti-ischemic (antianginal) drugs is emphasized: First lines - beta-blockers (BB) and calcium antagonists (CCB) with sublingual nitroglycerin, and Second lines - long-acting nitrates (LAN), with newer options: ivabradine, nicorandil, trimethazidine, allopuronol, etc. Drugs that improve the prognosis of CCS are statins and acetylsalicylic acid (ASA) and other antiplatelet drugs and recently low dose rivaroxaban and additionally angiotensin converting enzyme inhibitors (ACEI) and again BB in specific indications. Anti-ischemic treatment must be tailored to the individual patient based on comorbidities, other concomitant therapies, expected tolerances and adherence, and patient preferences. The choice of anti-ischemic drugs for the treatment of CCS should be adjusted to the heart rhythm, blood pressure and heart function. BB and ACEI are recommended for patients with LVD or HF with reduced left ventricular ejection fraction (HFrEF). Antithrombotic therapy is a key part of secondary prevention in patients with CCS. Patients with previous acute myocardial infarction (AMI), who are at high risk of ischemic events and low risk of fatal bleeding, should consider long-term dual antiplatelet therapy with aspirin and either P_2Y_{12} receptor inhibitor or a very low-dose rivaroxaban, unless there is an indication for oral anticoagulation, is atrial fibrillation (AF). Proton pump inhibitors are recommended in patients receiving only aspirin or a combination of antithrombotic therapy who are at risk of gastrointestinal bleeding. Statins are recommended for all patients with CCS, regardless of LDL level. ACEIs (or angiotensin receptor blockers, ARBs) are recommended in the presence of SI, diabetes, and hypertension and should be considered in patients at high risk for adverse events.

Keywords: Angina pectoris/stable, Angina Pectoris/Unstable, microvascular angina, angina pectoris with normal coronary arteriogram, ischemic heart disease, coronary heart disease, Acute coronary syndrome, Myocardial infarction, Myocardial ischemia/diagnosis/prevention and control/pharmacotherapy, Myocardial revascularization/percutaneous coronary intervention-PCI/coronary artery bypass-CABG

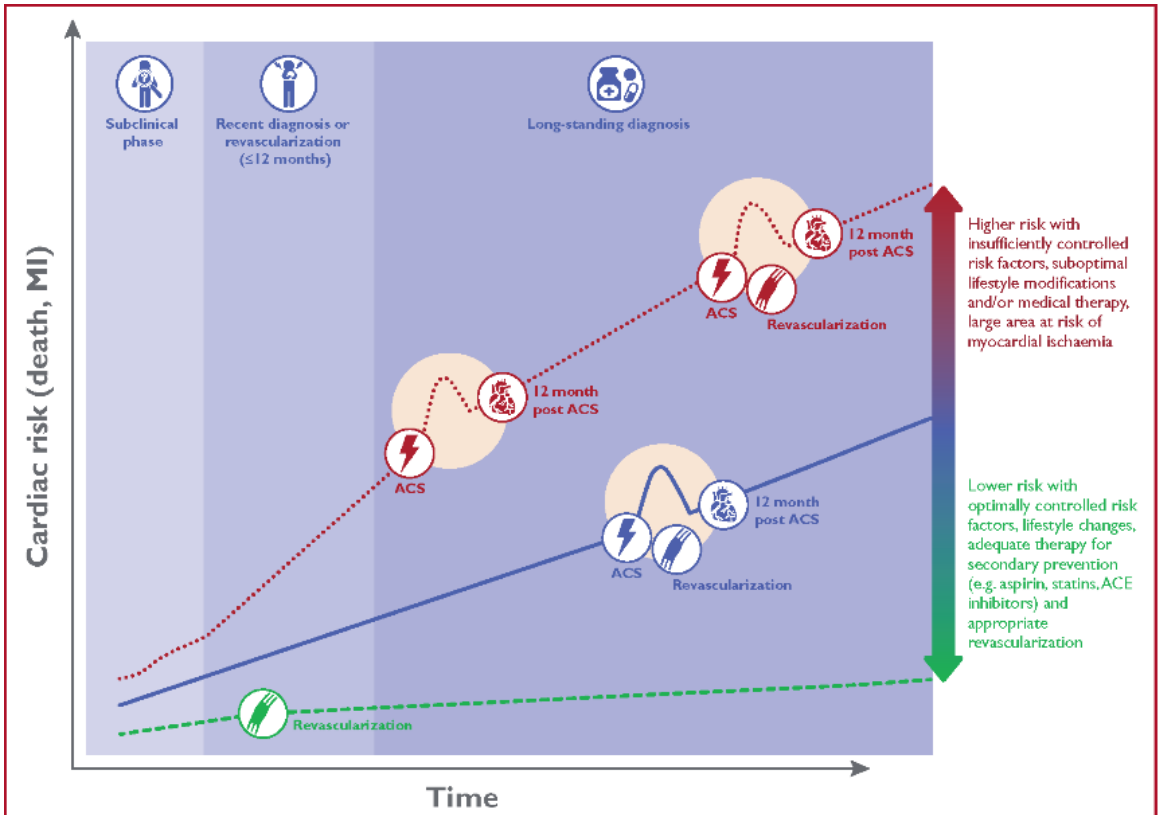
INTRODUCTION AND SIGNIFICANCE OF THE PROBLEM

The new 2019 European Society of Cardiology (ESC) guide for the diagnosis and management of chronic coronary syndromes [1] focuses on the new comprehensive term Chronic Coronary Syndromes (CCS) for all forms of chronic coronary artery disease (CCAD) except acute coronary syndromes [2,3], rather than only stable coronary artery disease (SCAD), as a previous ESC guide from 2013 [4]. The new guide of the European Association of Cardiologists from 2019 primarily brings a paradigm shift for stable coronary heart disease to the comprehensive term chronic coronary syndromes (CCS), which essentially means that CAD has complex clinical scenarios and can have periods of instability at any evolutionary stage. Essentially, the clinical presentation of coronary heart disease is categorized into either acute coronary syndromes (ACS) [2,3,5] or chronic coronary syndromes (CCS) [1]. Coronary heart disease (CAD) is a dynamic pathological process of appearance and growth of atherosclerotic plaques in epicardial coronary arteries, but also in their smaller intramyocardial branches [6,7, 8,9] (microvascular disease) with or without coronary vasospasm [10-13], without whether they are functionally fixed obstructive (stenotic) or non-obstructive [14,15]. This dynamic process leads to a functional alteration of the

Vol. 45 (2020) No. 1-2 TIMOK MEDICAL GAZETTE Review article

coronary blood flow or myocardial ischemia. Myocardial ischemia can be reduced, stabilized or stagnation or regression of atherosclerotic plaques can be achieved through therapeutic interventions: optimal non-invasive medical ie. (medical therapy-OMT) which consists of lifestyle changes, reduction of risk factors and optimal pharmacotherapy (OPhT) and optimal invasive interventions - percutaneous or surgical myocardial revascularization (RM). [16-21]. CAD has long stable periods, but may also become unstable at some period due to acute atherothrombotic events — breakup or erosion of atherosclerotic plaque. However, the disease is chronic, most often progressive and therefore serious, even in clinically asymptomatic periods [1] (FIGURE 1).

FIGURE 1: CLINICAL PRESENTATION - CLINICAL SCENARIOS OF CHRONIC CORONARY SYNDROMES



Retrieved from https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

The dynamic nature of the CAD process results in different clinical presentations or clinical scenarios, acute coronary syndromes (ACS) [2,3,5] or chronic coronary syndromes (CCS) [1].

CLINICAL PRESENTATION - CLINICAL SCENARIOS OF CHRONIC CORONARY SYNDROMES (CCS).

The clinical presentation of CCS consists of 6 leading and most common clinical scenarios [1]:

1.Patients with suspected CAD and stable angina pectoris (AP) and / or dyspnea on exertion.

2. Patients with newly developed heart failure (HF) or left ventricular dysfunction (LVD) and suspected CAD.

3. Asymptomatic and symptomatic patients with stabilized symptoms up to 1 year after ACS or myocardial revascularization (RM).

4. Asymptomatic and symptomatic patients more than 1 year after ACS orRM.

5. Patients with AP and suspected vasospastic or microvascular disease.

6. Asymptomatic individuals in whom CAD was detected at screening.

Each of these scenarios is classified as CCS, is a consequence of different evolutionary phases of CAD and has a different risk for future adverse CV events (death or myocardial infarction) and this risk may change over time [1].

NEW CONCEPTS AND RECOMMENDATIONS FOR CCS

New concepts and recommendations for CCS and revised concepts and recommendations from the previous ESC guide in 2013 [4], in this 2019 ESC

guide [1], based on current available evidence from a large number of randomized studies, registers and expert consensus (cited a huge number of scientific papers: 529 references) have a holistic approach, give quite clear guidelines for the diagnosis and therapy of CCAD and systematically process all clinical presentations of CCAD in a clear and clinically applicable way. This ESC Guide and its recommendations should facilitate clinical decision-making by physicians in their day-to-day practice [1].

NEW MAIN RECOMMENDATIONS OF CLASS I (There is evidence and / or general agreement that a given treatment or procedure is benefitial, useful and effective: Wording to use: Is recommended or is indicated)

1. Non-invasive functional imaging diagnostic test for the detection of myocardial ischemia or coronary MSCT angiography should be the initial test for the diagnosis of CAD in symptomatic patients in whom obstructive coronary heart disease cannot be ruled out by clinical judgment alone.
2. It is recommended that the selection of the optimal test for the diagnosis of CAD be based on the Clinical Probability of CAD and other patient characteristics that affect test performance, local availability, and expertise.
3. Non-invasive functional imaging test for myocardial ischemia is recommended if coronary MSCT angiography shows CAD of uncertain functional significance or is non-diagnostic, inclusive.
4. Invasive coronary angiography (ICA) is recommended as an alternative test for the diagnosis of coronary artery disease (CHD) in patients with high clinical probability and severe symptoms refractory to medical therapy (nonpharmacological and pharmacological) or typical angina at low exercise and when clinical evaluation indicates at high risk of adverse CV events. Invasive functional assessment (FFR, iwFR) must be available and used to evaluate stenosis prior to coronary revascularization, except in the case of a very high degree of coronary stenosis ≥90% of the stenosis diameter.
5. In patients with atrial fibrillation (AF) with a CHA_2DS_2-VASc score ≥ 2 for males and ≥ 3 for females, non-vitamin K antagonists (NOAC, DOAC) are preferred if there are no contraindications.
6. After percutaneous coronary revascularization (postPCI) in patients with AF, NOACs: Apixaban 2 x 5 mg, Dabigatran 2 x150 mg, Edoxaban 60 mg and Rivaroxaban 20 mg once daily have an advantage over vitamin K antagonists (VKA) in combination with in combination with antiplatelet therapy (mono- or dual-DAPT at high hemorrhagic risk).
7. Proton pump inhibitors are recommended in patients at high risk of gastrointestinal bleeding, according to the HAS-BLED score, in the following subgroups: patients with aspirin monotherapy, dual antiplatelet therapy (DAPT) or oral anticoagulant monotherapy.
8. If the target value of serum LDL cholesterol is not reached with the maximum dose of statins, combination with ezetimibe is recommended, and in VERY HIGH RISK, a third drug PCSK9-inhibitor (Proprotein convertase subtilisin / kexin type 9) is added parenterally.
9. Sodium glucose-2-cotransporter inhibitors (SGLT2-I): empagliflozin, canagliflozin or dapagliflozin are recommended in patients with diabetes mellitus (DM) and CCS and cardiovascular disease.
10. Glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide or semaglutide are recommended in patients with DM and CCS and cardiovascular disease.

NEW AND / OR REVISED CLASS IIa MAIN RECOMMENDATIONS (There is conflicting evidence and / or divergence of opinion about the usefulness / efficacy of a given treatment or procedure, but weight of evidence/opinion favor of usefulness / efficacy. Wording to use: Should be considered)

1. Invasive coronary angiography with the availability of invasive functional evaluation should be considered to confirm the diagnosis of CAD in patients with an uncertain diagnosis on noninvasive tests.
2. Coronary MSCT angiography should be considered as an alternative to invasive coronary angiography if other non-invasive tests are ambiguous or non-diagnostic.
3. The addition of another antiplatelet drug to aspirin for long-term secondary prevention should be considered in patients with a high ischemic risk and without a high risk of bleeding.
4. Long-term oral anticoagulant therapy (OAC) should be considered with AF and CHA2DS2-VASc = 1 for males and 2 for females, non-vitamin K antagonists (NOAC) are preferred, if there are no contraindications
5. In patients with AF and NOAC, where the risk of haemorrhagic risk outweighs the risk of stent thrombosis or ischemic stroke, a lower dose of NOAC should be given (Rivaroxaban 15 mg once

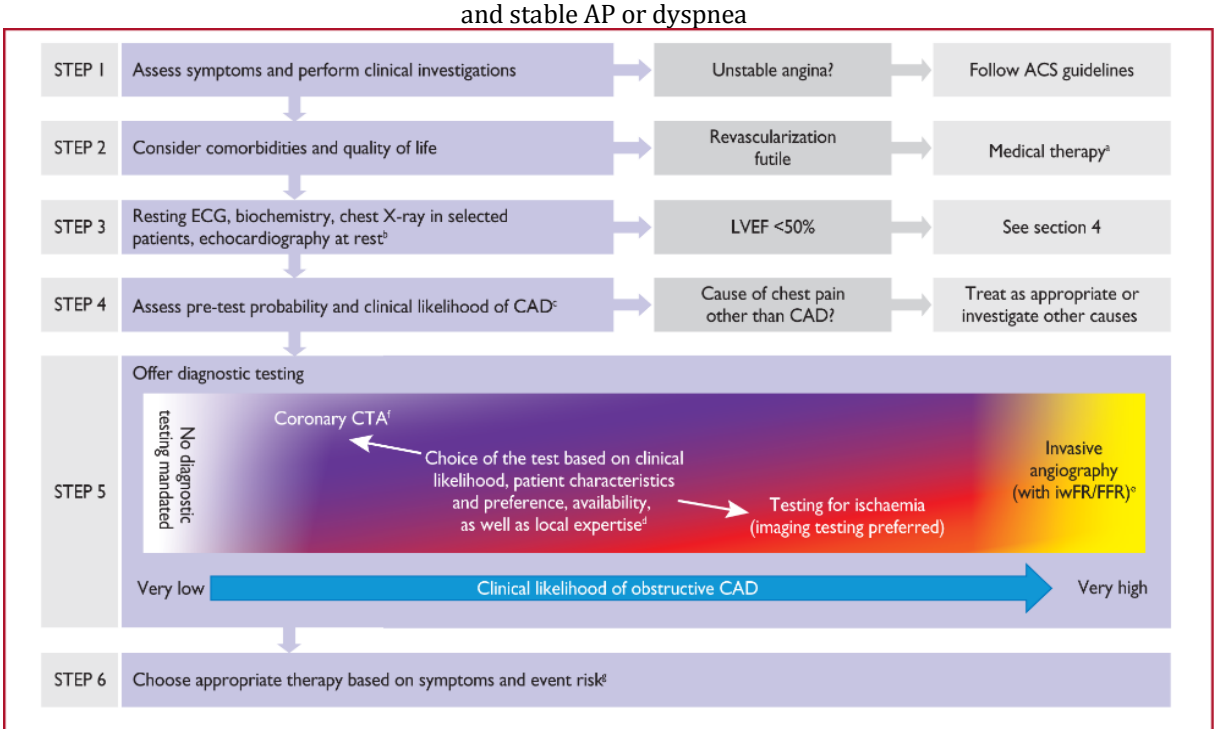
daily or Dabigatran 2 x 110 mg in combination with mono or double antiplatelet therapy).
6. In post-PCI patients with AF or other indications for OAC, triple therapy with aspirin, clopidogrel, and OAC should be considered for at least one month or longer when the risk of stent thrombosis outweighs the haemorrhagic risk, with a total duration of up to 6 months. both risks and is clearly stated on discharge from the hospital!
7. Angiotensin converting enzyme (ACEI) inhibitors should be considered in CCS patients at very high risk of adverse cardiovascular events.
8. Ranolazine, nicorandil, ivabradine and trimetazine are converted to IIa (from class IIb-utility / efficacy is much less based on evidence / views).

CLASS III MAIN RECOMMENDATIONS. There is evidence and / or general agreement that a given treatment or procedure is not useful/ effective and in some cases may be harmful: Wording to use: Is not recommended
1. Coronary MSCT / MDCT angiography is not recommended when there are extensive coronary calcifications, irregular heart rate, significant obesity, inability of the patient to hold his breath long enough and any other factors that would affect the failure to obtain a quality image.
2. Changes in the ST segment of the ECG during PSVT should not be used as evidence of CAD.
3. Outpatient ECG monitoring (Holter ECG) should not be routinely used in the examination of patients with suspected CCS.
4. Coronary calcium score via MSCT is not recommended for identification of persons with obstructive CAD.
5. Exercise ECG test (ergometric ECG stress test on a treadmill or bicycle) in patients with ≥0.1Mv (1mm) ST segment depression on an ECG at rest, or digitalis treatment is not recommended for diagnostic purposes of CCS.
6. Invasive coronary angiography (ICA) is not recommended as the only method for risk stratification in CCS.
7. Nitrates are not recommended for the treatment of CCS in patients with hypertrophic obstructive cardiomyopathy or in concomitant therapy with phosphodiesterase inhibitors (Sildenafil et al.).
8. The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with acetyl-salicylic acid (ASA) and oral anticoagulant therapy (OAC).
9. Coronary MSCT angiography is not recommended as a routine test to monitor patients diagnosed with chronic coronary syndrome (CCS).
10. Carotid echosonography with determination of intimomedial layer thickness is not recommended for CCS risk stratification.
11. In low-risk asymptomatic adult non-diabetics, coronary MSCT angiography or functional imaging tests for ischemia are not indicated for further diagnostic evaluation.
12. Routine determination of circulating cardiac biomarkers is not recommended for stratification of cardiovascular risk in patients with CCS.
13. The combination of drugs from the ACEI and ARB groups is not recommended for CCS.
14. In severe heart valve disease, stress stress tests should not be used routinely to detect CAD, due to low diagnostic benefit and potential risk of complications.
15. Sex hormone replacement therapy is not recommended for risk reduction in postmenopausal women.
16. Transmyocardial revascularization is not recommended for patients with severe AP refractory to optimal medical treatment (OMT) and myocardial revascularization (RM) strategies.

SCENARIO 1: PATIENTS WITH SUSPECT CAD-CCS AND STABLE AP and / or EFFORT DYSPNEA.
The procedure (algorithm) in 6 steps in the approach to initial care of patients with suspected CCS and stable AP or dyspnea on exertion is given in Figure 2.

Vol. 45 (2020) No. 1-2 TMOK MEDICAL GAZETTE Review article

FIGURE 2. **6-step procedure (algorithm)** in the approach to initial care of patients with suspected CCS and stable AP or dyspnea



Retrieved from https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

Instead of the previous 3 steps according to the ESC guide from 2013 [4,22], a procedure or algorithm has now been introduced in 6 STEPS [1] in the approach to initial care of patients with suspected CCS:

STEP 1: Assessment of symptoms (TABLE 1) uses the traditional clinical classification of suspected anginal symptoms: chest discomfort - discomfort (pain) on exertion usually shorter than 10 minutes (pain lasting seconds is usually not anginal) and conducting clinical trials, identifying patients with unstable angina and other forms of ACS. AP can paradoxically decrease with further effort (walk-through angina) or with the next effort (warm-up angina) [23].

TABLE 1. The traditional clinical classification of suspected anginal symptoms: chest discomfort

Patients with angina and/or dyspnoea and suspected coronary artery disease

ESC European Society of Cardiology

Clinical classification of suspected angina

Typical angina	Meets the following three characteristics: 1. Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm; 2. Precipitated by physical exertion; 3. Relieved by rest or nitrates within 5 min.
Atypical angina	Meets two of these characteristics.
Non-anginal chest pain	Meets only one or none of these characteristics.

©ESC

www.escardio.org/guidelines

ESC Guidelines on the diagnosis and management of chronic coronary syndromes (European Heart Journal 2019; 10.1093/eurheartj/ehz425)

15

It should not be emphasized how important it is to quickly rule out other acute acute cardiac conditions: acute coronary syndrome (ACS) - unstable angina pectoris- identical pain as in AP but lasting> 20 minutes. One should always think of a dissecting aortic aneurysm, ie Acute

aortic syndrome (AAS), pulmonary embolism, pericarditis and myocarditis. In the differential diagnosis, consider non-cardiac diseases that may resemble anginal pain. The most common diseases that can mimic angina pectoris: gastroesophageal diseases (40%), thorax wall syndromes (Costochondritis and Titze syndrome), some lung diseases, pneumothorax, pleuritis and herpes zoster intercostalis

STEP 2- Consider the general condition and condition of the patient,

assess the quality of life and the presence of comorbidities that potentially affect the therapeutic decision. If performance of load tests and coronary revascularization are unlikely due to the general condition, immediately introduce OMT, especially antianginal pharmacological therapy.

STEP 3. Basic clinical supplementary trial.

Includes basic examination: electrocardiogram (ECG), in selected patient ambulatory ECG Holter monitoring, biochemical analysis, radiography of the thorax in selected patients. An ECG is crucial for the diagnosis of myocardial ischemia, typically a reversible horizontal depression of the ST segment in two or more adjacent ECG leads during or immediately after an anginal attack. The descending ST-segment depression is less specific and the slow-ascending depression is the least specific for the diagnosis of ischemia, while the fast-ascending ST-segment depression is a normal variant in tachycardia [24]; Holter ECG often reveals asymptomatic myocardial ischemia in the form of horizontal depression of the ST segment on exertion [24,25,26]; The ECG may also indicate indirect signs of CAD: pathological Q tooth [27]; left bundle branch block (LBBB) or atrioventricular (AV) blocks, extrasystoles [27]; In an episode of atrial fibrillation (AF) with asymptomatic myocardial ischemia - ST depression [28,29]. In contrast to AF, ST depression during paroxysmal supraventricular tachycardia (PSVT) is not predictive of ischemia. Echocardiographic assessment of left ventricular function (LV), primarily left ventricular ejection fraction (EF), is mandatory. When the EF is <50% the patient is referred directly for invasive coronary angiography (ICA). Transthoracic echocardiography (TTE) as the single most informative diagnostic method in cardiology has a crucial role in excluding alternative causes of chest discomfort [30] and for risk stratification. In the case of suboptimal echo imaging (<10% of cases), transesophageal echocardiography (TOE) and cardiomagnetic resonance imaging (CMR) are used [31].

STEP 4 Assessment of pre-test probability and clinical probability of CAD-CHD

The European Guide 2019 gives increased and renewed importance to the determination of pre-test probability (PTP) of obstructive coronary heart disease, but the classic PTP, Diamond and Forrester based on age, sex and nature of symptoms [31] have undergone major changes based on new evidence [32]. The mean PTP is 15% to 85%. Using the new table (TABLE 2) reduces the overestimation of the incidence of coronary heart disease. [1, 31, 32].

TABLE 2. NEW REVISED PRESTEST PROBABILITY

Foldyna B, Udelson JE, Karady J, et al. insights from the PROMISE trial. Eur Heart J Cardiovasc Imaging 2018; 20:574 581.

Patients with angina and/or dyspnoea and suspected coronary artery disease

ESC European Society of Cardiology

Pre-test probability of coronary artery disease

	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	M	W	M	W	M	W	M	W
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

[a] In addition to the classic Diamond and Forrester classes, patients with dyspnoea only or dyspnoea as the primary symptom are included. The dark green shaded regions denote the groups in which non-invasive testing is most beneficial (pre-test probability >15%). The light green shaded regions denote the groups with pre-test probability of CAD between 5-15% in which the testing for diagnosis may be considered after assessing the overall clinical likelihood based on modifiers of pre-test probability.

©ESC

www.escardio.org/guidelines

ESC Guidelines on the diagnosis and management of chronic coronary syndromes (European Heart Journal 2019; 10.1093/eurheartj/ehz425)

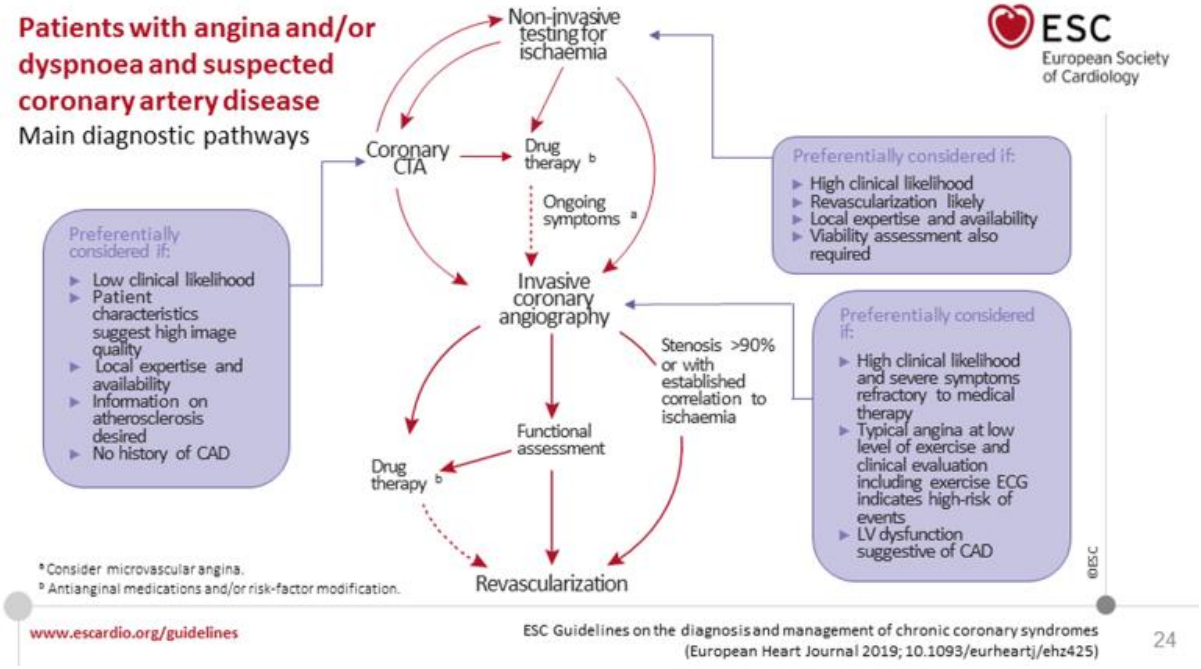
22

Retrieved from https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

A new term, Clinical Probability of Obstructive Coronary Disease (CPCAD), is introduced, which uses different risk factors for CAD as modifiers of PTP probability. Reduction of probability for obstructive CAD: normal ECG test with physical load and normal calcium score of coronary arteries (Agatston = 0) [1, 33]. Factors that increase CPCAD:
A) dyslipidemia, diabetes, hypertension, smoking, family history of CAD and sudden death.
B) Changes in the ECG at rest: Q wave and changes in the ST segment and T wave.
C) Left ventricular dysfunction referring to CAD
D) Abnormal exercise ECG test
E) increased calcium score by CT
The selection of the initial non-invasive diagnostic test (functional or anatomical image) is based on PTP or CPCAD.

STEP 5. Selection of the optimal diagnostic test for diagnosing CAD
Selection of the optimal diagnostic test for diagnosing CAD, based on patient profile, local availability and expertise. [1, 36-42] is shown in Figure 3.

Figure 3. MAIN DIAGNOSTIC PATHWAYS IN SYMPTOMATIC PATIENTS WITH SUSPECT OBSTRUCTIVE CAD CCS



Retrieved from https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

In patients in whom revascularization is "futile" due to comorbidity and overall quality of life (STEP 2), the diagnosis of CAD can be made clinically and only OMT- optimal medical therapy is required. If the diagnosis of CAD is uncertain, making a diagnosis using non-invasive functional tests to record myocardial ischemia before treatment is a reasonable option; on the other hand in a patient with a high clinical probability of CAD, when symptoms have not responded to medical therapy or severe typical low-grade angina is present and / or initial clinical assessment (including echocardiogram and in selected patients ECG exercise test or Ergometric ECG test) indicates a high risk of adverse events, switch directly to invasive coronary angiography (ICA) without further diagnostic testing. Under such circumstances, the indication for MR should be based on appropriate invasive confirmation of the hemodynamic significance of the stenosis: FFR, CFR [43, 44].
Existing guidelines recommend the use of either noninvasive functional imaging imaging of ischemia or anatomical imaging using coronary CT angiography (CTA) as an initial test for the diagnosis of CAD. Functional non-invasive ischemia tests for the diagnosis of obstructive CAD are designed to detect myocardial ischemia by ECG changes, irregularities of wall movement using CMR stress or stress echocardiography, or perfusion changes by myocardial scintigraphy

(SPECT), positron emission cardiography or contrast CMR. Ischemia can be caused by physical exertion (erggometrically) or pharmacological stressors, either through increased myocardial function and oxygen demand, or by heterogeneity in myocardial perfusion by vasodilation. Non-invasive functional tests have high accuracy for detecting coronary stenosis that restricts flow compared to invasive functional examination by fractional flow reserve (FFR) [45].

However, insignificant coronary stenoses and atherosclerotic plaques not associated with ischemia remain undetected by functional testing and in the presence of a negative functional test, patients should receive risk factor modification based on ESC recommendations for CV prevention [6].

Anatomical non-invasive assessment

Anatomical noninvasive assessment by visualization of coronary arteries, imaging and lumen of the coronary artery wall can be reported using intravenous contrast agent by coronary CT angiography (CTA), which provides high accuracy for detecting obstructive coronary stenoses, as well as invasive coronary angiography [45A] the recordings are based on anatomy. However, stenoses that amount to 50 to 90% by visual examination are not necessarily functionally significant, ie. they do not always cause myocardial ischemia. [45.46]. Therefore, non-invasive or invasive functional testing is recommended for further assessment of angiographic stenosis detected by coronary CTA or ICA, unless high-grade stenosis (> 90% of diameter) is detected by invasive angiography. The presence or absence of non-obstructive coronary atherosclerosis on coronary CTA provides prognostic information and can be used for preventive therapy. [47].

The role of Exercise (ergo) ECG test

The ECG ergometric stress test has poorer diagnostic performance compared to diagnostic visualization tests and has limited power to rule out obstructive CAD. [45]. Therefore, these guidelines recommend the use of diagnostic imaging tests instead of exercise ECG as an initial test for the diagnosis of constructive CAD. Exercise ECG test can be considered as an alternative for the diagnosis of obstructive CAD, if visualization (imaging tests) are not available, bearing in mind the risk of false negative and false positive test results. [45]. Exercise ECG has no diagnostic value in patients with ECG abnormalities that prevent the interpretation of ST-segment changes.

Influence of clinical probability on the choice of diagnostic test

Each non-invasive diagnostic test has a certain range of clinical probability for obstructive CAD where the usefulness of its application is maximum. Test probability coefficients are a useful parameter of their ability to properly classify patients and can be used to facilitate the selection of the most useful test for any patient. [45]. Given the clinical probability of obstructive CAD and the probability coefficient of a particular test, a post-test probability for obstructive CAD after performing such a test can be assessed.

Using this approach, the optimal range of clinical probability for each test can be estimated, where patients can be reclassified from medium (15–85%) to any: low (<15%) or high probability of CAD> 85% after the test [45]. Coronary CTA is preferred in patients with a lower range of clinical probability of CAD (previously numerically PTP 15-65%), without prior diagnosis of CAD and important conditions associated with a high probability of good image quality. Coronary CTA detects subclinical coronary atherosclerosis, but can also rule out anatomically and functionally significant CAD.

Non-invasive functional tests for ischemia have the advantage because they directly show the area of myocardial ischemia by provoking ischemia. Before revascularization, functional assessment and [45]. schemes (non-invasive or invasive method) is required in most patients.

In addition to diagnostic accuracy and clinical probability, the choice of a non-invasive test depends on other patient characteristics, local expertise, and test availability. Some diagnostic tests may be better in some patients than others. For example, tachyarrhythmia and the presence of extensive coronary calcification are associated with an increased likelihood of non-diagnostic quality of the coronary CTA image and are not recommended in such patients. [51]. Stress echocardiography or SPECT myocardial perfusion imaging may be combined with dynamic TFO and may be desirable if additional information is available during the TFO ECG test. TFP cannot be used for diagnostic purposes in the presence of ECG abnormalities that prevent the assessment of ischemia. The risks associated with different diagnostic tests must be weighed for and against the benefit to the particular patient [52]. Similarly, contraindications for pharmacological stressors and contrast agents (iodine- and gadolinium-based contrast agents) chelates) should be considered. When testing is used appropriately, the clinical benefit of

accurate diagnosis and therapy outweighs the projected risks of testing itself [52].

Invasive examination

For strictly diagnostic purposes, ICA is required only in patients suspected of having obstructive CB in the case of unconvincing, ambiguous or inclusive non-invasive testing or, exceptionally, in patients of certain public occupations of special importance (drivers, pilots, machine workers, police officers). and the like), due to security and regulatory issues. [53]. However, ICA may also be necessary when a noninvasive assessment suggests a very high risk of adverse events to determine revascularization options. [53]. In a patient with a high clinical likelihood of CAD and symptoms not responding to medical therapy or with typical low-effort angina, and an initial clinical assessment indicating a high risk of events, early ICA without prior noninvasive risk stratification may be a reasonable solution to identify lesions that may be suitable for myocardial revascularization (FIGURE 3). Invasive functional assessment should complement the ICA, especially in patients with 50 to 90% coronary stenosis or multivessel disease, given the frequent discrepancies in the angiographic and hemodynamic severity of coronary stenosis. [53-58]. ICA should not be performed in patients with angina who refuse invasive procedures and avoid revascularization, who are not candidates for percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or in whom myocardial revascularization is not expected to improve functional status or quality of life

STEP 6 After the diagnosis of CCS is made, the risk of adverse events is stratified by functional stress tests: isotopic stress-rest SPECT, the most available pharmacological stress echo dobutamine or dipyridamole and the least available cardiomagnetic resonance (CMR) stress with dobutamine and contrast perfusion. The decision on further treatment is based on determining the level of risk [1]. Definition of risk levels according to annual mortality: no ischemia, mortality from adverse events less than 1%; medium risk - annual mortality between 1% and 3%; high annual mortality is over 3% (Table 3).

TABLE 3. DEFINITION OF HIGH RISK LEVEL (HIGH EVENT RISK) FOR FUNCTIONAL IMAGE TESTS AND NON-INVASIVE ANATOMICAL CT CORONARY ANGIOGRAPHY

Patients with angina and/or dyspnoea and suspected coronary artery disease

ESC European Society of Cardiology

Definitions of high event risk for different tests

Exercise ECG	Cardiovascular mortality >3% per year according to Duke Treadmill Score.
SPECT or PET perfusion imaging	Area of ischaemia ≥10% of the left ventricle myocardium.
Stress echocardiography	≥3 of 16 segments with stress-induced hypokinesia or akinesia.
CMR	≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments.
Coronary CTA or ICA	Three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease.
Invasive functional testing	FFR ≤0.8, iwFR ≤0.89.

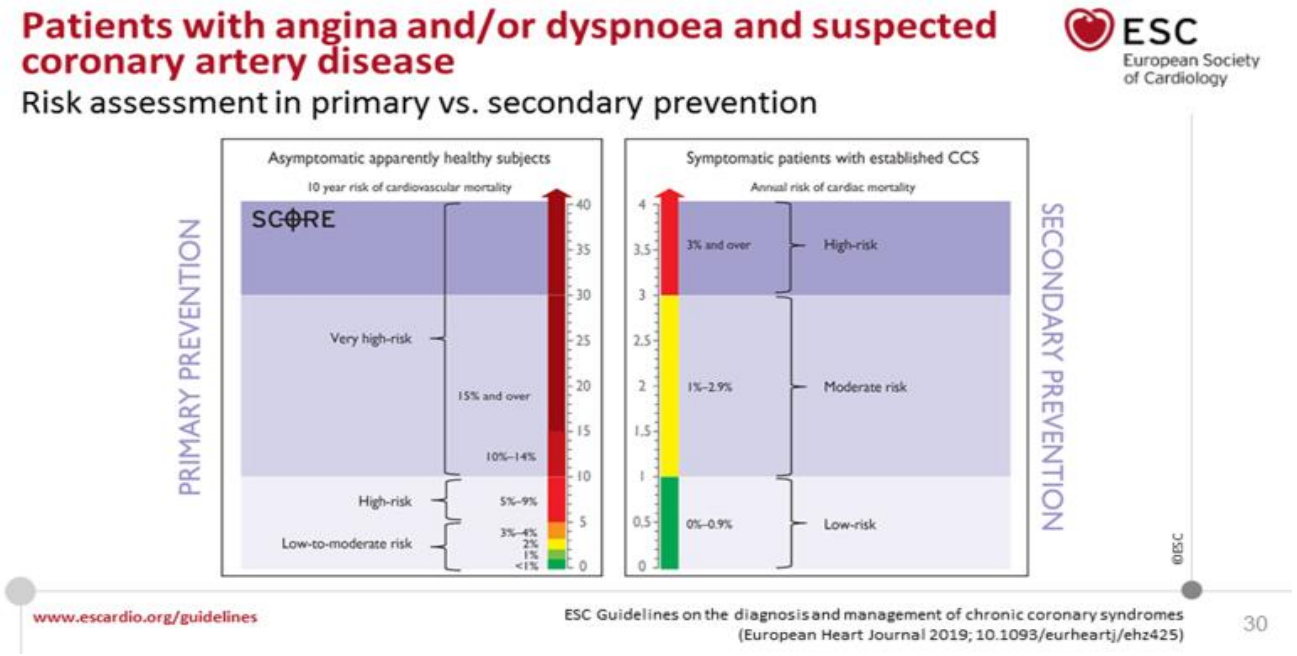
©ESC

www.escardio.org/guidelines

ESC Guidelines on the diagnosis and management of chronic coronary syndromes (European Heart Journal 2019; 10.1093/eurheartj/ehz425)

29

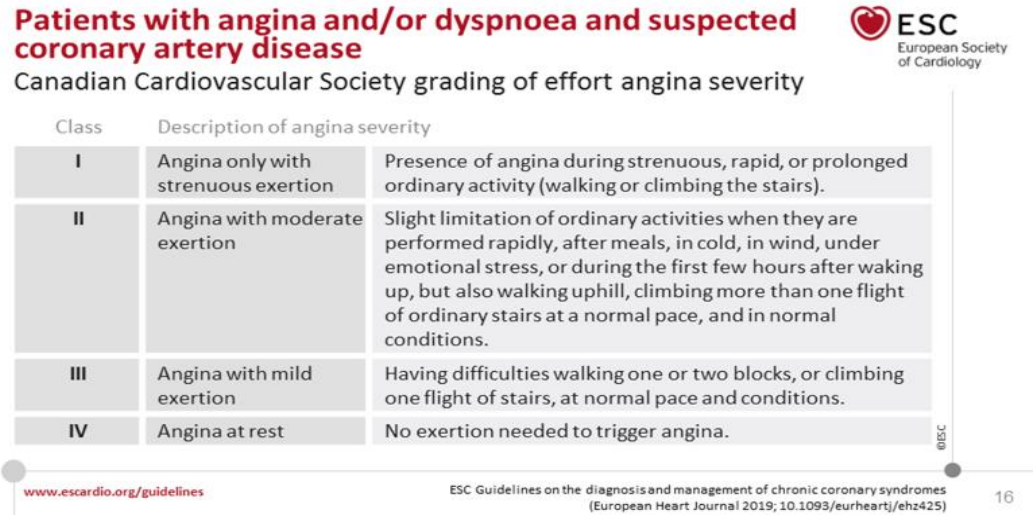
Figure 4. COMPARISON OF CV RISK LEVELS OF ASYMPTOMATIC PERSONS IN PRIMARY PREVENTION OF ADVERSE CV EVENTS AND IN ESTABLISHED CCS IN SECONDARY PREVENTION



Retrieved from https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

If the angina is very severe but not unstable, according to the well-known Canadian Classification of the Canadian Class IV Association (TABLE 4), with a pretest probability greater than 85% according to Bayes' theorem, ICA is performed immediately without previous noninvasive tests, but with coronary fractional flow reserve assessment. (FFR) [45, 56, 59].

TABLE 4. Classification of severity of angina pectoris and / or dyspnea on exertion according to the Canadian Cardiovascular Association



The role of coronary MSCT angiography is to rule out significant disease in patients with a lower intermediate probability of 15 to 50%. Finally, the choice of adequate therapy is made: lifestyle change, pharmacological therapy of CAD

and myocardial revascularization (MR), based on symptoms and risk of adverse CV events.

NON-PHARMACOLOGICAL MEASURES IN THE TREATMENT OF CHRONIC CORONARY SYNDROMES (for all ccs, especially for scenario 1)

The guide underlines the crucial role of a healthy lifestyle or other preventive measures to reduce the risk of consequent cardiovascular events and mortality [1], as shown in the essential studies COURAGE [60] and FAME [44]. Regular taking of medications for the treatment of hypertension, hyperlipidemia, diabetes, etc. should ensure the achievement of target values of blood pressure, LDL cholesterol, HDL, triglycerides and glycemia (HbA1c), which leads to stagnation and regression of atherosclerosis, which is discussed in detail in the ESC Guide for CV prevention 2016 [6].

The involvement of a multidisciplinary team in preventive work is recommended: cardiologist, general practitioner (GP), nurses, nutritionist, psychologist, psychotherapist and pharmacist (class I evidence B) [1]. The use of a healthy lifestyle, as a preventive intervention, reduces the risk of subsequent development of adverse CV events and mortality. The application of healthy behavior is important: smoking cessation, recommended physical activity, healthy diet, maintaining a healthy weight, which significantly reduces the risk of future cardiovascular events and death, and which is based on evidence. [1, 61, 62]. The benefits are obvious as early as 6 months after the index event [1, 61, 62]. Primary health care plays an important role in prevention, the EUROACTION study showed that a program coordinated by a primary care nurse improves the reduction of risk factors. [63].

Smoking cessation improves the prognosis in patients with HCV, including a 36% reduction in the risk of death for those who successfully quit. Measures to promote smoking cessation include brief tips and advice on behavioral intervention and pharmacological therapy including nicotine replacement. Patients should also avoid passive smoking. Short doctor's advice doubles the likelihood of smoking cessation in the short term, but more intensive advice and support (behavioral interventions, telephone support or self-help measures) is more effective than short advice, especially if continued for one month [62,63]. All forms of nicotine replacement therapy, bupropion, and varenicline are more effective in smoking cessation than self-control; combining a behavioral and pharmacological approach to smoking cessation is effective and recommended. [64].

Healthy eating [65]: Diet rich in vegetables, fruits and whole grains. Limit saturated fat intake to <10% of total intake. Limit alcohol to <100 g / week or 15 g / day.

Healthy body mass gain and maintain a healthy mass (BMI <25 kg / m2) or lose weight through recommended energy intake and increased physical activity.

Obesity is associated with shorter overall life expectancy and overweight is associated with the development of cardiovascular disease (CVD) [66]. Waist circumference is a sign of central obesity and metabolic syndrome [30] and is strongly associated with the development of CVD and diabetes. The recommended waist circumference is ≤94 cm for men and ≤80 cm for women. In people with CVD, intentional weight loss is associated with a significantly lower risk of adverse events [67].

Moderate alcohol intake (1-2 drinks per day) does not increase the risk of AMI.

Physical activity. The exercise is called "pollypill" because of its many beneficial effects on CV risk factors and the CV system [21, 68, 69, 70]. Physical activity reduces AP severity, improves oxygen transport in the myocardium and increases exercise capacity, and is an independent predictor of increased survival in men and women with CCS [21, 68, 69, 70]. Every 1 mL / kg / min increase in peak oxygen consumption was associated with a 14% reduction in CVD risk and an all-cause cause of death in women and men. [21]. Recommendations for physical activity for patients with CCS are 30 to 60 min of moderate-intensity aerobic activity ≥5 days per week. [6, 69]. Even irregular physical activity in leisure time reduces the risk of mortality in previously seated patients [72] and increasing activity is associated with lower CV mortality [73]. Strength exercises maintain muscle mass and function, and in addition to aerobic activity (fast walking, swimming, etc.), they give beneficial effects in terms of lowering insulin resistance, lipid levels and blood pressure.

CV rehabilitation based on physical exercise has constantly shown efficacy in reducing CV mortality and hospitalizations compared to the control group in patients with CAD and this benefit remains at the present time [74,75,76, 77].

Psychosocial factors. Patients with CAD have a twice-increased risk of depression and anxiety disorders compared to people without heart

disease [78]. Psychosocial stress, depression and anxiety are associated with poorer CCS outcomes. Clinical trials have shown that psychological (eg, counseling and / or cognitive-behavioral therapy) and pharmacological interventions with psychopharmaceuticals have had beneficial effects on depression, anxiety, and stress, with some evidence of reduced cardiac mortality and adverse events compared with placebo. [79,80,81].

Environmental factors. Air pollutants are estimated as one of the 10 leading risk factors for global mortality. Exposure to air pollution also increases the risk of AMI as well as hospitalization and death from HF, stroke and arrhythmias. [82]. Patients with CCS should avoid areas with heavy traffic due to pollution and noise [82,83]

Sexual activity. Patients with CCS are often concerned about the CV risk of sexual activity and / or sexual dysfunction. [84,85]. The risk of causing sudden death or AMI is very small, especially when sexual activity with a stable partner in a known environment is stress-free or without excessive food or alcohol intake [86]. Although sexual activity transiently increases the risk of MI, it causes only <1% of acute MI and <1.7% for sudden death during sexual activity. [86]. Energy expenditure during sexual activity is generally low to moderate (3 - 5 METs, metabolic equivalents) and climbing stairs to the second floor is often used as equivalent activity in terms of energy expenditure. Phosphodiesterase-5 inhibitors for the treatment of erectile dysfunction are usually safe in CCS patients, but are contraindicated in those who take nitrates and who have severe hypotension [86]. Healthcare professionals should ask patients about sexual activity, give them information and provide advice

Adhering to lifestyle modifications and taking medication regularly is a big challenge. A systematic review of epidemiological studies has shown that a significant proportion of patients do not adhere to regular CV medications and that 9% of cardiovascular adverse events in Europe can be attributed to poor patient adherence (compliance) to regular therapy [87, 88]. In older men with CKD, greater adherence to medication guidelines was positively associated with better clinical outcomes, independent of other conditions. Polypharmacy plays a negative role in adherence to treatment [88] and the complexity of the medication regimen is associated with non-adherence and a higher hospitalization rate [89]. Physicians who prescribe drugs should give preference to drugs that have proven their benefit with the highest level of evidence and those that are most beneficial to the patient, without significant side effects of the drug. Regime simplification helps adhere to treatment and there is evidence of the benefits of cognitive education strategies, electronically monitored feedback, and telephone support from nurses and technicians. Reviewing and controlling the type and dose of drugs by primary care physicians is a significant factor in helping all patients, especially patients with more comorbidities, to simplify the treatment regimen, detect drug interactions and minimize the risk of drug side effects [89,90,91]. Long-term support (intensive for the first 6 months, then every 6 months for 3 years) in the GOSPEL study (Global Secondary Prevention Strategies to Limit Recurrence after Myocardial Infarction) resulted in significant improvements in risk factors and a reduction in some adverse outcomes [20].

Sex hormone replacement therapy in menopausal women with CCS is not recommended.

Annual vaccination against influenza is recommended for all patients with CCS because it improves the prevention of AMI, reduces CV mortality in adults aged> 65 years

PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES SCENARIO 1

PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES: CLINICAL SCENARIO 1- Patients with suspected coronary heart disease and stable angina and / or dyspnea on exertion.

The goals of pharmacological treatment of patients with CCS are: to reduce the symptoms of angina and ischemia caused by physical exertion and exercise and to prevent unwanted CV events. Anti-ischemic drugs - but also lifestyle changes, regular exercise training, patient education and eventual revascularization - all play a role in minimizing or eradicating symptoms during long-term prevention. Prevention of cardiovascular adverse events: ACS, AMI, HFrEF, HFmEF, HFpEF), ventricular arrhythmias and heart blocks, VT, AF, stroke and CV deaths associated with CCS focuses on reducing the incidence of acute atherothrombotic events and and the development of LV dysfunction. Optimal pharmacological therapy (OPhT)can be defined as a treatment that satisfactorily controls symptoms and prevents CAD-related adverse events, with maximum patient adherence to treatment and with minimal drug side effects.

The modern role of first-line antianginal drugs: beta-blockers (BB) and calcium antagonists (CCB) and second-line long-acting nitrates (LANs) was highlighted, including new options: ivabradine, nicorandil, trimetazidine and ranolazine (and possibly allopurinol), and drugs that improve prognosis (acetylsalicylic acid (ASA) and other antiplatelet drugs, statins, ACEI, BB). There are two therapeutic goals in the treatment of CCS:

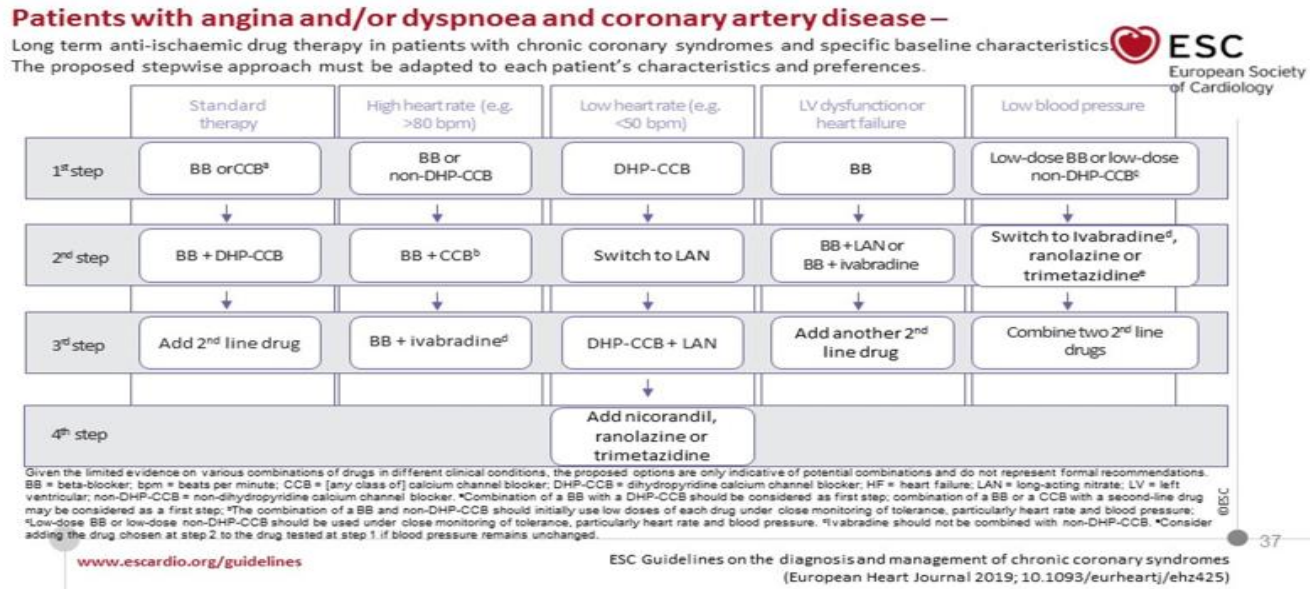
1. Improving the prognosis by reducing the risk of atherosclerosis progression and preventing acute coronary events and sudden death and prolonging life
2. Minimize symptoms with improved quality of life.

ANTI-ISCHEMIC (ANTIANGINAL) DRUGS

Immediate alleviation of anginal symptoms or prevention of symptoms under circumstances that are likely to cause angina is usually obtained by fast-acting formulations of nitroglycerin sublingually, which is one of the first-line antianginal drugs. However, there is no universal definition of optimal treatment in patients with HCV and drug therapy must be tailored to the individual characteristics and preferences of the patient. Initial drug therapy usually consists of one or two antianginal drugs in addition to drugs for the secondary prevention of CVD. [92-95]. The initial choice of antianginal drugs depends on the expected tolerance associated with the patient's profile and comorbidities, potential drug interactions used concomitantly in therapy, patient preferences after notification of potential adverse drug effects, and drug availability. Combination therapy with two antianginal drugs e.g. beta-blocker (BB) and calcium antagonist (CCB) are better than monotherapy with any class of antianginal drugs, but the effect in reducing clinical events remains unclear [95-98]. BB or CCB are recommended as first-line drugs, although to date no randomized controlled trial (RCT) has compared this strategy with alternative strategies that use initial prescribing of other anti-ischemic drugs or a combination of BB and CCB [92-95]. The results of a meta-analysis of 46 studies and 71 treatment comparisons, support the initial combination of BB and CCB. [98]. The same meta-analysis suggested several other initial first-line combinations of antiischemic drugs (long-acting nitrates, ranolazine, trimetazidine, and to a lesser extent, ivabradine) that may prove useful in combination with BB or CCB as first-line therapy, with no data for nicorandil. No study or meta-analysis has yet sufficiently assessed the impact of combining beta-blockers or CCBs with another line of anti-ischemic drugs against adverse events: morbidity or mortality [98]. Regardless of the initial strategy, the response to initial antianginal therapy should be reconsidered 2 to 4 weeks after starting treatment.

The algorithm of treatment with antiischemic drugs in patients with suspected CCS and stable angina and / or dyspnea on exertion is shown in TABLE 5.

TABLE 5 PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES



Retrieved from https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

FIRST LINE TREATMENTS CCS

SHORT-ACTING NITRATES are given for an acute AP attack on exertion. Sublingual tablets (lingvalete) and nitroglycerin spray provide immediate relief of angina on exertion. The nitroglycerin spray works faster than the sublingual nitroglycerin tablet [99]. At the onset of angina symptoms, the patient should rest in a sitting position (standing promotes syncope) and take nitroglycerin (tablet 0.3-0.6 mg sublingually, not swallowed, or 0.4 mg spray under the tongue and not swallowed and not swallowed. inhale) every 5 min until the pain ceases or a maximum of 1.2 mg is taken within 15 min. Within that time frame, if the angina lasts for more than 15 minutes, the patient must call an ambulance for hospital treatment, due to the suspicion of ACS. Nitroglycerin can be used for prophylaxis before physical activities that are known to cause angina

BETA BLOCKERS (BB-blockers of beta 1- β1-adrenergic receptors).

Selective β1-adrenergic receptor blockers are preferred in CCS. The efficacy of OMT in stable angina where BB is the central component of treatment is similar to the effect of percutaneous coronary intervention (PCI) with a stent, according to W. Boden, principal investigator of the COURAGE study [16, 60]. The dose of beta-blockers should be adjusted so that the heart rate is 55-60 beats per minute [100, 101]. Discontinuation should be gradual dose reduction and not abrupt. Abrupt cessation of intake due to an increase in the number of β1 receptors in the heart causes worsening of angina, sometimes even myocardial infarction. Dosing according to the target heart rate of 55-60 / min is common, but is acceptable below 50 / min in an individual patient without blocks. Target doses of β1-blockers in CCS: metoprolol 2 x 100mg. maximum 400 mg, bisoprolol 1 x 1.25-10 mg, maximum in Europe 30 mg, in the USA up to 40 mg; (L.Opie, Drugs for the Heart, 2013); nebivolol 1.25-5 mg x 1, up to a maximum of 15 mg in practice. BBs are effective in silent ischemia. During the effort, the goal is for the heart rate not to be over 100 / min. All BBs are potentially equally effective in CCS and selection is made according to comorbidities. BBs can be combined with dihydropyridine (DHP) CCBs to reduce DHP-induced tachycardia. Caution is warranted when a beta-blocker is combined with verapamil or diltiazem due to the potential for the development of worsening SI, excessive bradycardia, and / or atrioventricular block (formerly an absolute, now a relative contraindication). The combination of a beta blocker with nitrate reduces reflex tachycardia. The main side effects of beta blockers are fatigue, mental depression, bradycardia, AV block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, and masking the symptoms of hypoglycemia. In comorbidities, the most selective β1 blockers bisoprolol and nebivolol are preferred. In patients with recent AMI and those with chronic SI with reduced EF (HFrEF), BB is associated with a significant reduction in mortality and cardiovascular events [102–104], about a 30% reduction in mortality and reinfarction, and a similar effect in ischemic SI. The benefit in patients with CAD without previous AMI or SI is less well established and placebo-controlled trials are lacking. [105]. A retrospective analysis of 21860 matching patients from the REACH registry did not show a reduction in cardiovascular mortality with beta-blockers in patients with CAD and risk factors, with or without previous AMI [106], but this is still the subject of debate and further research.

CALCIUM ANTAGONISTS (CCBs or calcium channel blockers).

While CCB improves the symptoms of myocardial ischemia, it has not been shown to reduce adverse events and mortality in patients with CCS [107]. However, they have been shown to have an advantage in the prevention of exercise ischemia over BB.

NON-DIHYDROPYRIDINE CALCIUM ANTAGONISTS (NE-DHP): VERAPAMIL AND DILTIAZEM

Verapamil has a number of approved indications, including all types of angina (on exertion, vasospastic and unstable), supraventricular tachycardia and hypertension. Indirect evidence suggests good safety, but with the risk of heart blocks, bradycardia and HF. Compared with metoprolol, antianginal activity was similar. Combined beta-blockade with verapamil is not recommended (previously absolutely contraindicated due to the risk of cardiac SA and AV blocks). Diltiazem, with its profile of effects, has advantages over verapamil in the treatment of exertion angina. Like verapamil, it acts by peripheral vasodilation, reducing afterload while preventing coronary vasospasm. It has a moderate negative inotropic, chronotropic and dromotropic effect. There were no test results comparing diltiazem and verapamil. The use of non-DHP is not recommended for CCB in patients with LV dysfunction

CALCIUM DIHYDROPYRIDINE ANTAGONISTS (DHP-CCB)

Long-acting nifedipine

Nifedipine, a potent arterial vasodilator, is particularly well tested in hypertensive anginal patients when added with beta-blockade. In large placebo-controlled ACTION, the addition of long-acting nifedipine [60 mg once daily] to conventional angina treatment had no effect on prognosis. Long-acting nifedipine has been shown to be safe and has reduced the need for coronary angiography and cardiovascular interventions [108]. Relative contraindications for nifedipine are: small cardiac output (severe aortic stenosis, hypertrophic obstructive cardiomyopathy or HF); Careful combination with beta-blockade is usually feasible and desirable. Vasodilator side effects include headaches and ankle edema.

Amlodipine.

The very long half-life of amlodipine and its good tolerability make it an effective antianginal and antihypertensive drug taken once a day. There are few side effects, mostly ankle edema. In patients with CCS and without SI, amlodipine at a dose of 10 mg / day reduced the number of coronary revascularizations and hospitalization for AP in a 24-month study [109]. Exercise-induced ischemia is reduced more effectively with amlodipine, 10 mg / day, than with the beta-blocker atenolol, 50 mg / day, and their combination is even better. However, the CCB-BB combination is underused, as are other combinations of antichemical drugs, even in some studies that report that "optimal treatment of stable AP on exertion" has been applied [110]

SECOND LINE DRUGS

Long-acting nitrates for the prophylaxis of angina (eg, nitroglycerin patch, isosorbide dinitrate, and isosorbide mononitrate) are second-line drugs for relieving AP, when initial therapy with BB or NE-DHP CCB is contraindicated, poorly tolerated, or insufficient to control symptoms. There is essentially a lack of data comparing nitrates with BB and CCB, in order to draw firm conclusions about their relative efficacy [110]. When taken over a long period of time, long-acting nitrates cause tolerance with loss of efficacy, so it is necessary to prescribe a drug-free interval of 10-14 hours. The bioavailability of isosorbide dinitrate depends on inter-individual liver variability while isosorbide mononitrate, its active metabolite, is 100% bioavailable. Dose titration is essential to obtain maximum symptom control at a tolerable dose. Discontinuation should be a gradual dose reduction and not abruptly avoid worsening of AP. The most common side effects are hypotension, headache and redness. Contraindications include hypertrophic obstructive cardiomyopathy, severe aortic stenosis, and concomitant use of phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, or vardenafil) or riociguata.

Molsidomin is an unfairly neglected drug (even in the new ESC guide from 2019 [1]), which acts similarly to nitrates, but does not develop tolerance to its action, has an effective anti-ischemic effect and good tolerability. Dosage 3 x 2mg to 4mg or retractable form 2 x 8mg. Unfortunately, there are no studies on the effect on the prognosis of CCS [111,112]

Ivabradine is not inferior to atenolol or amlodipine in the treatment of angina and ischemia in patients with CCS [111]. By adding ivabradine 7.5 mg twice daily, atenolol therapy provided better control of heart rate and anginal symptoms. Overall, the results of the study support the use of ivabradine as a second-line drug in patients with CCS, when they do not tolerate or have contraindications for BB.

Nicorandil is a nitrate derivative of nicotinamide, with antianginal effects similar to those of nitrates or beta blockers. Side effects include nausea, vomiting, and potentially severe ulceration of the oral, intestinal, and mucous membranes. In a placebo-controlled IONA study (n = 5126), nicorandil significantly reduced nonfatal AMI or hospitalization in patients with CCS, but there was no effect on death from ischemic heart disease or fatal AMI [113]. These results support the use of nicorandil as a second-line drug in patients with CCS.

Ranolazine is a selective inhibitor of late internal sodium current. Side effects include dizziness, nausea and constipation. In addition, ranolazine increases QTc, and should therefore be used with caution in patients with QTc prolongation or with QTc prolonging drugs. In a placebo-controlled study in 6560 patients with NSTEMI ACS, the addition of ranolazine to standard treatment did not prove effective in reducing primary outcomes and CV mortality, AMI, or recurrent ischemia. [114]. However, ranolazine in the relatively large CCS subgroup (n = 3565) significantly reduced recurrent ischemia and worsening angina [115]. These results support the use of ranolazine as a second-line drug in patients with CCS with angina despite frequently used antianginal agents such as beta-blockers, CCB, and / or long-acting nitrates. In contrast, there is a lack of evidence to support the use of

ranolazine in patients with CCS after PCI with incomplete revascularization

Trimetazidine reduces ischemia by affecting myocardial metabolism without hemodynamic effects, unlike many anti-ischemic drugs [116]. Trimetazidine 35 mg twice daily BB (atenolol) reduces exertion-induced ischemia [117]. It is contraindicated in Parkinson's disease and movement disorders.
A study of 1628 patients showed that treatment with trimetazidine along with other antianginal drugs resulted in a lower mean number of mild angina attacks.
Allopurinol, a xanthine oxidase inhibitor, has recently been proposed for the treatment of CCS. Allopurinol has a double effect of energy conservation, reduces the consumption of O2 in the myocardium by inhibiting xanthine oxidase and transfers from creatine phosphate to ATP. Norman et al [118] in a randomized study of 65 patients with CCS found that 600 mg / day of allopurinol prolongs the time to onset of ST depression and pain by reducing vascular oxidative stress. the development of acute myocardial infarction (ACS) in the elderly, especially when taken for more than 2 years [119,]. However, the role of allopurinol in reducing clinical events in CAD remains unclear [120].

PATIENTS WITH CCS AND LOW BLOOD PRESSURE
Therapy with anti-ischemic drugs should be started with very low doses, BB or non-DHP-CCB with vigilant monitoring of tolerance to these drugs, and in case of severe hypotension, therapy should be discontinued. Preference should be given to drugs that do not affect blood pressure, such as: Trimetazidine, Ranolazine and Ivabradine in patients with sinus rhythm

PATIENTS WITH CCS AND BRADICARDIA
Elevated resting heart rate is a strong independent risk factor for adverse events in patients with CCS and the therapeutic goal is a heart rate (SF) of less than 60 / min. But with HR <50 / min, drugs that have a negative chronotropic effect (BB and NON-DHP-CCB, ivabradine) should be avoided or used with caution if necessary. Treatment should begin with a very low dose. Drugs that do not have a heart rate slowing effect should be preferred (DHP-CCB, LAN, Trimetazidine, Ranolazine, Nicorandil)

PHARMACOLOGICAL TREATMENT TO IMPROVE PROGNOSIS AND PREVENT ADVERSE EVENTS

ANTI-PLATELET MEDICINES
Platelet activation and aggregation is the initiator of symptomatic coronary atherothrombosis, which is the basis for the use of antiplatelet - antiplatelet drugs in patients with CCS, given the favorable balance of prevention of ischemic events and increased risk of bleeding. Dual antiplatelet therapy (DAPT) with aspirin and oral P2Y12 inhibitors is the basis of antithrombotic therapy after AMI and / or PCI.
ACETYLSALICYLIC ACID (ASPIRIN) IN SMALL DOSES acts by irreversibly inhibiting platelet cyclooxygenase-1 and thus thromboxane, which occurs with a chronic dosage of ≥75 mg / day. Gastrointestinal side effects at higher doses justify a daily dose of 75-100 mg for the prevention of ischemic events in CAD patients with or without a history of AMI. As inhibition of cyclooxygenase-1 by aspirin is consistent and predictable in adequate patients, there is no need to test for platelet function.

P2Y12 INHIBITORS block platelet receptors P2Y12, which plays a key role in platelet activation and arterial thrombus formation. Clopidogrel and prasugrel are thienopyridine prodrugs that irreversibly block P2I12 with active metabolites. Clopidogrel is a well-known standard antiplatelet drug, but relatively often there is resistance to its action. Prasugrel does not show significant resistance, reduces ischemic events and stent thrombosis, but without affecting mortality, but therefore to the detriment of increased nonfatal bleeding. Ticagrelor is a reversibly binding inhibitor of P2Y12, which does not require metabolic activation. Ticagrelor has the most predictable and consistently high level of P2Y12 inhibition during maintenance therapy in susceptible patients and also has a faster onset of action compared to clopidogrel. Ticagrelor monotherapy appears to have similar efficacy and safety as aspirin in patients with previous PCI. Ticagrelor increases non-fatal but not fatal bleeding. Equivalent efficacy and similar safety of two doses of ticagrelor were explained by similar levels of platelet inhibition. Ticagrelor can cause dyspnoea, which is often transient and usually mild and tolerable, but sometimes a switch to thienopyridine is required. There are opinions and limited pharmacodynamic studies that support the unlicensed use of prasugrel or

ticagrelor in stable patients undergoing elective PCI who are at high risk for stent thrombosis.

DURATION OF DOUBLE ANTIAGREGATION THERAPY AFTER PCI

After 6 months, DAPT achieves an optimal balance of efficacy and safety in most patients [121]. Premature discontinuation of P2Y12 inhibitors is associated with an increased risk of stent thrombosis and is not recommended [121]. However, a shorter duration of DAPT may be considered in individuals at high risk for life-threatening bleeding given the very low risk of stent thrombosis after 3 months. However, the official position is: 12 months of DAPT recommended after ACS and PCI.

Greater benefit from prolonged therapy with clopidogrel or prasugrel has been observed in patients treated with AMI. The PEGASUS-TIMI 54 study showed that long-term therapy with ticagrelor 60 or 90 mg 2 x 1, initiated in stable patients more than 1 year after AMI, reduced ischemic events at the expense of increased multiple nonfatal bleeding. [121]. The 60 mg dose appears to be better tolerated and has been approved in many countries for this indication. Absolute reduction of ischemic events in CCS SCENARIO 4 with long-term ticagrelor (60 mg 2 x 1) with a low dose of ASA in high-risk patients after AMI with DM, peripheral arterial disease or multivessel CAD was demonstrated by Bhatt DL and associates in the subgroup of the mentioned study PEGASUS- TIMI 54. [122].

ORAL ANTICOAGULANT MEDICINES (AOK)

ANTICOAGULANT DRUGS IN SINUS RHYTHM

Anticoagulant drugs inhibit the action and / or production of thrombin, which plays a key role in both coagulation and platelet activation. Recently published studies have renewed interest in combining lower anticoagulant doses with antiplatelet therapy.

RIVAROXABANE IN SMALL DOSES. Rivaroxaban is a factor Xa inhibitor that has been studied at a low dose of 2.5 mg 2 x 1 daily in several populations of patients with sinus rhythm, and this dose is 1/4 of the standard dose used for anticoagulation in patients with AF. In the ATLAS ACS 2TIMI 51 study, rivaroxaban 2.5 mg 2 x 1, compared with placebo, reduced the complex outcome of AMI, stroke, or CV death in stabilized patients treated with aspirin and clopidogrel after ACS, with increased nonfatal bleeding, but with evidence reductions in cardiovascular mortality [123]. Subsequently, in the COMPAS study (124), the same regimen in combination with aspirin and clopidogrel, with or without rivaroxaban 2 x 5 mg, in patients with CCS showed reduced ischemic events at the expense of an increased risk of predominantly nonfatal bleeding. [124].

ANTICOAGULANT DRUGS IN ATRIAL FIBRILLATION

OAC is recommended for patients with AF and CCS to reduce ischemic stroke and other ischemic events. OAC in patients with AF has shown superiority over aspirin monotherapy or clopidogrel-based DAPT for stroke prevention and is therefore recommended for this indication. [124]. When administering OAC to a patient with AF and CCS, based on the CHA_2DS_2-VAS score and HASBLED score, non-vitamin K antagonists -NOAC (i.e., apicaban, dabigatran, edoxaban, or rivaroxaban) have an advantage over vitamin K (VKA) antagonists. [1]

Proton pump inhibitors

Proton pump inhibitors reduce the risk of gastrointestinal bleeding in patients treated with antiplatelet drugs and are given to anyone with a high risk of bleeding (HASBLED score) and monotherapy, to improve safety. [124]

STATINS

When target LDL cholesterol values cannot be achieved, it has been shown that the addition of ezetimibe reduces LDL cholesterol but also reduces CV events in patients with ACS, in diabetics [1] without further impact on mortality. In addition to exercise, diet, and weight control, which should be recommended to all patients, dietary supplements, including phytosterols, may lower LDL-C to a lesser extent, but no improvement in clinical outcomes has been shown [1]. Phytosterols are also used in patients with statin intolerance, which is a group with a higher risk of cardiovascular events. Studies from 2015 show that subtilinin-kexin type 9 proprotein convertase inhibitors (PCSK9) (evolocumab and alirocumab) are very effective in lowering cholesterol, lowering LDL-C in a consistently stable manner to <-1.3 mmol / L. In outcome studies, these agents have been shown to reduce cardiovascular and mostly ischemic events, with little or no effect on mortality. [1] Very low cholesterol is well tolerated and associated with fewer events, but the high cost of PCSK9 inhibitors and their unknown long-term safety has limited their low-density lipoprotein apheresis and new therapies such as mipomersen and lomitapid need further investigation. For patients undergoing PCI, a

high dose of atorvastatin reduces the incidence of periprocedural events [1].

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKERS

ACE INHIBITORS can reduce mortality, AMI, stroke, and HF among patients with LV dysfunction, previous peripheral vascular disease, and high-risk DM. It is recommended that ACE inhibitors (or ARBs, angiotensin AT2 receptor blockers in cases of ACEI intolerance) be considered for the treatment of patients with CCS with coexisting hypertension, LVEF <40%, DM or chronic renal disease and insufficiency (CKD), unless contraindicated (eg severe renal impairment, hyperkalaemia, etc.). However, not all studies have shown that ACE inhibitors reduce all-cause mortality, as well as cardiovascular death, nonfatal AMI, stroke, or HF in patients with atherosclerosis and without impaired LC function. A meta-analysis, including 24 trials and 61961 patients, documented in CCS patients without HF [1] that renin-angiotensin system (RAS) inhibitors reduced cardiovascular events and death only compared to placebo, but not when compared to active controls. . Therefore, ACE inhibitor therapy in CCS patients without HF or high CV risk is generally not recommended unless necessary to achieve target blood pressure values.

Neprilysin is an endogenous enzyme that degrades vasoactive peptides such as bradykinin and natriuretic peptides. Pharmacological inhibition of neprilysin raises the level of these peptides, enhancing diuresis, natriuresis, myocardial relaxation, and antiremodeling and reducing renin and aldosterone secretion. The first drug in the class is LCZ696, which combines valsartan and sacubitril (a neprilysin inhibitor) in one tablet. patients with HF (LVEF <_35%) who remain symptomatic despite optimal treatment with ACE inhibitor, beta blocker and mineralocorticoid receptor antagonist (MRA), sacubitril / valsartan is recommended as a replacement for ACE inhibitor to further reduce the risk of HF hospitalization and death in outpatients.337 Aldosterone blockade with spironolactone or eplerenone is recommended for use in post-MI patients who are already receiving therapeutic doses of ACE inhibitors and beta blockers and have LVEF <35%, or diabetes or SI-HF. Caution should be exercised when using MRA in patients with impaired renal function [estimated GFR (eGFR) <45 mL / min / 1.73 m2] and in those with serum potassium> _5.0 mmol / L.

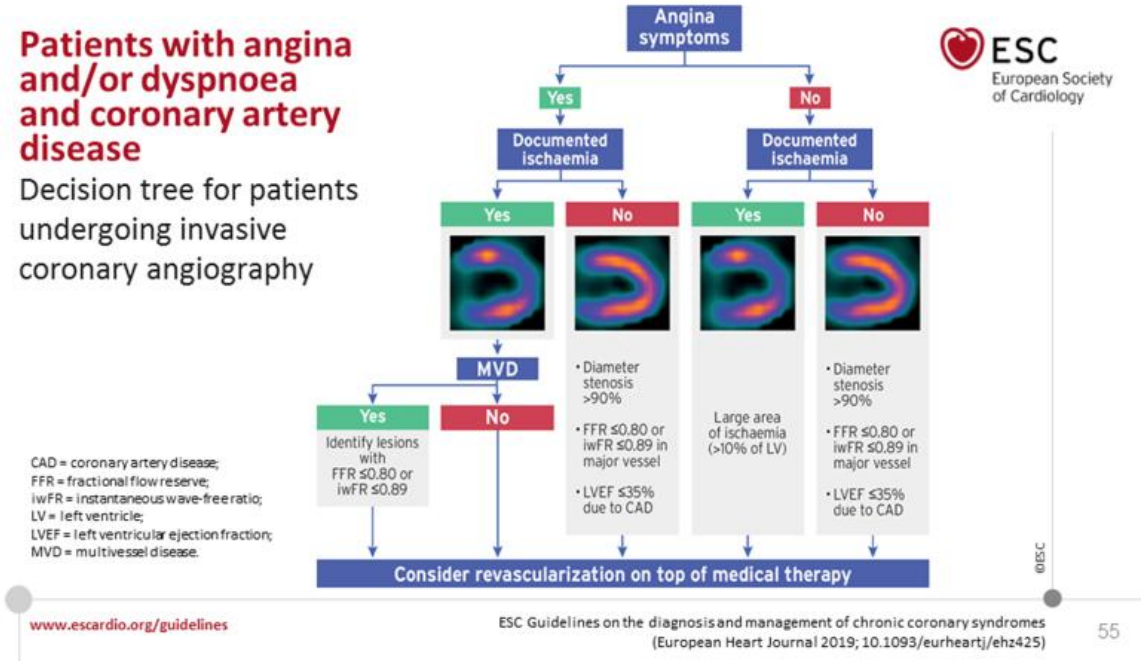
The combination of anti-ischemic drugs and drugs that affect the prognosis and survival in practice are insufficiently used both in the world [110] and in the part of Serbia - Timok region. Doses are not titrated to achieve optimal effects of pharmacological therapy [112]. The analysis of the treatment of DE NOVO coronary heart disease in consecutive 101 pts is presented from the clinical practice of the Dr. Bastać Practice. At the first examination, patients, previously treated or understood as stable angina pectoris, had pharmacological therapy by the attending physician or cardiologist (only 26% had a definitive diagnosis of coronary heart disease by exercise ECG test) attached to TABLE 6.

Table 6. Analysis of prescribed drugs for the treatment of suspected chronic coronary syndrome (CCS) in the Practice "Dr Bastać" on the 101st consecutive patient in 2017

Antiischemic drugs		Drugs that act on the prognosis of coronary heart disease
I lines	II lines	
65% beta blockers (also have hypertension)	**36% long-acting nitrates** molsidomin is not prescribed	**48% acetyl salicylic acid** (ASA) **9% Clopidogrel**
31% Ant CA (due to hypertension)	**16% trimetazidine**	**23% statin**
20% Ntg sublinvally as needed	Not prescribed: ranolazine, ivabradine, nicorandil	**61% ACE inhibitors** (also have hypertension) **65% beta blockers** (also have hypertension)

MYOCARDIAL REVASCULARIZATION (MR). The role of coronary myocardial revascularization (MR) in the treatment of chronic coronary syndromes SCENARIO 1. Figure 5

FIGURE 5. The role of coronary myocardial revascularization (RM) in the treatment of chronic coronary syndromes SCENARIO 1



Retrieved from https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

In patients with CCS, optimal medical therapy (lifestyle change, risk factor reduction and pharmacological-drug therapy, do not equate medical and drug therapy) -OMT is key to reducing symptoms, stopping the progression of atherosclerosis and preventing atherothrombotic events. Myocardial revascularization (RM) plays a central role in the management of the most severe forms of CCS as a last resort, but always as an adjunct to optimal medical therapy (OMT), without its elimination. The goals of MR are to alleviate symptoms in patients with angina and / or to improve the prognosis. These recommendations suggest that revascularization in patients with AP and significant stenosis is often second-line therapy when OMT has not been successful. Myocardial revascularization: PCI or CABG can effectively alleviate angina, reduce the use of antianginal drugs, and improve exercise ability and quality of life in a small number of selected patients compared to the OMT-only strategy. Revascularization with either PCI or CABG also aims to effectively eliminate myocardial ischemia and its adverse clinical manifestations among patients with significant coronary stenosis and to reduce the risk of major acute adverse CV events including AMI and cardiovascular death.

Numerous meta-analyzes comparing MR strategy by PCI with initial OMT in patients with CCS show either no benefit [126, 127] or myocardial revascularization provides a modest benefit [128, 129,] in terms of survival or lower incidence of AMI and SI. In this regard, previous ESC guidelines from 2013 [4] identified specific subgroups of patients (based on coronary anatomy, size of myocardial ischemia zone, risk factors, cardiac status, etc.) in whom MR may improve prognosis, indicating that in other subgroups it has no effect. FIGURE 5 summarizes the practical approach to MR indications in CCS according to the presence or absence of symptoms and documented myocardial ischemia by noninvasive functional imaging tests. However, the risk-benefit relationship in an individual case should always be evaluated and the MR is considered only if the expected benefit outweighs the potential risk. Also, the aspect of joint team decision-making is crucial, with complete information given to the patient about the expected advantages and disadvantages of the two strategies, including the risk of bleeding associated with DAPT in cases of revascularization via PCI.

A detailed discussion of the best choice between PCI or CABG revascularization modalities for an individual patient on the HEART team was published in the 2018 ESC guidelines for myocardial revascularization [131].
The role of MR has been placed in the context of recent evidence relating to the prognostic role of percutaneous coronary interventions (PCI) or coronary artery bypass grafting or native a. mammario internal and other arteries (CABG) in this low-risk population. MR is now reserved for patients where there is strong evidence to improve prognosis based on evidence of regional ischemia by visual noninvasive tests - perfusion imaging or assessment of FFR and iwFR [131]. The typical constellation is in a patient with a large area of myocardial ischemia corresponding to left main stenosis (left main stenosis> 50%) and multivessel disease that always involves stenosis ≥70% of the proximal anterior-descending branch of the left coronary artery (LAD). There is unequivocal evidence that percutaneous coronary revascularization (PCI) in acute coronary syndromes with ST-segment elevation reduces mortality relative to fibrinolysis, and both relative to those where no reperfusion has been performed.

In other forms of CAD -chronic coronary syndromes (CCS), the role of PCI revascularization is controversial in terms of mortality reduction [132, 133]. A recent meta-analysis of 46 studies in 37,757 individuals examined the PCI benefit of various categories of coronary patients, including true stable angina without a recent heart attack. In stable angina pectoris, the chronic coronary syndrome PCI categories did not reduce overall mortality (RR, 0.98, p = 0.11]), cardiac death (RR, 0.89, p = 0.33), or myocardial infarction (RR, 0.96; P = 0.54). PCI prevents death, cardiac death, and AMI primarily in patients with unstable AP. For patients with stable CAD, PCI shows no effects on any of these outcomes. [132-134]. However, it is now becoming evident that OMT is still underused in recent studies [132]. Mohee K. et al show that OMT is still suboptimal in patients before PCI and becomes optimal only after PCI due to increased compliance. [132]. Argument: OMT is the definitive therapy for patients with stable coronary heart disease and low risk of CV events (mortality <1% per year).

COURAGE STUDIES [16,60,133,134]. (Boden WE et al., Published in NEJM 2007) - initial PCI with a stent does not reduce the risk of death, AMI and hospitalization and has no advantage in stable AP according to OMT on 2287 randomized pts with known significant stable CAD and proven myocardial ischemia who were only on OMT OR OMT + PCI. Between 1999 and 2004, a COURAGE (Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation) study randomized 2287 pts with objective evidence of ischemia and proximal angiographic CAD (≥ 70% visual visual stenosis) to OMT with or without PCI. The aim and design of the study was to test the strategy of routine, anatomically-indicated PCI, if necessary, for the failure of the initial OMT. Follow-up of 2.5 to 7 years (median 4.6 g) showed that death or AMI occurred with the same frequency in both subgroups (PCI + OMT vs OMT = 1.05, p = 0.62). After 4.6 years of follow-up, there was no statistically significant difference between the groups for cumulative mortality and nonfatal myocardial infarction -18.5% vs 19%, as well as for stroke and hospitalization due to new unstable AP. Important: COURAGE study patients had marked symptoms at enrollment and had significant comorbidities, a high prevalence of objectively established ischemia, and extensive angiographic coronary heart disease, and were in the population where clinical benefit from PCI was expected.

Subgroup analysis reveals consistency among clinically relevant subgroups. There is no difference only OMT versus OMT + PCI in terms of multidisciplinary disease, low EF, class III-IV angina and the presence of Diabetes Mellitus. By comparison, there was no difference in hospitalization for ACS either. The main result of the study showed that PCI as an initial strategy in patients with stable AP CCS does not reduce death, AMI and other major events (MACE) when OMT is added. Patients with PCI had less angina in the first and 3rd year, but not in the 5th year of follow-up. As initially expected, revascularization was more common in OMT in 16.5% of the first year of follow-up alone. The efficacy of OMT in stable AP where the optimal dose of beta-blocker is a central component is similar to the effect of percutaneous coronary intervention (PCI) with a stent (Boden and Courage, 2007). [133,134].
Comparison between PCI and OMT (Braunwald s Heart disease, 2015- Morow D, Boden WE) [135]. n-) in terms of earlier techniques balloon angioplasty vs medical therapy, belongs to history, now in the era of new PCI techniques and new optimal drug therapy. In 16 studies of about 9000 pts, PCI vs OMT, the invasive strategy did not provide a reduction in mortality

or AMI, but only a reduction in AP severity and a better quality of life- QoL.

META-ANALYSIS OF VINDECKER et al. Reports reduction in death and AMI by revascularization versus OMT only in patients with CCS when CABG revascularization or next-generation drug-coated stent (DES) was performed, as opposed to balloon angioplasty, metal BMS stents, and old earlier DES [129].
FAME 2 [130]: Statistically significant risk reduction with PCI + OMT versus OMT alone, discontinued after 7 months, but had significant limitations, was not randomized, and was not a double-blind controlled study. Nevertheless, Xaplanteris P. I et al. Indicate a potentially broader prognostic impact of the revascularization strategy when targeted with a functional invasive assessment of coronary stenosis via FFR or iwFR. A five-year follow-up of the FAME 2 study confirmed clinical benefit in a subset of patients specifically treated with PCI targeting only ischemia-producing stenoses (i.e., FFR <0.80) plus OMT, which yielded significantly lower rates of emergency revascularization and lower rates of spontaneous AMI [130] but without a clear effect on mortality.

ORBITA A new ORBITA study (a randomized, controlled, double-blind study) comparing OMT or angioplasty with an anatomically significant coronary stenosis (PCI) stent in stable angina, with a false invasive procedure (shame) in the control group, found no advantage of PCI in significantly improving functional capacity. [125]. The study highlights a significant placebo component on clinical effects and warns us of the pitfalls of interpreting end-points that are subject to bias in the absence of false control. However, the results of the ORBITA study cannot provide definitive guidance due to the limited size of the study, the short observation time to treatment crossover, and insufficient strength to assess clinical outcomes.

ISCHEMIA The largest international randomized double-blind controlled follow-up study ISCHEMIA [137-139] recruited patients with stable CAD with moderate or severe ischemia on a stress test and aimed to assess whether there were differences in clinical outcomes - mortality and CV morbidity in patients. with stable chronic coronary heart disease (SCAD) between the invasive strategy + OMT and OMT alone. Out of a total of 8518 recruited patients, 5179 were randomly selected by randomization and were still randomized by type of treatment: Invasive PCI with stent plus medical therapy (n = 2588) versus only medical therapy (n = 2591). Coronary CT angiography was performed in most participants and was examined by the baseline laboratory to rule out main stable stenosis ≥ 50%. Randomized participants had a mean age of 64 years, with 1168 women (22.6%) and 2122 diabetes (41.0%)). Among the 3909 participants randomized after the functional imaging stress test for ischemia, the assessment of the severity of ischemia in 3901 participants was as follows: severe 1748 (44.8%), moderate 1600 (41.0%) and mild 317 (8.1%); 79.0% had multivessel CAD (n = 2679 of 3390) and anterior descending branch (LAD) proximal stenosis 46.8%. During an average of 3.3 years of follow-up, there was no significant statistical difference between primary outcomes: death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, cardiac arrest -13.3% in the invasive strategy versus 15.5% in the medical treatment group. (p = 0.34). The key secondary outcome was death from cardiovascular causes or myocardial infarction: 11.7% in the routine invasive group versus 13.9% of the OMT group (p = 0.21). Total mortality (cardiovascular and all other causes): 6.4% in the routine invasive group versus 6.5% in the OMT group (p = 0.67). Periprocedural AMI: 2.98%. The invasive versus conservative relationship to mortality was similar regardless of the degree of ischemia (p value for interaction = 0.23), which is also true for AMI. (p value for interaction = 0.15). Among patients with stable CAD and moderate to severe ischemia on a noninvasive visualization stress test, routine invasive treatment showed a reduction in major adverse outcomes compared with OMT. There is no benefit from invasive PCI therapy in terms of a complex end result: Overall, CV mortality, and nonfatal myocardial infarction.
The ACC / AHA American Guide to Chronic CAD [140] discourages the use of PCI or CABG for single-vessel or double-vessel CAD without significant proximal LAD involvement in the absence of unacceptable AP after adequate guidance-guided OMT, especially if noninvasive tests show a small area of exacerbated viable ischemia or reduced EF.

CLINICAL SCENARIO 2.
Patients with new-onset heart failure or left ventricular dysfunction and suspected coronary artery disease
CAD is the most common cause of chronic heart failure (HSI) in Europe. Most studies provide evidence to support recommendations for the

study of pts with ischemic cardiomyopathy (CMP) - the pathophysiological basis of ischemic CMP is systolic dysfunction EF <40%, although patients with CCS may also have HSI with preserved EF. Patients with symptomatic HF should be diagnosed according to the 2016 ESC HF Guide [141]. In addition to standard medical history, physical examination, ECG and chest radiography, Doppler echocardiography should be included in the image to evaluate the evidence of diagnosis of ischemic cardiomyopathy with HF with: a) reduced EF; b) mid-range EF; C) preserved EF with focal or diffuse echocardiographic signs of left and / or right ventricular systolic dysfunction, evidence of diastolic dysfunction, compensatory hypertrophy, valve function (ischemic mitral regurgitation) and evidence of secondary pulmonary hypertension [1]. In addition to routine hematological and biochemical analyzes, it is especially important to assess renal function, potassium, and sodium initially and during pharmacotherapy titration.

Measurement of serum natriuretic peptide levels serves to rule out HF if NT-proBNP levels are normal. The degree of increase in GNP titer is used to estimate the severity of HF [142]. The basic treatment in the NYHA II-III class is antianginal or antischemic therapy with drugs that affect the prognosis and prevention of events. BBs are also an essential component in the relief of anginal attacks and event prevention as well as mortality reduction in HF (Class I level A) [142-149]. Amlodipine may be included as an anti-ischemic drug, in those who do not tolerate BB I the only calcium antagonist is considered safe in HIS (Class IIb level B recommendation) [150-151]. Short-acting nitrates by sublingual or transcutaneous patches are also recommended. Patients with symptomatic HF should be treated according to the 2016 ESC Guide to HF [141], with an emphasis on adding to the standard therapy the newer drug angiotensin receptor-neprilysin inhibitor (sacubitril-valsartan) [141]. Doses of drugs: diuretics [152], ACEI, BB, spironolactone or eplerenone possibly and ivabradine should be gradually increased to avoid hypotension, bradycardia, azotemia hyperkalemia. ACEIs are crucial (CLASS I, LE A) in asymptomatic left ventricular dysfunction after myocardial infarction and in symptomatic HF for symptom relief and reduction of morbidity and mortality [153].

Implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) [154] can provide improvement in symptoms and improve survival [154]. Myocardial revascularization should be considered in suitable patients with ischemic HF based on symptoms, coronary anatomy, and evidence of current ischemia and myocardial viability by imaging tests in akinesia-cicatricial zones, through a multidisciplinary team. Myocardial revascularization is recommended when anginal discomfort and / or dyspnoea persist despite optimal antiaginal therapy (CLASS I, level of evidence A).

THE GROUP OF PATIENTS WITH LONG-TERM Dg CHRONIC CORONARY SYNDROMES INCLUDE:
CLINICAL SCENARIO 3. ASYMPTOMATIC AND SYMPTOMATIC PATIENTS WITH STABILIZED SYMPTOMS UP TO 1 YEAR LAST AFTER ACS OR CORONARY REVASCULARIZATION.
CLINICAL SCENARIO 4: THE SAME ONLY AFTER A YEAR)

Common to both groups, clinical scenarios 3 and 4 are lifelong treatment and follow-up [1]. The clinical course may be favorable for a longer period. However, patients with CCS may develop various CV complications: episode de novo ACS, complications due to therapeutic procedures due to CAD or due to interactions with comorbidities. The risk of complications also exists in asymptomatic patients, so the risk assessment must be applied to both symptomatic and asymptomatic patients. Therefore, a risk based on biomarkers in 2017 was developed and validated [155].

CLINICAL SCENARIO 3
ASYMPTOMATIC AND SYMPTOMATIC PATIENTS WITHIN 1 YEAR OF ACS OR REVASCULARIZATION
After revascularization or stabilization of ACS within one year, the patient must be closely monitored due to the increased risk of complications and the need to adjust pharmacological treatment [35]. It is recommended to have at least two visits to the doctor in the first year of follow-up, while those with systolic LC dysfunction before revascularization or after ACS should report for cardiac examination 8-12 weeks after ACS or revascularization. Cardiac function can be improved by recovering from stunning or hibernating myocardium by revascularization based on the results of the ADVISE II study by invasively assessing whether epicardial coronary stenosis is the cause of ischemia by iwFR [52,53]. However, exacerbations can occur

due to concomitant CV disorders (valvular diseases, infections, arrhythmias, etc.) and these disorders need to be identified and treated. Non-invasive post-revascularization assessment may be considered to rule out residual ischemia or to document a reference ischemia finding to plan treatment intensification and further periodic follow-up [1].

CLINICAL SCENARIO 4.
ASYMPTOMATIC AND SYMPTOMATIC PATIENTS MORE THAN 1 YEAR LAST OF ACS OR REVASCULARIZATION.

Once a year, the patient needs to be evaluated by a cardiologist, even when the patient is without problems. The recommendation is an annual clinical examination and assessment of adherence to pharmacotherapy and non-pharmacological measures with the determination of risk profiles through risk scores. Laboratory analyzes: lipid profile, renal function, blood count and cardiac biomarkers should be performed every two years [1, 45]. An elevated marker of hsCRP inflammation is associated with an increased risk of adverse events. Von Willebrandt factor, interleukin-6 and NTpro BNP are predictors of outcome [25]. Other biomarkers for pts with CCS also have prognostic significance: heart rate, hemoglobin, leukocyte count [156]. Multiple biomarker scores showed prognostic significance: combining: hsCRP, fibrin degrading products, and heat shock protein 70; [157]. For patients with an exacerbated risk score during follow-up, it is warranted to intensify therapy and diagnostic re-evaluation, although risk-guided therapy has not yet been shown to improve prognosis. A 12-channel ECG should be part of each follow-up to record heart rate and rhythm and to detect changes suggestive of symptomatic myocardial ischemia / infarction and to evaluate PR, QRS, and QT intervals. It would be useful to echocardiographically assess systolic and diastolic LV function, valve status, heart size, and volume in apparently (seemingly) asymptomatic patients at 3 to 5 years of age. [1,52,53]. In case of unexplained reduction of left ventricular systolic function, especially regional, it would be useful to do an image of coronary anat 55 Asymptomatic, silent ischemia should also be sought in seemingly asymptomatic patients through periodic stress imaging tests [1, 52].

CLINICAL SCENARIO 5.
PATIENTS WITH ANGINA PEKTORIS AND SUSPECT VASOPASTIC OR MICROVASCULAR DISEASE.

Angina without obstructive disease in the epicardial coronary arteries (INOCA). In clinical practice, there is a discrepancy between the findings concerning coronary anatomy, the presence of symptoms and the results of non-invasive tests often occur [13]. These patients deserve attention because APs with nonobstructive CAD are associated with an increased risk of adverse clinical events [14,15]. The low diagnostic contribution of ICA can be explained by the presence of: (1) mild stenosis or diffuse coronary narrowing, with underestimated functional significance; (2) microcirculation disorders; (3) dynamic epicardial vessel stenosis caused by coronary spasm or intramyocardial bridges that are not apparent during CTA or ICA. Intracoronary pressure measurements are useful in resolving the first case. At diagnostic processing, patients with angina and / or myocardial ischemia who have coronary stenoses with nonischemic FFR or ivFR values may also be referred to as non-obstructive diseases of the epicardial coronary arteries. The presence of clearly defined anginal symptoms and pathological findings of non-invasive tests in patients with normal coronary epicardial arteries should lead to suspicion of a non-obstructive cause of ischemia. Often and mainly as a result of persistence of symptoms, patients with angina and without obstructive CAD undergo multiple diagnostic tests, including repeated coronary CTA or ICA, which contribute to increased health care costs [158]. It is important to emphasize that in everyday practice, there is often a significant discrepancy between the findings of coronary anatomy, the presence of symptoms, and the results of noninvasive tests. Diagnostic pathways investigating microcirculatory or vasomotor coronary disorders are often not performed, so a definitive, evidence-based diagnosis is rarely made. Due to that, patient anxiety and depression are not uncommon in this clinical population. [159]. A 2018 randomized controlled trial of CorMicA found in patients with nonobstructive coronary heart disease, through customized treatment guided by the results of an intracoronary trial: coronary flow reserve (CFR), microcirculatory resistance, and acetylcholine test resulted in a significant reduction in anginal symptoms compared with treatment [160].

Microvascular angina

Patients with microvascular angina typically have chest pain on exertion, a positive ischemia test, either exercise ECG test or noninvasive

imaging tests, without obstructive CAD or with mild to moderate stenosis (40-60%) of the epicardial coronary arteries, which is detected by IC CTA and these stenoses are considered functionally insignificant. The microvascular origin of angina is usually suspected after the exclusion of obstructive coronary epicardial stenosis, during the diagnostic processing of patients with proven myocardial ischemia on the exercise ECG test. Regional abnormalities of wall movement rarely develop during exercise or stress in patients with microvascular angina. Some patients may have a mixed form of microvascular + vasospotic angina, with occasional episodes at rest, especially associated with exposure to cold. Secondary microvascular angina, without obstructive CAD, may be due to cardiac or systemic conditions, including those that cause LV hypertrophy (such as hypertrophic cardiomyopathy, aortic stenosis, and hypertensive heart disease) [161] or inflammation (such as myocarditis or vasculitis).) [162]. Risk stratification in microvascular AP is quite complex. The presence of microcirculatory dysfunction in patients with CCS entails a worse prognosis than originally thought, based on the latest evidence based on monitoring patients with objective microcirculation disorders proven by invasive or noninvasive techniques. [163-167]. Microcirculation dysfunction precedes the development of epicardial coronary lesions, especially in women, and is associated with impairment and adverse outcome events. Among diabetic patients undergoing diagnostic processing, those without obstructive epicardial disease but with abnormal coronary flow reserve (CFR) have a similarly poor long-term prognosis as those with obstructive epicardial disease [165]. In patients with significant CAD with significant stenosis at FFR ≤ 0.80, the presence of abnormal CFR <2.0 is associated with additional exacerbation and a significant number of adverse events especially when the microcirculatory resistance index (IMR) is also abnormal [166].

The possibility of microcirculatory origin of angina should be considered in patients with clear angina, abnormal non-invasive functional tests, and coronary arteries that are either normal or with mild stenosis, which are considered functionally insignificant on ICA or CTA. One of the challenges in performing a comprehensive assessment of microvascular function is to test the two main mechanisms of dysfunction separately:

1. Weakened microcirculatory conductivity (or increased microcirculatory resistance)
and
2. Arteriolar dysregulation. [168-170].

However, it should be clarified which of these two pathways is critical to the choice of pharmacological treatment to minimize the symptoms of these patients. [160]. Weakened or disturbed microcirculatory conduction can be diagnosed by measuring coronary flow reserve (CFR) or minimal microcirculatory resistance. CFR can be measured by noninvasive transthoracic color and pulsed Doppler echocardiography [visualization and measurement of basal flow rate and with vasodilatation test with adenosine or dipyridamole] [171] as well as magnetic resonance imaging (myocardial perfusion index is less available or PET). Microcirculatory resistance can be measured in a catheterization laboratory by combining intracoronary pressure with thermodilution-based data (to calculate IMR) or Doppler flow rates (to calculate hyperemic microvascular resistance or HMR) [172,173]. The decision on abnormal microcirculation is made when the value of the microcirculatory resistance index is greater than 25 units (IMR> 25 J) or CFR <2.0. In contrast, the diagnosis of arteriolar dysregulation requires assessment of endothelial function in coronary microcirculation by selective intracoronary infusion of acetylcholine. Acetylcholine is an endothelium-dependent vasodilator that acts directly on arteriole smooth muscle cells and causes paradoxical arteriolar vasoconstriction — microvascular spasm of dysfunctional vascular endothelium or abnormal smooth muscle cell function [174]. This arteriolar response to acetylcholine causes anginal symptoms with or without concomitant ischemic ECG changes and a decrease in coronary blood flow velocities if simultaneous Doppler measurements are performed. Peripheral pulse tonometry during reactive hyperemia may also reveal abnormal systemic endothelial function in patients with AP and non-obstructive CAD [175].

Vasospastic angina

Vasospastic angina should be suspected in patients with AP when the symptoms occur mainly at rest, with maintained tolerance to exertion. The likelihood of vasospastic angina increases when the attacks follow a circadian pattern, with multiple episodes at night and in the early morning hours. Patients are often younger and have fewer CV risk factors than patients who have AP on exertion, except that

they are most often cigarette smokers [176]. Coronary vasospasm is also suspected in patients with transient coronary stents and persistent AP. [177-178]. The diagnosis of vasospastic AP is based on the detection of transient ischemic changes in depression or elevation of the ST segment during an angina attack (usually at rest rest AP). Patients with Prinzmetal's AP represent a special subgroup where resting AP is accompanied by transient ST-segment elevation [176-179]. This ST elevation on the ECG correlates with proximal occlusion by vasospasm. As most vasospastic AP attacks are self-limiting, it is difficult to register without multi-day ambulatory Holter monitoring by 12-channel recording. The appearance of ST-segment changes at normal pulse supports the probability of myocardial ischemia caused by spasm. In patients with suspected vasospastic AP and documented ECG changes, coronary CTA or ICA is important to rule out the presence of fixed coronary stenosis. Angiographic documentation of coronary spasm requires the use of a provocation test in a catheterization laboratory. Due to the low sensitivity of the hyperventilation test and the cold water test, intracoronary administration of acetylcholine or ergonovine during ICA are preferred provocative tests. [176-179]. 176. Both pharmacological agents are safe, provided that they are selectively inserted into the left or right coronary arteries and that activated spasm is easily controlled by intracoronary nitrates. A small percentage of patients may develop ventricular tachycardia / ventricular fibrillation or bradyarrhythmia during a provocative test (3.2 and 2.7%, respectively), similar to that during spontaneous spasm attacks (7%) [180]. Intravenous administration of ergonovine for non-invasive tests is contraindicated due to the risk of causing long-term spasm in multiple coronary arteries, which can be very difficult to stop and can be fatal.

A provocative test for coronary spasm is considered positive when it causes: (1) anginal symptoms, (2) ischemic ECG changes, and (3) severe vasoconstriction of the epicardial coronary artery. If the test fails to run all three components, this should be considered ambiguous [176]. The development of AP in response to acetylcholine injections in the absence of angiographically evident spasm, with or without concomitant ECG changes in the ST segment, may indicate microvascular spasm and is often seen in patients with microvascular AP [179]. In patients with epicardial or microcirculatory vasomotor disorders, CCB and long-acting nitrates (LANs) are the treatment of choice, in addition to controlling CV risk factors and lifestyle changes. Nifedipine has been shown to be effective in reducing coronary spasm associated with stent implantation. In all patients with vasospastic angina, optimal control of risk factors should be achieved, especially smoking cessation and aspirin use. Exclude drugs that may be narrow vasospasm - cocaine or amphetamine abuse. Chronic preventive treatment of vasospastic angina is mainly based on higher doses of calcium antagonists. Average doses of these drugs verapamil or diltiazem from 240 to 360 mg / day or nifedipine from 40 to 60 mg usually prevent spasm in about 90% of patients. Sometimes high doses of calcium antagonists must be given to prevent spasms: up to 960 mg a day of Verapamil or Diltiazem or up to 100 mg / day of Nifedipine. Long-acting nitrates should be added to some patients. Beta-blockers should be avoided, as they may increase spasm because by blocking the beta-dilating effects, vasoconstriction by unblocked alpha receptors predominates. About 10% of patients are refractory to this treatment, so the addition of guanethidine or clonidine may rarely be indicated. Stent implantation at the site of spasm and without stenosis, as well as surgical or chemical sympathectomy, are extreme measures.

CLINICAL SCENARIO 6. ASYMPTOMATIC PERSONS IN WHICH CAD WAS DETECTED AT SCREENING.

In an effort to reduce the high incidence of coronary sudden death in asymptomatic adults, numerous studies of risk factors and risk indicators, as well as stress tests, are often performed as screening tests. The European guidelines for CVD prevention in 2016 in clinical practice focused in detail on these issues. [15]. In general, the use of a risk assessment system such as ESC SCORE is recommended. People with a family history of premature CAD should be screened for familial hypercholesterolemia. Coronary calcium score, ABI index, and Color Doppler echosonography of the carotid arteries in plaque detection may provide useful information on atherosclerotic risk in selected patients. Routine use of biomarkers or imaging tests for CAD is not recommended. New biomarkers have an increasing predictive value compared to classical ones, but the net improvement in reclassification risk is still only modest (7.18%) compared, for example, with the coronary calcium score, which has a net

improvement in reclassification of 66%. Only persons at high risk of events should be considered for further non-invasive or invasive examination. There are no data on how to treat asymptomatic subjects with a positive CAD test outside the recommendations outlined in these guidelines. However, the principles of risk stratification, as described above for symptomatic patients, also apply to these individuals. It is important to know that there is no data that showed an improved prognosis after appropriate care based on new biomarkers. It is important to note that cancer patients and those undergoing treatment for cancer, chronic inflammatory and systemic autoimmune diseases deserve a more intensive risk evaluation. People whose occupations include public safety (eg pilots or truck or bus drivers, workers) or professional athletes are usually periodically tested to assess the ECG with a TFO test and assess possible heart disease, including CAD, although there is insufficient data to justify this. However, these evaluations can be performed for medical-legal reasons. The threshold for performing a visualization stress test for CAD in such persons is lower than in the average patient.

REFRACTORY ANGINA PEKTORIS (RAP)

RAP as a form of chronic coronary syndrome (CCS) is defined as a chronic condition caused by clinically established reversible ischemia in the presence of CAD, which cannot be adequately controlled by a combination of medical therapy, angioplasty with stenting (PCI) or surgical coronary revascularization (CABG) [1]: The following treatment options are considered:

1- Forced external counterpulsation (EECP) should be considered to alleviate and minimize discomfort in patients with AP Refractory to optimal pharmacological therapy and revascularization strategy

2-Transcutaneous electrical nerve stimulation (TENS) can be used to alleviate the symptoms of refractory AP on optimal pharmacotherapy and revascularization strategy

3-Spinal cord stimulation (SCS) can be used to alleviate the symptoms of refractory angina to optimal pharmacol Th and revascularizа strategy

4-Transmyocardial revascularization (TMR) is not indicated in patients with symptoms of refractory angina on optimal pharmacological Th and revascularization strategy

FUTURE PERSPECTIVES OF CHRONIC CORONARY SYNDROMES CCS - Quote from Brownwald's textbook of cardiology, authors David Morrow, J. J. A. De Lemos and William Boden [135]:

Our understanding of CHRONIC CORONARY SYNDROMES (CCS), both as a cause, optimal approach and treatment, is constantly evolving.

1. Complex and probably heterogeneous causes of myocardial ischemia require continuous multidisciplinary research through experimental studies in genetics, molecular biology, biochemistry, morphological and functional aspects of coronary circulation, and pathological morphology and pathophysiology of myocardial ischemia, which should then be confirmed in clinical studies with sufficient statistical power to generate new guidelines for more precise and simpler diagnosis and effective therapy of CCS. Today, we are confronted with the essential data that challenge the paradigm that Ischemic CAD requires critical coronary atherosclerosis of the subepicardial coronary artery or other structural heart disease that results in a dramatic increase in oxygen consumption. Preclinical, translational and clinical epidemiological data demonstrate abnormalities in coronary artery function, which can lead to myocardial ischemia in the absence of atherosclerotic obstruction.

2. However, so far, the treatments proposed for this important syndrome-CHRONIC CORONARY SYNDROME have proved insufficient. Additional insight into the pathobiology of ischemia could lead to new directions in treatment.

3. An initial approach to targeted secondary-preventive therapy and coronary revascularization, when necessary, is the best approach for most patients with CCS. There are subgroups of patients with high-risk indicators for whom coronary myocardial revascularization should be logical. However, clinical controversy and doubt remains as to whether such patients, including those with moderate or severe ischemia on a noninvasive test, should be routinely subjected to coronary myocardial revascularization in the absence of symptoms of refractory to optimal preventive and pharmacological therapy (OMT).

4.. Definitive evidence for the care of patients with stable CCS and other consequences of ischemia, especially left ventricular dysfunction and mitral ischemic regurgitation, remains incomplete. In our opinion, complete myocardial revascularization, usually surgical -CABG, remains a reasonable option for patients with multivessel CAD, LC dysfunction, and viable myocardium, especially when there is objective evidence of ischemia. However, some recent studies call this view into question. Despite our

good experience with CCS, there are no answers to important questions [135].

FUTURE PERSPECTIVES OF CHRONIC CORONARY SYNDROME CCS - quote from Braunald's textbook of cardiology, authors David Morrow and William Boden [181]: Our understanding of CCS, as a cause, optimal approach and treatment, is constantly evolving.

1. Complex and probably heterogeneous causes of myocardial ischemia require continuous multidisciplinary research through experimental studies in genetics, molecular biology, biochemistry, morphological and functional aspects of coronary circulation, and pathological morphology and pathophysiology of myocardial ischemia, which should then be confirmed randomly studies with sufficient statistical power to generate new guidelines for more precise and simpler diagnosis and effective therapy of CCS. Today, we are confronted with the essential data that challenge the paradigm that Ischemic CAD requires critical coronary atherosclerosis of the subepicardial coronary artery or other structural heart disease that results in a dramatic increase in oxygen consumption. Preclinical, translational and clinical epidemiological data demonstrate abnormalities in coronary artery function, which can lead to myocardial ischemia in the absence of atherosclerotic obstruction.

2. However, so far, the treatments proposed for this important syndrome-CHRONIC CORONARY SYNDROME have proved insufficient. Additional insight into the pathobiology of ischemia could lead to new directions in Th.

3. An initial approach to guided-targeted secondary-preventive therapy and coronary revascularization, when necessary, is the best approach for most patients with CCS. There are subgroups of patients with high-risk indicators for whom coronary myocardial revascularization should be logical. However, clinical controversy and doubt remains as to whether such patients, including those with moderate or severe ischemia on a noninvasive test, should routinely undergo coronary myocardial revascularization in the absence of symptoms of refractory to optimal preventive and pharmacological therapy (OMT).

4.. Definitive evidence for the care of patients with stable CCS and other consequences of ischemia, especially left ventricular dysfunction and mitral ischemic regurgitation, remains incomplete. In our opinion, complete myocardial revascularization, usually surgical -CABG, remains a reasonable option for pts with multivessel CAD, LC dysfunction, and viable myocardium, especially when there is objective evidence of ischemia. However, some recent studies call this view into question. Despite our good experience with CCS, there are no answers to important questions [181].

CONCLUSION:

Careful and studious evaluation of the anamnesis, including characterization of anginal symptoms and assessment of risk factors and manifestations of cardiovascular diseases, as well as appropriate physical examination and basic supplementary, basic examination is essential for the diagnosis of chronic coronary syndromes. If obstructive coronary artery disease (mean pre-test probability) cannot be ruled out by clinical evaluation alone, noninvasive diagnostic functional imaging tests with physical or pharmacological loading or anatomical imaging should be used as the initial test to exclude or diagnose chronic coronary syndromes (clinical scenario 1). via coronary CT angiography. The selection of the initial non-invasive diagnostic test is based on the probability test for obstructive coronary heart disease (PTP), its clinical probability, characteristics and test availability. An anatomical and functional evaluation should be performed to decide on revascularization. Either non-invasive or invasive functional evaluation is required to assess the size of myocardial ischemia associated with angiographic coronary artery stenosis, except for very high-grade stenosis (> 90% of diameter stenosis). The risk assessment for adverse events and mortality serves to determine for which patients with CCS the prognostic benefit of revascularization is predicted.

Assessment of left ventricular function by echocardiography is a mandatory part of risk stratification. Patients at high risk of adverse events undergo invasive examination to consider revascularization, even when asymptomatic. The application of a healthy lifestyle reduces the risk of subsequent CV events and mortality and is always included in the program of appropriate measures and therapy of secondary prevention. Clinicians should advise and encourage the necessary lifestyle changes at each clinical encounter with patients. Cognitive-behavioral psychological interventions such as supporting patients to set realistic goals, self-control, planning to implement change, coping with difficult situations, adapting to the environment, and

including social support are effective behavioral change interventions.

Multidisciplinary teams can support patients to change to a healthy lifestyle and guide them to avoid risk and risky behavior. Anti-ischemic treatment must be tailored to the individual patient based on comorbidity, concomitant therapy, expected tolerance and adherence to therapy, but also the patient's preference. The choice of anti-ischemic drugs for the treatment of CCS should be adjusted to heart rate, blood pressure and left ventricular function. Beta-blockers and / or calcium antagonists remain first-line drugs in patients with CCS. Antithrombotic therapy is a key part of secondary prevention in patients with CCS and requires careful consideration. Long-term (and after 12 months) dual antiplatelet therapy (DAPT) with aspirin or any P2I12 inhibitor should be considered in patients with previous myocardial infarction, with or without revascularization, who are at high risk of ischemic events and low risk of severe or fatal bleeding. or rivaroxaban with very low doses, unless they have an indication for oral anticoagulant therapy (OAK) such as the presence of atrial fibrillation (AF). Statins are recommended for all patients with CCS, regardless of the level of LDL cholesterol. ACE inhibitors (or ARBs) are recommended in the presence of heart failure (SI), diabetes, or hypertension and should be considered in all high-risk patients. Proton pump inhibitors are recommended in patients receiving aspirin or a combination of antithrombotic therapies that are at high risk for gastrointestinal bleeding. Efforts should be made to explain to patients the importance of taking prescribed medication regularly, based on evidence that regular adherence to treatment prevents adverse events, relieves the patient of pain, and improves quality of life. Repeated therapeutic education of patients is essential for every clinical encounter. Patients with a long-term diagnosis of CCS should visit a doctor periodically to assess possible changes in risk status, adhere to treatment goals, and develop comorbidities. Repeated physical or pharmacological stress tests, preferably imaging stress tests, or invasive coronary angiography with functional testing in case of worsening symptoms and / or increased risk status are recommended. Assessment of the function and dimensions of the heart cavities, myocardium and valves, as well as a functional test to rule out significant asymptomatic (silent) myocardial ischemia, should be considered every 3–5 years in asymptomatic patients with a long-term diagnosis of CCS. Assessment of coronary vasomotor function should be considered in patients without obstructive coronary disease or with minor epicardial coronary disease who have objective evidence of myocardial ischemia. Objectives of treatment of chronic coronary symptoms (CCS): improving prognosis, ie. reducing mortality by reducing the risk of progression of atherosclerosis and preventing acute coronary events and sudden death; and minimizing symptoms while improving quality of life. Efforts should be made to explain to patients the importance of evidence-based guidelines and guidelines for adherence to treatment.

All patients with stable coronary heart disease need lifestyle changes, risk factor reduction and pharmacological therapy, but all patients with coronary artery stenosis do not benefit from revascularization, which depends on the size of the ischemia and the anatomical involvement of the coronary arteries. Optimal medical therapy is the definitive therapy for patients with stable coronary heart disease and low risk of cardiovascular events. Revascularization and optimal medical therapy should be considered as complementary rather than competitive treatments.

In high-risk CCS patients with mortality> 3% per year or AP refractory to OMT, evidence of physical or pharmacological stress ischemia is required, preferably stress echocardiography to determine the size of ischemia on the stress echo test and anatomical assessment to determine coronary artery disease. to indicate revascularization leading to clinical benefit.

REFERENCES:

1. Juhani Knuuti (Chairperson), William Wijns (Chairperson), Antti Saraste, Davide Capodanno, Emanuele Barbato, Christian Funck-Brentano, Eva Prescott, Robert F. Storey, Christi Deaton, Thomas Cuisset et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal 2019:00, 1-71. ESC guidelines doi:10.1093/eurheartj/ehz425
2. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of ESC Guidelines. the European Society of Cardiology (ESC). Eur Heart J 2018; 39:119-177.
3. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37:267-315.
4. Gilles Montalescot, Udo Sechtem, Stephan Achenbach, Felicita Andreotti, Chris Arden, Andrzej Budaj et al. 2013 ESC guidelines on the management of stable coronary artery disease. European Heart Journal 2013; 34:2949-3003.
5. Bastać D, Milošević A, Radulović N, et al. Incidenca i karakteristike akutnog infarka miokarda u Zdravstvenom centru Zaječar u periodu 1980-2000. ČASOPIS URGENTNE MEDICINE 2002; Suppl 1:4-5.
6. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37:2315-2381.
7. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, Kaski JC, Bairey Merz CN; Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for microvascular angina. Int J Cardiol 2018; 250:1620.
8. Mygind ND, Michelsen MM, Pena A, Frestad D, Dose N, Aziz A, et al. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study. J Am Heart Assoc 2016; 5:e003-064.
9. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J 2014; 35:1101-1111.
10. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, Shimokawa H, Bairey Merz CN. Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2017; 38:2565-2568.
11. Ong P, Athanasiadis A, Perne A, Mahrholdt H, Schaufele T, Hill S, Sechtem U. Coronary vasomotor abnormalities in patients with stable angina after successful stent implantation but without in-stent restenosis. Clin Res Cardiol 2014; 103:11-19.
12. Tsuburaya R, Takahashi J, Nakamura A, Nozaki E, Sugi M, Yamamoto Y, et al. NOVEL Investigators. Beneficial effects of longacting nifedipine on coronary vasomotion abnormalities after drug-eluting stent implantation: the NOVEL study. Eur Heart J 2016; 37:2713-2721.
13. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J 2014; 78:2779-2801.
14. A De Vita A, Milo M, Sestito A, Lamendola P, Lanza GA, Crea F. Association of coronary microvascular dysfunction with restenosis of left anterior descending coronary artery disease treated by percutaneous intervention. Int J Cardiol. 2016 Jun 14; 219:322-325.
15. Reeh J, Therming CB, Heitmann M, Hojberg S, Sorum C, Bech J, Husum D, Dominguez H, Sehestedt T, Hermann T, Hansen KW, Simonsen L, Galatius S, Prescott E. Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. Eur Heart J 2018; 40:1426-1435.
16. Maron DJ, Boden WE, O'Rourke RA, Hartigan PM, Calfas KJ, Mancini GB, et al. COURAGE Trial Research Group. Intensive multifactorial intervention for stable coronary artery disease: optimal medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial. J Am Coll Cardiol 2010; 55:1348-1358.
17. Rotenstein LS, Huckman RS, Wagle NW. Making patients and doctors happier -the potential of patient-reported outcomes. N Engl J Med 2017; 377:1309-1312.
18. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation 2010; 121:750-758.
19. Booth JN III, Levitan EB, Brown TM, Farkouh ME, Safford MM, Muntner P. Effect of sustaining lifestyle modifications (nonsmoking, weight reduction, physical activity, and mediterranean diet) after healing of myocardial infarction, percutaneous intervention, or coronary bypass (from the REasons for Geographic and Racial Differences in Stroke Study). Am J Cardiol 2014; 113:1933-1940.
20. Giannuzzi P, Temporelli PL, Marchioli R, Maggioni AP, Balestroni G, Ceci V et al. GOSPEL Investigators. Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network. Arch Intern Med 2008; 168:2194-2204.
21. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, Aldred H, Ophaug K, Ades PA. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J 2008; 156:292-300.
22. Bastać D. Novi aspekti dijagnostičke i prognostičke procene stabilne koronarne bolesti –revidirani dijagnostički i prognostički algoritmi u 3 koraka. Zbornik abstrakta simpozijuma: STABILNA KORONARNA BOLEST-Šta novo donosi evropski vodič 2013, Zaječar, 2014.god, strana 6-16.
23. Williams RP, Manou-Stathopoulou V, Redwood SR, Marber MS. 'Warm-up Angina': harnessing the benefits of exercise and myocardial ischaemia. Heart 2014; 100:106-114.
24. Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. Circulation 2003; 108:1263-1277.
25. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997; 95:2037-2043.
26. Stone PH, Chaitman BR, Forman S, Andrews TC, Bittner V, Bourassa MG. Prognostic significance of myocardial ischemia detected by ambulatory electrocardiography, exercise treadmill testing, and electrocardiogram at rest to predict cardiac events by one year (the Asymptomatic Cardiac Ischemia Pilot [ACIP]study). Am J Cardiol 1997; 80:1395-1401.
27. Dušan Bastać. Uticaj veličine QRS skora na težinu ventrikularnih aritmija u akutnoj fazi infarkta miokarda. Timocki Med. Glasnik 1989; 14:229-233.
28. Androulakis A, Aznaouridis KA, Aggeli CJ, Roussakis GN, Michaelides AP, Kartalis AN. Transient ST-segment depression during paroxysms of atrial fibrillation in otherwise normal individuals: relation with underlying coronary artery disease. J Am Coll Cardiol 2007; 50:1909-1911.
29. Pradhan R, Chaudhary A, Donato AA. Predictive accuracy of ST depression during rapid atrial fibrillation on the presence of obstructive coronary artery disease. Am J Emerg Med 2012; 30:1042-1047.

30. Raščanin Anastasija, Aranđelović Ivana, Bastać Mila, Bastać Dušan. Uticaj metaboličkog sindroma na strukturne anomalije, sistolnu i dijastolnu funkciju leve komore određivanu ehokardiografijom u bolesnika sa atrijalnom fibrilacijom. Timočki medicinski glasnik 2017; 42(3):132-138.
31. Greenwood JP, Ripley DP, Berry C, McCann GP, Plein S, Bucciarelli-Ducci et al. CE-MARC 2 Investigators. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. JAMA 2016; 316:1051-1060.
32. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979; 300:1350-1358.
33. Foldyna B, Udelson JE, Karady J, Banerji D, Lu MT, Mayrhofer T, et al. Pretest probability for patients with suspected obstructive coronary artery disease: re-evaluating Diamond-Forrester for the contemporary era and clinical implications: insights from the PROMISE trial. Eur Heart J Cardiovasc Imaging 2018; 20:574 581.
34. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 2011; 32:1316-1330.
35. Daly C, Norrie J, Murdoch DL, Ford I, Dargie HJ, Fox K; TIBET (Total Ischaemic Burden European Trial) study group. The value of routine non-invasive tests to predict clinical outcome in stable angina. Eur Heart J 2003; 24:532-540.
36. Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT, Coles A, Jang J, Krishnam M, Douglas PS, Hoffmann U. PROMISE Investigators. Prognostic value of coronary artery calcium in the PROMISE study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017; 136:1993-2005.
37. Villines TC, Hulten EA, Shaw LJ, Goyal M, Dunning A, Achenbach S, et al. CONFIRM Registry Investigators. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter registry. J Am Coll Cardiol. 2011; 58:2533-2540.
38. Juarez-Orozco LE, Saraste A, Capodanno D, Prescott E, Ballo H, Bax JJ, Wijns W, Knuuti J. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. Eur Heart J Cardiovasc Imaging 2019; doi: 10.1093/ehjci/jez054.
39. Versteylen MO, Joosen IA, Shaw LJ, Narula J, Hofstra L. Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events. J Nucl Cardiol 2011; 18:904-911.
40. Fordyce CB, Douglas PS, Roberts RS, Hoffmann U, Al-Khalidi HR, Patel MR, Granger CB, Kostis J, Mark DB, Lee KL, Udelson JE; Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Investigators. Identification of patients with stable chest pain deriving minimal value from noninvasive testing: the PROMISE minimal-risk tool, a secondary analysis of a randomized clinical trial. JAMA Cardiol 2017; 2:400 408.
41. Jensen JM, Voss M, Hansen VB, Andersen LK, Johansen PB, Munkholm H, Norgaard BL. Risk stratification of patients suspected of coronary artery disease: comparison of five different models. Atherosclerosis 2012; 220:557-562.
42. Siontis GC, Mavridis D, Greenwood JP, Coles B, Nikolakopoulou A, Juni P, Salanti G, Windecker S. Outcomes of non-invasive diagnostic modalities for the detection of coronary artery disease: network meta-analysis of diagnostic randomized controlled trials. BMJ 2018; 360: k504.
43. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF. FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012; 367:991-1001.
44. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009; 360:213-224.
45. Knuuti J, Ballo H, Juarez-Orozco LE, Saraste A, Kolh P, Rutjes AWS, Juni P. Windecker S, Bax JJ, Wijns W. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. Eur Heart J 2018; 39:3322-3330.
46. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010; 55:2816-2821.
47. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, Huang M, Pencina M, Mark DB, Heitner JF, Fordyce CB, Pellikka PA, Tardif JC, Budoff M, Nahhas G, Chow B, Kosinski AS, Lee KL, Douglas PS; PROMISE Investigators. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). Circulation 2017;135: 2320-2332.
48. Dusan Bastac, Zoran Joksimović et al. Dipirydamole stress echocardiography in the evaluation of myocardial ischemia in obese subjects with hypertension. European Journal of Echocardiography 2002; 3 (Suppl I).
49. Mitov V, Aleksic Z, Paunkovic N, Bastać D. Myocardial perfusion scintigraphy in selection of patients with positive and inconclusive finding of ECG exercise stress tests. European Heart Journal 2007; 28(Supp l):625.
50. Lubbers M, Dedic A, Coenen A, Galema T, Akkerhuis J, Bruning T, Krenning B, Musters P, Ouhlous M, Liem A, Niezen A, Hunink M, de Feijter P, Nieman K. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre randomized CRESCENT trial. Eur Heart J 2016; 37:1232-1243.
51. Gueret P, Deux JF, Bonello L, Sarran A, Tron C, Christiaens L. Diagnostic performance of computed tomography coronary angiography (from the prospective national multicenter multivendor EVASCAN study). Am J Cardiol 2013; 111:471-478.
52. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019; 40:87-165.
53. Escaned J, Echavarria-Pinto M, Garcia-Garcia HM, van de Hoef TP, de Vries T, Kaul P, ADVISE II Study Group. Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISEII international, multicenter study (ADenosine Vasodilator Independent Stenosis Evaluation II). JACC Cardiovasc Interv 2015; 8:824-833.
54. Toth G, Hamilos M, Pyxaras S, Mangiacapra F, Nelis O, De Vroey F, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. Eur Heart J 2014; 35:2831-2838.
55. Jeremias A, Maehara A, Genereux P, Asrress KN, Berry C, De Bruyne B, et al. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. J Am Coll Cardiol 2014; 63:1253-1261.
56. Van Belle E, Rioufol G, Pouillot C, Cuisset T, Bougrini K, Teiger E, et al; Investigators of the Registre Franc¸ais de la

FFRR3F. Outcome impact of coronary revascularization strategy reclassification with fractional flow reserve at time of diagnostic angiography: insights from a large French multicenter fractional flow reserve registry. Circulation 2014; 129:173-185.
57. Toth G, Hamilos M, Pyxaras S, Mangiacapra F, Nelis O, De Vroey F, et al. Evolving concepts of angiogram: fractional flow reserve discordances in 4000 coronary stenoses. Eur Heart J 2014; 35:2831-2838.
58. Julien Adjedj, Bernard De Bruyne, Vincent Floré, Giuseppe Di Gioia, Angela Ferrara, Mariano Pellicano et al. Significance of Intermediate Values of Fractional Flow Reserve in Patients with Coronary Artery Disease. Circulation 2016;133(5):502-8.
59. Collet C, Onuma Y, Andreini D, Sonck J, Pompilio G, Mushtaq S, et al. Coronary computed tomography angiography for heart team decision-making in multivessel coronary artery disease. Eur Heart J 2018; 39:3689-3698.
60. Maron DJ, Boden WE, O'Rourke RA, Hartigan PM, Calfas KJ, Mancini GB, et al. COURAGE Trial Research Group. Intensive multifactorial intervention for stable coronary artery disease: optimal medical therapy in the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial. J Am Coll Cardiol 2010; 55:1348-1358.
61. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. Circulation 2010; 21:750-758.
62. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, Aldred H, Ophaug K, Ades PA. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J 2008; 156:292-300.
63. Prochaska JJ, Benowitz NL. The past, present, and future of nicotine addiction therapy. Annu Rev Med 2016; 67:467-486.
64. Barth J, Jacob T, Daha I, Critchley JA. Psychosocial interventions for smoking cessation in patients with coronary heart disease. Cochrane Database Syst Rev 2015; 7:CD006886.
65. Freeman AM, Morris PB, Barnard N, Esselstyn CB, Ros E, Agatston A, et al. Trending cardiovascular nutrition controversies. J Am Coll Cardiol 2017; 69:1172-1187.
66. Khan SS, Ning H, Wilkins JT, Allen N, Carnethon M, Berry JD, Sweis RN, Lloyd-Jones DM. Association of body mass index with lifetime risk of cardiovascular disease and compression of morbidity. JAMA Cardiol 2018; 3:280-287.
67. Pack QR, Rodriguez-Escudero JP, Thomas RJ, Ades PA, West CP, Somers VK, Lopez-Jimenez F. The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis. Mayo Clin Proc 2014; 89:1368-1377.
68. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. Physiology (Bethesda) 2013; 28:330-358.
69. Bruning RS, Sturek M. Benefits of exercise training on coronary blood flow in coronary artery disease patients. Prog Cardiovasc Dis 2015; 57:443-453.
70. Cheng W, Zhang Z, Cheng W, Yang C, Diao L, Liu W. Associations of leisuretime physical activity with cardiovascular mortality: a systematic review and meta-analysis of 44 prospective cohort studies. Eur J Prev Cardiol 2018; 25:1864-1872.
71. Keteyian SJ, Brawner CA, Savage PD, Ehrman JK, Schairer J, Divine G, Aldred H, Ophaug K, Ades PA. Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J 2008; 156:292-300.
72. Lahtinen M, Toukola T, Junttila MJ, Piira OP, Lepojarvi S, Kaariainen M, Huikuri HV, Tulppo MP, Kiviniemi AM. Effect of changes in physical activity on risk for cardiac death in patients with coronary artery disease. Am J Cardiol 2018; 121:143-148.
73. Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, et al; STABILITY Investigators. Physical activity and mortality in patients with stable coronary heart disease. J Am Coll Cardiol 2017; 70:1689-1700.
74. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database Syst Rev 2016;1:CD001800.
75. Rauch B, Davos CH, Doherty P, Saure D, Metzendorf MI, Salzwedel A, Voller H, Jensen K, Schmid JP. The prognostic effect of cardiac rehabilitation in the era of acute revascularization and statin therapy: A systematic review and meta-analysis of randomized and non-randomized studies - The Cardiac Rehabilitation Outcome Study (CROS). Eur J Prev Cardiol 2016; 23:1914-1939.
76. de Vries H, Kemps HM, van Engen-Verheul MM, Kraaijenhagen RA, Peek N. Cardiac rehabilitation and survival in a large representative community cohort of Dutch patients. Eur Heart J 2015; 36:1519 -1528.
77. Benzer W, Rauch B, Schmid JP, Zwisler AD, Dendale P, Davos CH, Kouidi E, Simon A, Abreu A, Pogosova N, Gaita D, Miletic B, Bonner G, Ouarrak T, McGee H; EuroCaReD study group. Exercise-based cardiac rehabilitation in twelve European countries results of the European cardiac rehabilitation registry. Int J Cardiol 2017; 228:58-67.
78. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. Biol Psychiatry 2003; 54:227-240.
79. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. Cochrane Database Syst Rev 2011; 9:CD008012.
80. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, Bennett P, Liu Z, West R, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease: Cochrane systematic review and meta-analysis. Eur J Prev Cardiol 2018; 25:247-259.
81. Rutledge T, Redwine LS, Linke SE, Mills PJ. A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease. Psychosom Med 2013; 75:335-349.
82. Brook RD, Newby DE, Rajagopalan S. Air pollution and cardiometabolic disease:an update and call for clinical trials. Am J Hypertens 2017; 31:110.
83. Munzel T, Schmidt FP, Steven S, Herzog J, Daiber A, Sorensen M. Environmental noise and the cardiovascular system. J Am Coll Cardiol 2018; 71:688-697.
84. Steinke EE, Jaarsma T, Barnason SA, Byrne M, Doherty S, Dougherty CM, et al. Sexual counselling for individuals with cardiovascular disease and their partners: a consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP). Eur Heart J 2013;34:3217-3235.
85. Stein R, Sardinha A, Araujo CG. Sexual activity and heart patients: a contemporary perspective. Can J Cardiol 2016; 32:410-420.
86. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, Stricker B, Mendis S, Hofman A, Mant J, Franco OH. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J 2013; 34:2940-2948.
87. Gnjidic D, Bennett A, Le Couteur DG, Blyth FM, Cumming RG, Waite L, Handelsman D, Naganathan V, Matthews S, Hilmer SN. Ischemic heart disease, prescription of optimal medical therapy and geriatric syndromes in communitydwelling older men: a population-based study. Int J Cardiol 2015; 192:49-55.
88. Mohammed S, Arabi A, El-Menyar A, Abdulkarim S, AlJundi A, Alqahtani A, Arafa S, Al Suwaidi J. Impact of polypharmacy on adherence to evidence-based medication in patients who underwent percutaneous coronary intervention. Curr Vasc Pharmacol 2016; 14:388-393.
89. Wimmer BC, Cross AJ, Jokanovic N, Wiese MD, George J, Johnell K, Diug B, Bell JS. Clinical outcomes associated with medication regimen complexity in older people: a systematic review. J Am Geriatr Soc 2017; 65:747-753.

90. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2014;11:CD000011.
91. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P, De Geest S, Dobbels F, Lewek P, Urquhart J, Vrijens B; ABC project team. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. Drugs 2013; 73:545-562.
92. Husted SE, Ohman EM. Pharmacological and emerging therapies in the treatment of chronic angina. Lancet 2015; 386:691-701.
93. National Institute for Health and Care Excellence (NICE). Stable angina: management. Clinical guideline [CG126]. https://www.nice.org.uk/guidance/cg126 (28 March 2019).
94. Klein WW, Jackson G, Tavazzi L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta-analysis. Coron Artery Dis 2002; 13:427-436.
95. Rousan TA, Mathew ST, Thadani U. Drug therapy for stable angina pectoris. Drugs 2017; 77:265-284.
96. Pehrsson SK, Ringqvist I, Ekdahl S, Karlson BW, Ulvenstam G, Persson S. Monotherapy with amlodipine or atenolol versus their combination in stable angina pectoris. Clin Cardiol 2000; 23:763-770.
97. Emanuelsson H, Egstrup K, Nikus K, Ellstrom J, Glud T, Pater C, Scheibel M, Tisell A, Totterman KJ, Forsby M. Antianginal efficacy of the combination of felodipine-metoprolol 10/100 mg compared with each drug alone in patients with stable effort-induced angina pectoris: a multicenter parallel group study. The TRAFFIC Study Group. Am Heart J 1999; 137:854-862.
98. Belsey J, Savelieva I, Mugelli A, Camm AJ. Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: a systematic review and meta-analysis. Eur J Prev Cardiol 2015; 22:837-848.
99. Wight LJ, VandenBurg MJ, Potter CE, Freeth CJ. A large scale comparative study in general practice with nitroglycerin spray and tablet formulations in elderly patients with angina pectoris. Eur J Clin Pharmacol 1992; 42:341-342.
100. Diaz A, Bourassa MG, Guertin MC, Tardif JC. Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 2005; 26:967-974.
101. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med 2005;3 52:1951-1958.
102. Bangalore S, Bhatt DL, Steg PG, Weber MA, Boden WE, Hamm CW, Montalescot G, Hsu A, Fox KA, Lincoff AM. beta-blockers and cardiovascular events in patients with and without myocardial infarction: post hoc analysis from the CHARISMA trial. Circ Cardiovasc Qual Outcomes 2014; 7:872-881.
103. Andersson C, Shilane D, Go AS, Chang TI, Kazi D, Solomon MD, Boothroyd DB, Hlatky MA. b-blocker therapy and cardiac events among patients with newly diagnosed coronary heart disease. J Am Coll Cardiol 2014; 64:247-252.
104. Hwang D, Lee JM, Kim HK, Choi KH, Rhee TM, Park J, Park TK, Yang JH, Song YB, Choi JH, Hahn JY, Choi SH, Koo BK, Kim YJ, Chae SC, Cho MC, Kim CJ, Gwon HC, Jeong MH, Kim HS; KAMIR Investigators. Prognostic impact of betablocker dose after acute myocardial infarction. Circ J 2019; 83:410-417.
105. Dahl Aarvik M, Sandven I, Dondo TB, Gale CP, Ruddox V, Munkhaugen J, Atar D, Otterstad JE. Effect of oral beta-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother 2019; 5:1220.
106. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, Ohman EM, Cannon CP, Smith SC, Zeymer U, Hoffman EB, Messerli FH, Bhatt DL; REACH Registry Investigators. b-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012; 308:1340-1349.
107. Padala SK, Lavelle MP, Sidhu MS, Cabral KP, Morrone D, Boden WE, Toth PP. Antianginal therapy for stable ischemic heart disease: a contemporary review. J Cardiovasc Pharmacol Ther 2017; 22:499-510.
108. Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, et al. Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomized controlled trial. Lancet 2004; 364:849-857.
109. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ; CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA 2004; 292:2217-2225.
110. Heidenreich PA, McDonald KM, Hastie T, Fadel B, Hagan V, Lee BK, Hlatky MA. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. JAMA 1999; 281:1927-1936.
111. K Mohee, SB Wheatcroft. Optimal Medical Therapy and Percutaneous Coronary Intervention for Stable Angina: Why Patients Should 'Be Taking' and 'Keep Taking' the Tablets. J Clin Pharm Ther. 2014; 39(4):331-3.
112. Bastać D. Farmakološka terapija stabilne koronarne bolesti-u fokusu podgrupe s terapijskim izazovom. Zbornik abstrakta STABILNA KORONARNA BOLEST Šta novo donosi evropski vodič 2013, Zaječar, 2014.god, strana 22-24.
113. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: The Impact of Nicorandil in Angina (IONA) randomised trial. Lancet 2002; 359:1269-1275.
114. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, Murphy SA, Budaj A, Braunwald E et al. MERLIN-TIMI 36 Trial Investigators. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. JAMA 2007; 297:1775-1783.
115. Wilson SR, Scirica BM, Braunwald E, Murphy SA, Karwatowska-Prokopczuk E, et al. Efficacy of ranolazine in patients with chronic angina observations from the randomized, double-blind, placebo-controlled MERLIN-TIMI (Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-Segment Elevation Acute Coronary Syndromes) 36 Trial. J Am Coll Cardiol 2009; 53:1510-1516.
116. McCarthy CP, Mullins KV, Kerins DM. The role of trimetazidine in cardiovascular disease: beyond an anti-anginal agent. Eur Heart J Cardiovasc Pharmacother 2016; 2:266 -272.
117. European Medicines Agency. Questions and answers on the review of medicines containing trimetazidine (20 mg tablets, 35 mg modified release tablet and 20 mg/ml oral solution). https://www.ema.europa.eu/en/documents/referral/questions-answers-review-medicines-containing-trimetazidine-20-mg-tablets- 35-mg-modified-release/ml-oral-solution_en.pdf (28 March 2019).
118. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo-controlled crossover trial. Lancet 2010; 375:2161-2167.
119. Singh JA, Yu S. Allopurinol reduces the risk of myocardial infarction (MI) in the elderly: a study of Medicare claims. Arthritis Res Ther 2016; 18:209.

120. Aviv A. Shaul and David Hasdai: Chronic ischaemic heart disease: Pharmacological therapy. IN A. John Camm, Thomas F. Lusher, Gerald Maurer and Patrick W. Serreys, editors. The ESC Textbook of Cardiovascular Medicine, 3rd ed. Oxford Univesity press; 2019. P.1387-1393.
121. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018; 39:213-260.
122. Bhatt DL, Bonaca MP, Bansilal S, Angiolillo DJ, Cohen M, Storey RF, Im K, Murphy SA, Held P, Braunwald E, Sabatine MS, Steg PG. Reduction in ischemic events with ticagrelor in diabetic patients with prior myocardial infarction in PEGASUS-TIMI 54. J Am Coll Cardiol 2016; 67:2732-2740.
123. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, et al. ATLAS ACS 2TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012; 366:919.
124. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Yusuf S et al. COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377:1319-1330.
125. Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, et al; ORBITA investigators. Percutaneous coronary intervention in stable angina (ORBITA): a doubleblind, randomised controlled trial. Lancet 2018; 391:3140.
126. Trikalinos TA, Alsheikh-Ali AA, Tatsioni A, Nallamothu BK, Kent DM. Percutaneous coronary interventions for non-acute coronary artery disease: a quantitative 20-year synopsis and a network meta-analysis. Lancet 2009; 373:911-918.
127. Stergiopoulos K, Brown DL. Initial coronary stent implantation with medical therapy vs medical therapy alone for stable coronary artery disease: meta-analysis of randomized controlled trials. Arch Intern Med 2012; 172:312-319.
128. Bangalore S, Pursnani S, Kumar S, Bagos PG. Percutaneous coronary intervention versus optimal medical therapy for prevention of spontaneous myocardial infarction in subjects with stable ischemic heart disease. Circulation 2013; 127:769-781.
129. Windecker S, Stortecky S, Stefanini GG, da Costa BR, Rutjes AW, Di Nisio M, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis. BMJ 2014; 348: g3859.
130. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al. FAME 2 Investigators. Five-year outcomes with PCI guided by fractional flow reserve. N Engl J Med 2018; 379:250-259.
131. Franz-Josef Neumann, Miguel Sousa-Uva, Anders Ahlsson, Fernando Alfonso, Adrian P. Banning (UK), Umberto Benedetto et al. 2018 ESC/EACTS Guidelines on myocardial Revascularization. The Task Force on myocardial revascularization of the EuropeanSociety of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal (2019) 40, 87–165. doi:10.1093/eurheartj/ehy394
132. Mohee K, Wheatcroft S B. Optimal Medical Therapy and Percutaneous Coronary Intervention for Stable Angina: Why Patients Should 'Be Taking' and 'Keep Taking' the Tablets. J Clin Pharm Ther. 2014;39(4):331-333.
133. William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., ET al. for the COURAGE Trial Research Group. Optimal Medical Therapy with or without PCI for Stable Coronary Disease N Engl J Med 2007; 356:1503-1516. DOI: 10.1056/NEJMoa070829.
134. Bradley SM, Chan PS, Hartigan PM, Nallamothu BK, Weintraub WS, Sedlis SP, Dada M, Maron DJ, Kostuk WJ, Berman DS, Teo KK, Mancini GB, Boden WE, Spertus JA. Validation of the appropriate use criteria for percutaneous coronary intervention in patients with stable coronary artery disease (from the COURAGE trial). Am J Cardiol. 2015 ;116(2):167-73. doi: 10.1016/j.amjcard.2015.03.057. Epub 2015 Apr 17.
135. David Morow, James A. De Lemos, William E. Boden: Stable ischemic heart disease: Future perspective. IN Douglas P. Zipes, editor in chef. Braunwald's Heart Disease.11th ed. Elsevier; 2019. p.1254.
136. Mancini GBJ, Boden WE, Brooks MM, Vlachos H, Chaitman BR, Frye R, Bittner V, Hartigan PM, Dagenais GR. Impact of treatment strategies on outcomes in patients with stable coronary artery disease and type 2 diabetes mellitus according to presenting angina severity: A pooled analysis of three federally-funded randomized trials. Atherosclerosis. 2018; 277:186-194. doi: 10.1016/j.atherosclerosis.2018.04.005. Epub 2018 Jun 1.
137. David J. Maron, Judith S. Hochman, Harmony R. Reynolds, Sripal Bangalore, Sean M. O'Brien, William E. Boden, M.D et al., for the ISCHEMIA Research GroupApril 9, 2020. Initial Invasive or Conservative Strategy for Stable Coronary Disease. N Engl J Med 2020; 382:1395-1407. DOI: 10.1056/NEJMoa191592
138. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches - American College of Cardiology 4/21/2020. https://www.acc.org/latest-in-cardiology/clinical-trials/2019/11/15/17/27/ischemia 1/6
139. David J. Maron, Judith S. Hochman, Harmony R. Reynolds, Sripal Bangalore. Initial Invasive or Conservative Strategy for Stable Coronary Disease. N Engl J Med 2020; 382:1395-1407. https://www.nejm.org/doi/full/10.1056/NEJMoa1915922 1/7
140. Stephan D. Fihn et al. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons am vodič2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease. JACC 2012; 60:64-144.
141. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37:2129-2200.
142. Van Holten TC, Waanders LF, de Groot PG, Vissers J, Hoefer IE, Pasterkamp G, Prins MW, Roest M. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. PLoS One 2013; 8: e62080.
143. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-releasemetoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000; 283:1295-1302.
144. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344:1651-1658.
145. Dusan Bastać, Vladimir Mitov et al : Comparasion of the efect of Carvediol versus Metoprolol on Sistolic and Diastolic Left Ventricular Function in patients with Ischaemic Dilated cardiomyopathy. Journal of American College of Cardiology 1998; 31:78 C (abstract).
146. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival

(COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002; 106:2194-2199.
147. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353:913.
148. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA; SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patientsnwith heart failure (SENIORS). Eur Heart J 2005; 26:215-225.
149. Bastać Dušan, Jelenković Bratimirka, Joksimović Zoran, Aleksić Aleksandar. Šta je novo u dijagnostici i lečenju akutne srčane insuficijencije? Timočki medicinski glasnik. 2015;40 (4):281-293.
150. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med 1996; 335:1107-1114.
151. Wijeysundera HC, Hansen MS, Stanton E, Cropp AS, Hall C, Dhalla NS, Ghali J, Rouleau JL; PRAISE II Investigators. Neurohormones and oxidative stress in nonischemic cardiomyopathy: relationship to survival and the effect of treatment with amlodipine. Am Heart J 2003; 146:291-297.
152. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomized controlled trials. Int J Cardiol 2002; 82:149-158.
153. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-convertingenzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006; 368:581-588.
154. Gage RM, Burns KV, Bank AJ. Echocardiographic and clinical response to cardiac resynchronization therapy in heart failure patients with and without previous right ventricular pacing. Eur J Heart Fail 2014; 16:1199-1205.
155. Lindholm D, Lindback J, Armstrong PW, Budaj A, Cannon CP. Biomarker-based risk model to predict cardiovascular mortality in patients with stable coronary disease. J Am Coll Cardiol 2017; 70:813-826.
156. Eapen DJ, Manocha P, Patel RS, Hammadah M, Veledar E, Wassel C, Nanjundappa RA, Sikora S, Malayter D, Wilson PW, Sperling L, Quyyumi AA, Epstein SE. Aggregate risk score based on markers of inflammation, cell stress, and coagulation is an independent predictor of adverse cardiovascular outcomes. J Am Coll Cardiol 2013; 62:329-337.
157. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA 2005; 293:477-484.
158. Vermeltfoort IA, Raijmakers PG, Odekerken DA, Kuijper AF, Zwijnenburg A, Teule GJ. Association between anxiety disorder and the extent of ischemia observed in cardiac syndrome X. J Nucl Cardiol 2009; 16:405-410.
159. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. J Am Coll Cardiol 2018; 72:2841-2855.
160. Bastac D. et al. Routine assesment of left ventricular diastolic dysfunction in coronary artery disease by Doppler exercise stress testing. European Journal of Echocardiography 2003; 4 (Suppl.1):96.
161. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J 2014; 35:1101-1111.
162. van de Hoef TP, van Lavieren MA, Damman P, Delewi R, Piek MA, Chamuleau SA, Voskuil M, et al. Physiological basis and long-term clinical outcome of discordance between fractional flow reserve and coronary flow velocity reserve in coronary stenoses of intermediate severity. Circ Cardiovasc Interv 2014; 7:301-311.
163. Taqueti VR, Everett BM, Murthy VL, Gaber M, Foster CR, Hainer J, Blankstein R, Dorbala S, Di Carli MF. Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease. Circulation 2015; 131:528-535.
164. Murthy VL, Naya M, Foster CR, Gaber M, Hainer J, Klein J, Dorbala S, Blankstein R, Di Carli MF. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation 2012; 126:1858-1868.
165. Lee JM, Jung JH, Hwang D, Park J, Fan Y, Na SH, Doh JH, Nam CW, Shin ES, Koo BK. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. J Am Coll Cardiol 2016; 67:1158-1169.
166. Lee JM, Choi KH, Hwang D, Park J, Jung JH, Kim HY, Jung HW, Cho YK, Yoon HJ, Song YB, Hahn JY, Doh JH, Nam CW, Shin ES, Hur SH, Koo BK. Prognostic implication of thermodilution coronary flow reserve in patients undergoing fractional flow reserve measurement. JACC Cardiovasc Interv 2018; 11:1423-1433.
167. Radico F, Cicchitti V, Zimarino M, De Caterina R. Angina pectoris and myocardial ischemia in the absence of obstructive coronary artery disease: practical considerations for diagnostic tests. JACC Cardiovasc Interv 2014; 7:453-463.
168. Mejia-Renteria H, van der Hoeven N, van de Hoef TP, Heemelaar J, Ryan N, Lerman A, van Royen N, Escaned J. Targeting the dominant mechanism of coronary microvascular dysfunction with intracoronary physiology tests. Int J Cardiovasc Imaging 2017; 33:1041-1059.
169. Leung M, Juergens CP, Lo ST, Leung DY. Evaluation of coronary microvascular function by left ventricular contractile reserve with low-dose dobutamine echocardiography. EuroIntervention 2014; 9:1202-1209.
170. Sicari R, Rigo F, Cortigiani L, Gherardi S, Galderisi M, Picano E. Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. Am J Cardiol 2009; 103:626-631.
171. Echavarria-Pinto M, Escaned J, Macias E, Medina M, Gonzalo N, Petraco R, Sen S, Jimenez-Quevedo P, et al. Disturbed coronary hemodynamics in vessels with intermediate stenoses evaluated with fractional flow reserve: a combined analysis of epicardial and microcirculatory involvement in ischemic heart disease. Circulation 2013; 128:2557-2566.
172. Nolte F, van de Hoef TP, Meuwissen M, Voskuil M, Chamuleau SA, Henriques JP, Verberne HJ, van Eck-Smit BL, Koch KT, de Winter RJ, Spaan JA, Tijssen JG, Siebes M, Piek JJ. Increased hyperaemic coronary microvascular resistance adds to the presence of myocardial ischaemia. EuroIntervention 2014; 9:1423-1431.
173. Gutierrez E, Flammer AJ, Lerman LO, Elizaga J, Lerman A, Fernandez-Aviles F. Endothelial dysfunction over the course of coronary artery disease. Eur Heart J 2013; 34:3175-3181.
174. Matsuzawa Y, Sugiyama S, Sugamura K, Nozaki T, Ohba K, Konishi M, et al. Digital assessment of endothelial function and ischemic heart disease in women. J Am Coll Cardiol 2010; 55:1688-1696.
175. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, Shimokawa H, Bairey Merz CN. Coronary Vasomotion Disorders International Study Group (COVADIS). International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2017; 38:2565-2568.
176. Ong P, Athanasiadis A, Perne A, Mahrholdt H, Schaufele T, Hill S, Sechtem U. Coronary vasomotor abnormalities in patients with stable angina after successful stent implantation but without in-stent restenosis. Clin Res Cardiol 2014; 103:1119.
177. Tsuburaya R, Takahashi J, Nakamura A, Nozaki E, Sugi M, Yamamoto Y, Hiramoto T, Horiguchi S, Inoue K, Goto T,

Kato A, Shinozaki T, Ishida E, Miyata S, Yasuda S, Shimokawa H. NOVEL Investigators. Beneficial effects of longacting nifedipine on coronary vasomotion abnormalities after drug-eluting stent implantation: the NOVEL study. Eur Heart J 2016; 37:2713-2721.

178. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J 2014; 78:2779-2801.
179. Takagi Y, Yasuda S, Takahashi J, Tsunoda R, Ogata Y, Seki A, Sumiyoshi T, Matsui M, Goto T, Tanabe Y, Sueda S, Sato T, Ogawa S, Kubo N, Momomura S, Ogawa H, Shimokawa H; Japanese Coronary Spasm Association. Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications, and prognostic impact: multicentre registry study of the Japanese Coronary Spasm Association. Eur Heart J 2013;34 :258-267.
180. David Morow, James A. De Lemos, William E. Boden. Stable ischemic heart disease: Future perspective. In: Douglas P. Zipes, editor in chef. Braunwald's Heart Disease. 11th ed. Elsevier; 2019. p. 1254.

Vol. 45 (2020) No. 1-2 TIMOK MEDICAL GAZETTE Case report

UDK 616-008.9:577.152.3
COBISS.SR-ID 16549897

MACROAMYLASEMIA AS A CAUSE OF HYPERAMYLASEMIA IN CLINICALLY UNCLEAR CONDITIONS-CASE REPORT

Zoran Joksimović (1) , Dušan Bastać (2) , Snežana Pavlović (3)

(1) INTERNIST PRACTICE "JOKSIMOVIĆ" BOR, (2) INTERNIST'S OFFICE "DR. BASTAĆ" ZAJEČAR; (3) SPECIALIST PRACTICE FOR INTERNAL MEDICINE "DR PAVLOVIĆ CARDIOLOGY" BELGRADE

Abstract: Macroamylasemia is a rare condition characterized by elevated serum amylase levels due to the existence of macromolecules - complex amylase that cannot be secreted normally by the kidneys due to their size. It is a benign condition that is usually free of marked clinical symptoms and signs. The prevalence of macroamylasemia in the population is between 1 and 2%. The main clinical significance of macromylasemia is that it is often a diagnostic problem because it requires differentiation of this condition from other causes of hyperamylasemia. Therefore, it is rational to avoid unnecessary diagnostics and treatment, which burden both the patient and the health system. Macromalasemia as a diagnosis should be considered in any patient with elevated serum amylase activity in whom serum lipase and urine amylase levels are normal. Laboratory confirmation of the diagnosis of amylasemia rests on tests: electrophoresis or polyethylene glycol precipitation test. This paper presents a patient who has been routinely treated clinically due to non-specific gastrointestinal problems. During laboratory treatment, the patient's serum was found to have elevated amylase values. Additional diagnostics did not identify organic pancreatic diseases or other diseases that may be related to hyperamylasemia, and by calculating the ratio of renal amylase clearance to creatinine clearance of less than 1%, we conclude that it is most likely a macroamylasemia. Specific treatment was not required. The patient comes for a check-up once every 6 months.

INTRODUCTION:

Amylase is an amylolytic enzyme that helps digestion in the intestines by hydrolyzing polysaccharides to smaller molecules. In humans, there is α-amylase, which in healthy individuals originates mostly from the pancreas and salivary glands, but in clinically insignificant amounts from other organs (liver, kidneys, fallopian tubes, muscles, etc.). It can be found in two basic forms, the so-called isoenzymes - synthesized in the pancreas (pancreatic or P-isoamylase) and non-pancreatic origin (salivary - salivary or S-isoamylase). It is common to have low levels of amylase in the blood or urine. But if the pancreas or salivary glands are damaged, the level of amylase in the blood or urine increases. Serum amylase is elevated in at least 75% of cases of pancreatitis; Rarely, serum amylase may be normal, even if massive pancreatic necrosis occurs [1]

The detailed pathways of serum amylase metabolism have not yet been fully elucidated. Decreased metabolic clearance - renal failure may be the cause of elevated serum amylase levels. People who have had a nephrectomy or have kidney failure have an average serum amylase level that is 50% higher than healthy individuals. Therefore, it can be assumed that the kidneys play a major role in amylase metabolism. However, the kidney is not the only organ responsible for removing amylase in humans. The extrinsic mechanisms of amylase clearance are not clearly defined. Since high serum amylase levels are also observed in liver necrosis and cirrhosis, the liver is thought to play a role in amylase metabolism [2] Many conditions have been reported to cause hyperemylasemia. Although hyperamylasemia is usually assumed to be a consequence of the release of serum amylase by the diseased organ, the precise relationship between hyperemylasemia and pathological conditions is not entirely clear. Hyperamylasemia is most often the result of: pancreatitis or mumps, decreased metabolic clearance of amylase or amylase released from a damaged organ (outside the pancreas and salivary glands).

Acute or chronic pancreatitis is associated with an increase in type P isoamylase. Other causes of hyperemylasemia associated with pancreatitis are pseudocysts, pancreatic trauma, and choledolithiasis. Pancreatic trauma can be the result of blunt trauma, abdominal or retroperitoneal surgery, or endoscopic retrograde pancreatic canal cannulation (ERCP). In patients with biliary colic-type abdominal pain, a threefold increase in serum amylase levels returns to normal within 48-72 hours. suggests the passage of a stone through the common bile duct [3,4]. Mumps due to infection, trauma or radiation is associated with an increase in type S isoamylase. Salivary gland damage can also occur as a consequence of chronic alcoholism. The level of amylase in saliva is three times higher than normal in 10% of patients treated for chronic alcoholism. It is also discussed that this phenomenon in alcoholics is a consequence of and / or liver damage because liver disease (hepatitis or cirrhosis) also shows elevated levels of isoamylases of type S and P [2].

Intestinal diseases (inflammatory bowel diseases, infarct mesentery, ileus, peritonitis) can lead to increased levels of pancreatic amylase. Ruptured ectopic pregnancy, ovarian cysts, or inflammation of the ovaries and fallopian tubes can result in elevated salivary isoamylase. Ectopic amylase production is possible in malignancies of the lungs, ovaries, pancreas, and colon; pheochromocytoma; team; multiple myeloma, breast cancer. Increases in amylase levels may occur postoperatively, after extracorporeal circulation or non-abdominal surgery (e.g., 30% of patients undergoing cardiac surgery have elevated type C isoamylase). Rare cases of hyperamylasemia have been reported with ciprofloxacin treatment. Other causes of hyperamylasemia include pneumonia, cerebral trauma, burns, abdominal aortic aneurysms, anorexia nervosa, and organophosphate poisoning. (5,6) Elevated pancreatic enzymes can be found in critically injured patients with trauma even if there is no true pancreatitis [1,2].

Macroamylasemia - Macroamylasemia is a rare, benign condition in which the amylase molecule binds to large complex molecules, reducing renal clearance and prolonging its half-life. The prevalence of macroamylasemia in the population is between 1 and 2%. About 2% -5% of patients with hyperamylasemia have macroamylalasemia. Macroamylasamia is characterized by hyperamylasemia or elevated serum amylase levels without elevated urine amylase and other clinical signs or symptoms. In macroamylasmia, amylase is most often bound by immunoglobulin, making it 4 times larger than usual and the kidneys excrete it slowly and with difficulty, resulting in high serum amylase levels but normal urine levels [7-12]. In most cases, macromolecular amylase is a complex of normal amylase and immunoglobulin A or G. Different papers report different statistics on the incidence of macroamylasemia. It is most often present in adults (more often males), although cases have been reported in children and newborns. Elevated serum amylase levels are the main criterion for the diagnosis of pancreatitis. health system. This is important, among other things, because the main limitation of the use of serum amylase measurements in the diagnosis of the degree of pancreatitis is the lack of specificity of this test [1,7,13].

An accepted algorithm for the joint diagnosis of macroamylasemia, in elevated serum amylase without elevated urinary amylase, is subsequent serum lipase testing, which together with high amylase levels usually suggests pancreatitis [14]. If serum lipase is normal, renal function must be examined. because abnormal kidney function will also cause elevated amylase levels. Then when we conclude that renal function is normal, we should calculate the renal amylase clearance in relation to creatinine clearance - ACCR (Amylase-creatinine clearance ratio) according to the formula:

$$\text{ACCR} = \frac{\text{amylase in urine}}{\text{serum amylase}} \times \frac{\text{serum creatinine}}{\text{cereatinin in urine}} \times 100$$

The normal ratio of these clearance is between 3% and 5%, while a result of less than 1% suggests macroamylasemia [13]. The final confirmatory test is electrophoresis or polyethylene glycol precipitation test and chromatography [14]. As these are methods

used in specialized laboratories and are rarely used routinely, most authors agree that the calculation of ACCR ratios can be considered diagnostic, although there are some discrepancies that [7,13,15,16].

CASE REPORT: Patient P.Ž. The 65-year-old comes for a gastroenterological examination on July 10, 2019. due to an occasional feeling of bloating in the abdomen and elevated serum amylase in the laboratory findings. The problems last from October 2018 and occur occasionally, approximately once in 7-10 days, usually after meals and discounts after bowel movements. It denies severe and hereditary diseases in personal and family history. He received symptomatic therapy (spasmolytics) which he used as needed. During the physical examination, an orderly objective finding is ascertained. In the laboratory reports that the patient brings - complete blood count, erythrocyte sedimentation rate, and C-reactive protein level were within the reference values. Tumor marker CA19 / 9 was 31.6U / ml (normally up to 37 U/ml). Serum amylase levels were elevated - 235 IU / L (reference range: up to 100 IU / L). Other results in biochemical parameters, including serum lipase, nitrogen retention, aminotransferases, bilirubin, and serum iron were normal. Ultrasound and computed tomography of the abdomen showed a normal finding. An ultrasound examination of the neck (parotid gland region) is also normal. Laboratory parameters were monitored after 3 months (30.10.2019) including erythrocyte sedimentation rate, CRP, lipase, aminotransferase, bilirubin and serum iron as well as anti-tissue transglutaminase-IgA (anti-tTG-IgA). All findings were within normal limits. Elevated serum amylase remained 197 IU / l. Urine amylase was also at reference values of 32 IU / l. We determined serum creatinine 75 umol / L and urine creatinine 7003 umol to calculate ACCR. The ACCR is 0.174.

Based on the clinical picture of the performed diagnosis and calculated ACCR, we conclude that it is very likely macroamylasemia. Definitive laboratory diagnosis by electrophoresis or polyethylene glycol precipitation test was not available to us and the patient was not motivated for additional diagnostics. (macrogol) as needed. The patient was examined after two months (December 25, 2019). He was without problems, the clinical findings were orderly. Serum amylase levels were 210 IU / L, urine amylase 45 IU / L. Due to the patient's advanced age, lower digestive endoscopy was suggested, which the patient refused. A clinical control with new laboratory findings and an ultrasound examination of the abdomen is scheduled for 6 months. As the patient is older than 50, we anticipate monitoring the patient for another 1-2 years in order to definitely declare hypermilasemia benign.

DISCUSSION:

Amylase is an enzyme responsible for the breakdown of amylase and other starches during digestion. It exists as three subtypes, where α-amylase is found in animals, including humans, and it is the only one of clinical importance [6]. Although hyperamylasemia is particularly associated with pancreatitis, there are other conditions and diseases that can occur with hyperamylasemia, including sialadenitis, lung disease, ovarian cysts, ruptured ectopic pregnancy, abdominal trauma, mesenteric infarction, perforated peptic ulcer, appendicitis. renal failure, mumps, and some malignancies, all of which would require additional testing, unlike macroamylasemia [1,2,6,8,12].

Although macroamylasemia is mostly asymptomatic, diagnosis of this condition often begins with abdominal pain, including determination of serum and urine amylase. However, abdominal pain is not a symptom of macroamylasemia. It is usually just a coincidence, and amylase testing is often required when patients complain. to abdominal pain. According to one hypothesis, which has no confirmation, abdominal pain and macroamylasemia are detected together due to the deposition of macroamylase molecules in the pancreas [13], hematological malignancies [19,20] of systemic lupus erythematosus [21], rheumatoid arthritis [22] or celiac disease [23,24,25]. Several cases of celiac disease with macroamylasemia have been reported in which amylasemia has returned to normal after treatment with [26] Induced macroamylasemia has also been described, as shown by a study in which a group of subjects received infusions with a solution of hydroxyethyl starch (HES), a volemic colloid used in the treatment of hypovolaemia. with HES solution Hyperamylasemia has been shown to be due to

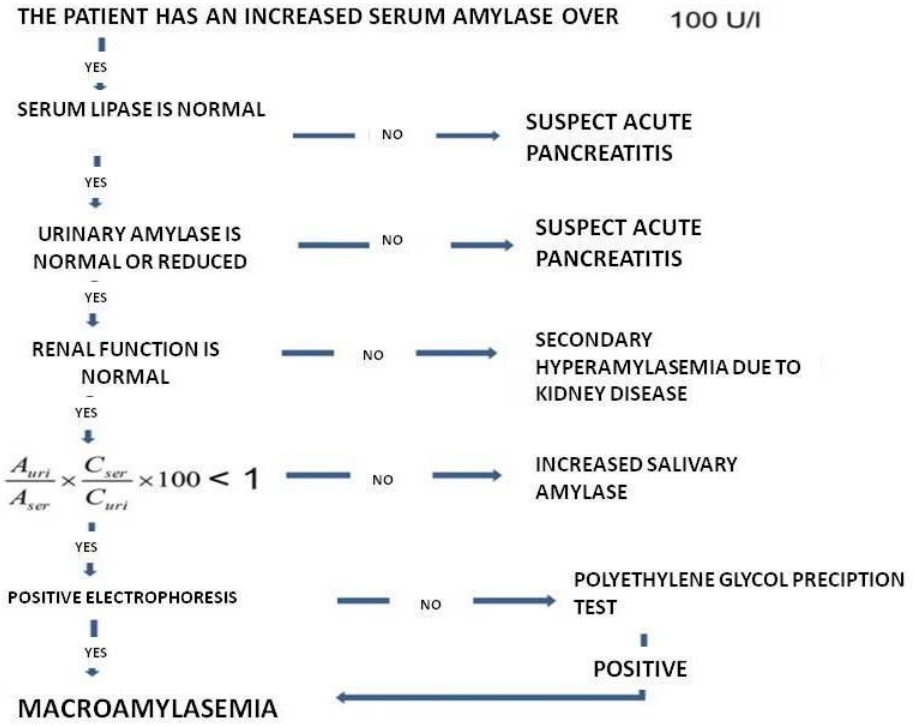
macroamylase amylase complex and HES). As HES molecules disintegrated, hyperamylasemia or macroamylasemia resolved on their own. This study demonstrated that macroamylasemia may also have iatrogenic induction [13].

Other cases of asymptomatic hyperamylasemia have been reported in the literature, including chronic nonpathological hyperamylasemia of pancreatic origin, ethnic hyperemylasemia, and familial hyperemylasemia [27].

The theory of the formation of macro molecules of amylase is based on the "dysregulation" of immune tolerance, which can occur in immune disorders [28]. Cross-reactivity to either gluten or other antigens is thought to lead to the formation of autoantibodies against pancreatic serum amylase at the intestinal level. In this way, antibodies are formed, in most cases immunoglobulin A, rarely immunoglobulin G, which react with amylazoam to form immune complexes [29].

Almost all patients who have hyperemylasemia undergo expensive, long, difficult and often unnecessarily repeated diagnostic procedures. In one study that followed patients for 4 years, 60.7% of patients were diagnosed with chronic pancreatitis, 24.5% with recurrent pancreatitis and 13.7% had no specific diagnosis. After detailed clinical processing (serum Ca19-9 level, ultrasound) abdomen, computed tomography and magnetic resonance imaging, endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography) in 35.2% of these patients it was concluded that it was macroamylasemia [30].

To avoid irrational diagnosis of elevated serum amylase in patients without clinical symptoms and symptoms, without elevated urinary amylase and normal serum lipase levels, renal function should be examined and renal amylase clearance calculated relative to creatinine clearance - ACCR at the beginning of the diagnostic program and assess the need for additional diagnostics. In that sense, the diagnostic algorithm of macroamylasemia, which dates back to 1989, is very practical. proposed by David LeVine and David Parrish [7].



Conclusion: In our patient, based on the clinical picture, performed diagnostics and calculated ACCR, we conclude that it is most likely macroamylasemia. These simple and inexpensive laboratory tests and calculations confirmed the diagnosis despite the lack of a

confirmatory laboratory test (Definitive diagnosis by electrophoresis or polyethylene glycol precipitation test was not available to us and the patient was not motivated for additional diagnosis). With the recommended diet and therapy, the patient was without any problems. Due to age, a colonoscopy was suggested, which the patient refused. A control clinical examination and ultrasound examination of the abdomen are scheduled for 6 months.

The diagnosis of macroamylasemia should be considered in the differential diagnosis of patients who have permanently elevated serum amylase, but do not show any characteristics of pancreatitis or inflammation of the salivary glands. ACCR can be a quick and inexpensive screening test to prevent unnecessary diagnosis and therapy.

REFERENCES:

1. Muniraj T, Dang S, Pitchumoni CS. Pancreatitis or not?--elevated lipase and amylase in ICU patients. J Crit Care. 2015 Dec. 30(6):1370-5.]
2. MacGregor IL, Zakim D. A cause of hyperamylasemia associated with chronic liver disease. Gastroenterology. 1977 Mar. 72(3):519-23.]
3. Malinoski DJ, Hadjizacharia P, Salim A, et al. Elevated serum pancreatic enzyme levels after hemorrhagic shock predict organ failure and death. J Trauma. 2009 Sep. 67(3):445-9].
4. Li GZ, Wang F, Fang J, Zha HL, Zhao Q. Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis: evidence from 1786 cases. Med Sci Monit. 2018 Nov 26. 24:8544-52]
5. Yilmaz UE, Yilmaz N, Titiz I, Basaranoglu M, Tarcin O. The utility of amylase and lipase as reliable predictive markers for functioning renal graft. Ann Transplant. 2012 Jul-Sep. 17(3):77-84.)
6. Gokel Y, Gulalp B, Acikalin A. Parotitis due to organophosphate intoxication. J Toxicol Clin Toxicol. 2002. 40(5):563-5
7. LeVine D, Parrish D. Macroamylasemia: a simple stepwise approach to diagnosis. J Gen JABFP 1989; 2: 279-82.
8. Klonof DC. Macroamylasemia and other immunoglobulin-complexed enzyme disorders. West J Med 1980; 133: 392-407.
9. Mark LK, McCord RG. Pancreatic scanning in diagnosis of macroamylasemia: case report. J Nucl Med 1977; 18: 130-132.
10. Agarwal J, Deepika G. Macroamylasemia: a benign cause for high serum amylase. Indian Pediatr 2015; 52: 533.
11. Sakallıoğlu O. Macroamylasemia; a dilemma in morbidity. Balkan Med J 2015; 32:330.
12. Um JW, Kim KH, Kang MS et al. Macroamylasemia in a patient with acute appendicitis: a case report. J Korean Med Sci 1999; 14: 679-681
13. D. V. Šimac, M. Špelić, B. Devčić, S. Rački Diagnosising macroamylasemia in unexplained hyperamylasemia Acta Med Croatica, 71 (2017) 63-67
14. Leclerc P, Forest JC. Variations in amylase isoenzymes and lipase during acute pancreatitis, and in other disorders causing hyperamylasemia. Clin Chem 1983; 29: 1020-1023)
15. Berk JE. Macroamylasemia: a biochemical aberration in search of a disease. West J Med 1980; 133: 433-435.
16. Kazmierczak SC, Van Lente F, McHugh AM, Katzin WE. Macroamylasemia with a markedly increased amylase clearance ratio in a patient with renal cell carcinoma. Clin Chem 1988; 34: 435-438.)
17. Fujimura Y, Nishishita C, Uchida J, Iida M. Macroamylasemia associated with ulcerative colitis. J Mol Med (Berl) 1995; 73: 95-7
18. Venkataraman D, Howarth L, Beattie RM, Afzal NA. A very high amylase can be benign in paediatric Crohn's disease. BMJ Case Rep 2012; 2012.
19. Sagristani M, Guariglia R, Pocali B, De Rienzo M, Guastafierro S, Romano G, et al. Macroamylasemia in a patient with multiple myeloma. Leuk Lymphoma 2002; 43: 1705-7.
20. Nakayama S, Yokote T, Kobayashi K, Hirata Y, Akioka T, Miyoshi T, et al. Macroamylasemia in a patient with acute myeloid leukemia. Leuk Res 2009; 33: e121-3.
21. Goto H, Wakui H, Komatsuda A, Imai H, Miura AB, Fujita K. Simultaneous macroamylasemia and macrolipasemia in a patient with systemic lupus erythematosus in remission. Intern Med 2000; 39: 1115-8.
22. Cutolo M, Sulli A, Barone A, Picciotto A, Mangraviti S, Seriolo B, et al. Macroamylasemia: a possible cause of unexplained hyperamylasemia in rheumatoid arthritis. Br J Rheumatol 1995; 34: 290-2
23. Rabsztyn A, Green PH, Berti I, Fasano A, Perman JA, Horvath K. Macroamylasemia in patients with celiac disease. Am J Gastroenterol 2001; 96: 1096-100.
24. De Almeida-Menezes M, Ribeiro-Cabral VL, Lorena SS, Nucci A, Andrade-Santana P, Queiroz Silva C. Rare association of celiac disease with myasthenia gravis in a patient with other immune disorders: a case report. Rev Esp Enferm Dig 2016; 108: 586-588.
25. Barera G, Bazzigaluppi E, Viscardi M et al. Macroamylasemia attributable to gluten-related amylase autoantibodies: a case report. Pediatrics 2001; 107: 93.
26. Depsames R, Fireman Z, Niv E, Kopelman Y. Macroamylasemia as the First Manifestation of Celiac Disease Case Rep Gastroenterol 2008; 2: 196-198.
27. Koda YK, Vidolin E. Familial hyperamylasemia. Rev Hosp Clin Fac Med Sao Paulo 2002; 57(2): 77-82.).
28. Türkçapar N, Ozyüncü N, Idilman R, Ensari A, Soylu K, Ozden A. Macroamylasemia in a patient with selective IgA deficiency and antiphospholipid antibodies. Turk J Gastroenterol. 2006;17:140–3.
29. Barera G, Bazzigaluppi E, Viscardi M, Renzetti F, Bianchi C, Chiumello G, et al. Macroamylasemia attributable to gluten related amylase autoantibodies: A case report. Pediatrics. 2001;107:E93.
30. Gallucci F1, Buono R, Ferrara L, Madrid E, Miraglia S, Uomo G.Chronic asymptomatic hyperamylasemia unrelated to pancreatic diseases. Adv Med Sci. 2010;55(2):143-5.

Vol. 45 (2020) No. 1-2 TIMOK MEDICAL GAZETTE Case report

UDK 159.964.2
COBISS.SR-ID 16470537

INCESTUOUS MOTIVES IN BORA STANKOVIC'S OPUS

Mirjana Stojkovic- Ivkovic

ZZZZ RADNIKA "ZELEZNICE SRBIJE ", BEOGRAD

MITKA (to Koštana): And now tell me that: How tuberculousis happened In Kumanovo town when **crazy and furious Stojan startet looking at Stamena**, his uncle's daughter so that he wanted to burn the town or **to take Stamena for a wife**. And churches were closed for three days and the downtown was closed too. Stamena cries and begs:

Stojan, listen, Stojan,
have it ever heard or seen
brother to take his sister for a wife?

And him, abandoned and furious Stojan replays:

Stamena, listen, Stamena,
Stamena, bunch of spring flowers
Stamena, grain of pearl
have you ever heard or seen;
small stones have no number
deep water has no bottom
tall tree has no shade
Beautiful woman, listen, has no relatives

Summary: This work is inspired by the theme of incestuous motives in Bora Stanković's opus. Incest implies a sexual contact between close relatives belonging to the same family (father-daughter,mother-son, brother-sister, father-son, and so on) or actions leading to that act. Incestuous acts or intentions occur stealthily and the causes of incest come from the perpetrator`s personality and the environment in which this personality developed and the conditions in which he or she lives. The method of work - we covered the material from "Koštana ", "Nečista krv (Impure blood)", "Jovča". "Aunt-Zlata'' along with biographical information about the writer himself. At the same time while Freud was explaining the unconscious psyche, incest, the Oedipal complex, dreams, etc., Bora Stanković was looking for answers for the breakup of his family and the reasons for an increasing number of the mentally ill members in the family. While writing, he came to the conclusion that incest, that is impure blood is to blame for it. From incestuous relationships they had children in whose veins impure blood flowed. This impure blood was the reason for various physical and mental diseases. Freud and Bora Stanković were trying to present sexuality and passion as the driving force that has to be controlled that is, one should not allow the violation of the oldest prohibitions (incest). The consequences of incest are devastating both for the person and the family, for posterity and even for all mankind.
Key words: Bora Stanković, incest, sexuality, impure blood.

INTRODUCTION

Every civilization begins and is based on giving up instincts and every culture on internalization of external prohibitions. [1] Perhaps everything started from incest and its prohibition, thus from the secret of sexual instinct, in wider sense Eros. It is highly likely that incestuous gratification of sexual needs of men in the past would lead to a blind alley in man's development. This separated man from other lower beings in nature. The first moral codex of humanity was the prohibition of incest. [2] One question arises: was this

prohibition respected and put into effect everywhere? Even nowadays incest hasn't disappeared, we face this demon, in fact, in a hidden and disguised form (hidden motive).
Freud explains incest trough the Oedipus complex, considering that it comes out as an obstacle to the impulse for reunion with mother. We know that the first choice of a sexual object for a boyis inscestuous, focused on his mother (forbidden object). Oedipus complex depends both on the child and on mother's affecting maturity.[3]

In order to better understand what happens and how it came to the motif of incest in Bora Stanković' opus, we must reconsider the notion-development of personality. There's no sexual instinct among children in the form that emerges in adolescence which manifests with irresistible attraction happening between two people: their aim is sexual act or at least acts leading to it. [4]

The instinct in a man is an extraordinary driving power made freely available to him however, the instict is not and cannot be something separated from the other parts of his personality. The personality determines the fate of the instinct. Animals are periodically sexual but man is always sexual. The sexual life of an animal is regulated by reflexes and instincts and men's sexual life is regulated by his reason, as well. This is the essential difference which enables man to do with his available instinct energy as he pleases.[5]

If parent's tenderness towards a child helped to awake child's sexual instinct before the onset of physical conditions and adolescence to such an extent that mental arousal evidently reached the genital system, then this tenderness can achieve its task, namely to see the child in the time of maturity when choosing his/her sexual object. A child would certainly choose for a sexual object the people closest to him/her that he/she has loved since childhood with his/her subdued libido. Delaying sexual maturity gains time to set boundaries for incest.[6]

PRESENTATION OF WORK

The incestuous motif presented in Bora Stanković's opus is not only characteristic for the environment described by the author but actually presents a universal problem of a man. Some biographers opine that it was the author`s struggle against some dark atavism of his own nature, widely based on his subconsciousness.

Although all the causes and consequences of forbidden love in Bora Stankovic's opus are clear and visible, however it would be one-sidedly interpreted if we didn't try to find out their sources in the author`s life, in his instinctuous nature, in his sanguine temperament and his impure origin. The patriarchal rules imposed from outside couldn`t change human nature however they gave their contribution so that the sin emerged where perhaps it wasn`t expected to: among servants, foreigners and relatives. Hence, we find pathological perversity and appearance of impure, incestuous love among Stankovic's characters. [7]

Sexual deviation in kinship relations is found in many places in Bora`s opus. And as Shakespeare speaks through Hamlet, , so does Bora Stanković through Mitke, . When Mitke asks Koštana to sing the song where Stojan wants to take his own sister Stamena to be his wife, one can wonder: are they Bora`s own wishes? Considering that this is a folk song, it was sung in taverns, oredered to be sung, sometimes, we can make a conclusion that people accepted it in spite of its describing an incestuous love. Bora Stanković started relatively early to sublimate Eros by writing shorts stories and later dramas. [8]

This deviation is also present in the work''Aunt Zlata" who is smelling her son`s head and when that smell reminds her of her late husband, ''it would start with her power trembling and soul dying, being unable to stand it any more and not being allowed to kiss him, she would only press her trembling lips on his head.
« Covert incest" is when a child becomes the object of parental preoccupation, love and passion. Those parents in hronically problematic marriage or partnership, make a surogat partner from their child. The line between healthy and incestuous parental love is crossed when the relation with a child has the purpose of satisfying parental but not child`s needs. As the marriage gets worse, the child becomes the object manipulated by the parent and used for avoiding pain and reality of a problematic marriage.
Father`s erotic affection towards his daughter was described in the novel "Jovča". Jovča is

delaying and stalling Naza`s marriage because his love for her is so big and cannot be hidden.
In boss Jovcha`s personality, we can find the portrait of a patriarchal despot, an inaccessible man, furious, of changeable mood and behaviour. An unusual love for his daughter started in his heart. Mysterious dark love confronts pathology. Boss Jovcha wanted to isolate Naza from society so that he himself could enjoy her beauty and her company.

Jovcha, when he comes home at night, as if rendered unconscious by the force of longing and lust, makes his wife take off her clothes and dance naked.

Naza, having a relationship with a servant, lives out of town with peasants; Jovcha took it as a huge mental stroke which led to his mental derangement. Obsessive thoughts about Naza led to degradation of his personality, to insanity.[9]

Sofka (the character from "Impure blood" grew up in afamily of social outcasts, she didn`t have friends in her social environment so that she wasn`t able to develop the object of her libido. It caused the augmentation of her narcissism and the strenghtening of incestuous relationships. Unrealized love with parents is most fatal for a child as the conditions to live out and overcome such a relationship do not exist. Effendi Mita felt and knew well the magic of money in a poverty-stricken class society and all the misery when you are left without it. He didn't have any other loves nor fear. Sofka, seeing her father poor, stopped idealising and loving him. As soon as her father-ideal was shatterred, she was ready to realize her love. Two times, she was standing at the edge of love but both times love had incestuous character and none was realized. The first love with her father- in -law, the man who had the role of her father. The second was also incestuous, however, that time Sofka had the role of a mother raising the child who was supposed to become – a husband. We can understand Efendi Mita's pathologic selfishness like father's incestuous jelousy of his daughter achieving happiness without him. [11]

By delaying sexual maturity, one can gain some time, apart from other sexual obstacles, to set the boundaries for incest and accept the moral rules which strictly exclude the choice of loved people from one's childhood as sexual objects. Respecting these obstacles is, first of all, a cultural demand of society which must stop wasting interest by a family needed for reaching higher social units. Early maturity or early involvment in sexual relations makes it difficult later to expect the control of sexual instinct using higher mental instances. It strengthens a violent character.

An occurrence of sensual lust and incestuous desires in Stankovic`s characters cannot be explained either with some special southern temperament and mentality or with some oriental influences on the relationship between a man and a woman nor with a sexual deviation. All of this is conditioned by difficult patriarchal morality which took every love for a sin. Reason should be sought in the characters, their development in the family and the environment. Bora`s characters are narcissistic and emotionally unstable and depressive. They protect themselves from emotions by withdrawal, isolation and negation. His marriages are not gardens where they raise children but arenas full of violence and hate.

Analyzing mother characters, the author describes them as possessive, controlling and pushing and fathers as cold, aggressive boems with no feelings. The mothers built strong symbiotic and possessive relations with their sons which, in an environment of changed moral values, with an inadequate father, already prepared a pathological base for incest. Very often in Bora`s works his characters (with covert or realized incest) in order to function (to protect their Ego and reduce aggressiveness), have to suppress their unpleasant memories and conflicting thoughts to protect themselves from worrisome and painful emotions.[10]

DISCUSSION

Sexuality is the basis and moving force of of how we experience the world. It is the place where the conflict between certain individual specificities and collective norms of societybecomes inevitable. Whenever traumas occur which reach into the domains of sexuality, and such is the trauma of incest, covert or realized, then sexuality is a realm between moral norms and desires, behavior and fantasies.

The primordial sin, impossibility of realizing our own intrapsychological conflicts, the feeling of guilt, anxiety and depression initiatethe self destructive impulses and latent suicidality in order to destroy this body which is the carrier of dangerous sexuality. In this way we can explain alcoholism, masochism or sadism and also the latent suicidality in the characters of Sofka, Jovča, Mitke,...

Bora`s works are an effort to penetrate the dark side of unconscious human psyche, actually the state of a primitive man. On the example from the real life there arise elementary emotions of fear, love, hate, pain, feeling of guilt. His strong instinct uncovered the unconscious part of psyche as well as collective unconscious in an indirect way through life stories. Guided by an instinct, he managed to perceive contradictions of life, he guessed diagnosis of mentaly ill people because he knew thehuman psyche very well. The author wanted to find elements of humanity and he found raw nature, complexes, aggressiveness, contradicton and other dark sides of personality. We have eternal fight of good and evil in our personality, especially in the unconscious part of psyche. Our conscious is here not to allow dark demons to prevail.

And finally I`ll cite Milan Bogdanovic"the whole Bora`s opus is a desperate song about unsatisfied passion". That is a song about everlasting interior struggle between a pure love impulse and uncontrolled instincts.

REFERENCES:

1. B.Stankoić Koštana , Izdavačko preduzeće RAD, 1974.: 49,50
2. Jerotić V. Psihoanaliza i kultura, Ars Libri; Zemun ;Neven 2006:11
3. Jerotić V.Psihoanaliza i kultura, Ars Libri ; Zemun; Neven 2006: 13
4. Frojd S. O seksualnoj teoriji, Totem i tabu;Izdavačko preduzeće Matice srpske,Novi Sad,1979: 124
5. Frojd S. O seksualnoj teoriji ,Totem i tabu ,Akademska kniga, Novi Sad ,2009.:11
6. Jerotić V. Psihoanaliza i kultura, Ars Libri; Zemun;Neven 2006: 32
7. Frojd S. O seksualnoj teoriji, Totem I tabu, Akademska knjiga ,Novi Sad 2009: 94
8. Vlatković D. Borisav Stanković (1875-1927), Izdavačko preduzeće RAD , Beograd 1974:10-1
9. Jerotić V. Darovi naših rodjaka:psihološki ogledi iz domaće književnosti, knjiga prva, Prosveta, Beograd,1997.
10. Kostić P. Bora Stanković, Nolit,Beograd 1956:9,13
11. Vladislav Panić, Psihoanaliza "Nečiste krvi", Medicinska knjiga Beograd-Zagreb,1985

Vol. 45 (2020) No. 1-2 TIMOK MEDICAL GAZETTE History of medicine

UDK 61(091)(497.11)
COBISS.SR-ID 16555785

SERBIAN PHYSICIAN AND POLITICIAN FROM ILICEVO - DR. MIHAILO ILIC

Katarina Janićijević (1), Maja Sazdanović (2), Mirjana A. Janićijević Petrović (3), Zoran Kovačević (4)

(1)DEPARTMENT OF SOCIAL MEDICINE, FACULTY OF MEDICAL SCIENCES, UNIVERSITY OF KRAGUJEVAC, KRAGUJEVAC, SERBIA; (2) DEPARTMENT OF HYSTOLOGY, FACULTY OF MEDICAL SCIENCES, UNIVERSITY OF KRAGUJEVAC, KRAGUJEVAC, SERBIA; (3) DEPARTMENT OF OPHTHALMOLOGY, FACULTY OF MEDICAL SCIENCES, UNIVERSITY OF KRAGUJEVAC, KRAGUJEVAC, SERBIA; (4) DEPARTMENT OF INTERNAL MEDICINE, CLINICAL CENTRE OF KRAGUJEVAC, KRAGUJEVAC, SERBIA

Serbian physician and politician, dr. Mihailo Ilic was a historical figure and a famous person with a well deserved memorial at Clinical Center "Kragujevac" in Kragujevac, Figure 1. Famous Serbian doctor was born in 1856 in the village of Meckovac near Kragujevac, which is called Ilicevo today (until 1954, the village was called Meckovac) (the origin of the population of the village of Meckovac as the City of Vranje - Pcinjski district, according to the book of John F. Trifunoski "Vranjska Kotlina", based on data collected from 1951 to 1955, prepared by an associate of Porekla Milodan) [1].

Figure 1. Monument of serbian physician and politician, dr. Mihailo Ilic (1856-1905)
Clinical Center "Kragujevac" of Kragujevac

Best Kragujevac images|Serbian
https://www.pinterest.com/SlavicTravels/kragujevac/

Dr. Mihailo Ilic was born in the Principality of Serbia, which lasted from 1815 to 1882. It was created after the Second Serbian Uprising and existed until 1882 when it was declared the Kingdom of Serbia [1].

Ilic's birthplace, Meckovac, belonged to the citymunicipality of Pivara from 2002 to 2008, and after that time, the municipalities were dissolved. It is located east of the center of Kragujevac. Due to immediate proximity of the city, and a large population growth of the village of Meckovac, there was a clear physiognomic fusion of this settlement with Kragujevac. Ilićevo was initially an independent settlement, and in 1991 it was officially dissolved as an independent settlement and annexed to Kragujevac (as a local community in the city of Kragujevac) [1,2]. The settlement was first mentioned as Mickovaz, during Austrian

occupation of Serbia, in the period 1718-1739. Meckovac had been primarily settled closer to the road and before the first Serbian uprising it was translocated. One historical reason for the translocation were frequent devastations caused by janissaries, as the settlement was located on a busy Kragujevac road. Another, demographic reason was a frequent overflowing of Lepenica, which flooded many buildings and the surrounding area. At the beginning of the nineteenth century in Serbian historical sources, this place was mentioned several times, as Meckovac. This was not the case with many foreign authors. By Riddle, in 1810, it was registered as Mescovacz, on Lapi's map in 1822 as Metskovatz, by Fried's in 1829 as Meskovacz, and by Kipert's as Metschkowats [2]. According to the census in 1903, Meckovac had 356 and seven years later – 48 inhabitants. In 1954, Meckovac changed its name to Ilicevo. It was named after a great Serbian doctor and member of Serbian Social Democratic Party, dr. Mihailo Ilic, who was born in Meckovac in 1856.. In his honour, his birthplace changed its name to Ilićevo, which was part of the city municipality of Pivara in Kragujevac [2]. After the first World War, Ilicevo had 515 inhabitants, which was unusual for a , e place on the banks of the Lepenica to have more inhabitants after the first World War. Ilicevo's territory is located in the central part of Serbia, in the eastern part of Sumadija and covers the catchment area of the middle flow of the Lepenica river. Ilicevo also spreads on both sides of a dry stream called Bara, which flows only after heavy rains, otherwise the riverbed has no water. That is why it is called the "Dry Stream". On the northwestern side of the townarea there flows the Lepenica, and on the west side there passes Kragujevac road and Lapovo - Kragujevac – Kraljevo railway, but there is no a train station there [2]. Just next to Ilicevo is the State Road IB 24, Batocina - Kragujevac, which is being turned (final construction in progress) into Kragujevac - Batocina Highway, Figure 2.

Figure 2. Ilicevo

Photo: The origin of the population of the village of Ilicevo (until 1954 Meckovac), City Municipality of Pivara, the City of Kragujevac - Sumadija District. (according to the books by Todor Radivojevic "Lepenica" and "Settlements in Lepenica". Prepared by an associate of Porekla Milodan).

A PATRIOT'S BIOGRAPHY

Mihailo Ilic was a famous and good physician. By the end of the 19th century, Kragujevac had changed several district physicians: Filip Tajsic (1865), Leonard Leontkievich (1880), Djura Gavric (1885), Ilija Kolovic (1891), amd Stevan Siber (1897). Dr. Mihajlo Ilić came to Kragujevac at the begining of the 20th century. Besides dedicated, professional medical service at the Military Technical Institute, he became the first deputy of the Social Democratic Party in 1905 [3]. In 1903, dr Mihailo Ilic became a member of the Serbian Social Democratic Party (SSDS). The Serbian Social Democratic Party was a political party, which operated in the Kingdom of Serbia and the Kingdom of Serbs, Croats and Slovenes, from 1903 to 1919. In parliamentary elections (September 8, 1903), dr Mihailo Ilic was elected a member of parliament (MP) of Kragujevac district. He was the only SSDS-MP in the National Assembly of the Kingdom of Serbia, and the first Social Democrat-MP in Serbian's history. In the short span of its activities and during the annexation crisis (Balkan wars, and the period before the First World War), this party implemented an anti-war program based on the idea of class revolution and unification of the Balkan peoples into a Confederation. The Social

Democratic Party of Serbia entered European history as the only party to vote against the war budget before the Great War [3]. In 1966, "Dr. Mihailo Ilic" Medical Center was established in Kragujevac. From 1975 Medical Center was reorganized into seven BOALs (Basic Organisations of Associated Labour). In 1986, BOAL "Hospital" was separated as Clinical Hospital Centre of Kragujevac, and the others continued to work as the Medical Center "Dr Mihailo Ilić", which in 1991 grew into the Health Center "Dr Mihailo Ilić". Clinical Hospital Centre of Kragujevac grew into Clinical Center of Kragujevac on 4 November 2005, as tertiary level of healthcare [3,4]. Dr. Mihailo Ilic died on October 22 (October 9, according to the Old Calendar) in Kragujevac, at the age of 48. He died at the time of the Kingdom of Serbia former official name of the state of Serbia), between 1882 and 1918. Serbia was proclaimed Kingdom by the decision of the National Assembly on March 6, 1882, which elevated the Principality of Serbia to the status of Kingdom [4]. Until the Second World War, many private dentists worked in Kragujevac. After the war, along with the development of other outpatient medical services, the dental service developed, too. This service operated within the Health Center and after the creation of the medical center ''Dr. Mihailo Ilic'' it was formed as one of its services. By the decree of the Government of the Republic Serbia in 1998, a decision was passed whereby the dental service was separated from the Health Center of Kragujevac, as an independent institution, with the name: Institute of Dentistry of Kragujevac [5]. Primary health care in Kragujevac was established as a separate functional form in 1966 as the Medical Center of Kragujevac's. Until 1990, this institution functioned within the BOAL ''Dom zdravlja'' (Health Center). Since 1990, the Medical Center was established as "Dr. Mihailo Ilic" Health Center, a part of which was the Health Center in Kragujevac. In its present form the Health Center in Kragujevacwas established in 1998 by a decree of the Government of the Republic Serbia. The history of health culture in Kragujevac and its impact on contemporary healthcare of this area was recognizably identified by the stature of "Dr. Mihailo Ilic", a famous figure of a great Serbian physician and politician [6]. And one of the most famous football clubs on the outskirts of the city of Kragujevac - "Serbia" from Ilicevo, has been celebrating more than eight decades since its founding. Nobody knows exactly when this club was founded, but everyone agrees that it was in the summer of 1935. The club was primarily named "Meckovac", which was renamed to Ilicevo in the memory of dr. Mihailo Ilic, the first Social Democrat-MP in the Balkans. In 1970, the club was named "Serbia" (pretty brave and radical move at that time), but with a curiosity, that it is now the only football club of that name in Serbia (not counting Diaspora and other sports teams) [7], Figure 3.

Figure 3. The stadium of the football club "Serbia" in Ilicevo

Foto - www.alcmedia.biz

In conclusion: Dr. Mihail Ilic's national contribution lies in that many institutions of his time and even today, such as places, institutions, sports clubs, streets in Kragujevac bear his name; and as a token of eternal gratitude, in order not to forget the good deeds of a military doctor, an his anti-war political orientation and the proper policies of the first Social Democrat member of parliament in the Balkans and in Serbian history in general. Dr. Mihail Ilic died as relatively young man, and we cannot rightly judge and analyze other contributions in the field of health culture and healthcare by a famous, Serbian patriot, physician and politician.

REFERENCES:

1. Serbian Biographical Dictionary (Book Four) "Matica Srpska", Novi Sad, 2009.
2. Todor Radivojevic: "Settlements in Lepenica" and "Lepenica"; Wikipedia, Belgrade, 1907.
3. Matovic DZ. 150 years of Kragujevac Hospital. Chronicle of the first permanent hospital in
1. Serbia. Kragujevac: District Branch of the Serbian Medical Association, Kragujevac, 2010.
4. Archive. Kragujevac: Clinical Center "Kragujevac", Kragujevac, 2012.
5. Archive of the Museum of Health Culture. Kragujevac: Clinical Center "Kragujevac", Kragujevac, 2012.
6. Zuzic Z, Nedeljkovic R, et al. History of Kragujevac Health Culture and its Impact on Contemporary Health Care in the Area. During Time 1998; 1-2: 40-49.
7. http://www.kragujevacke.rs/drugstvo ilićevo

INSTRUCTIONS TO ASSOCIATES OR AUTHORS

Timok medical GAZZETTE publishes previously unpublished scientific and professional papers bilingually, in Serbian and English language from all fields of medicine and related branches. Original papers, patient case reports, review articles, medical and health history articles, book and journal reviews, editorial letters and other medical information are received for publication. The authors propose a category of their work and the Editorial Board reserves the right to change the category with the consent of the author.

Manuscripts should be prepared in accordance with the Vancouver Recommendations: UNIFORM REQUIREMENTS FOR MANUSCRIPTS SUBMITTED TO BIOMEDICAL JOURNALS, recommended by ICMJE (International Committee of Medical Journal Editors - Ann Intern Med. 1997; 126: 36-47), or in accordance with the Serbian languageversion JEDNOBRAZNI ZAHTEVI ZA RUKOPISE KOJI SE PODNOSE BIOMEDICINSKIM ČASOPISIMA, Serbian Archives of Medicine, 2002; 130 (7–8): 293. The digital version is freely available on the ICMJE website, www.icmje.org, as well as at www. tmg.org.rs/saradn.htm

When writing atext in English, one should adhere to the American English language standard and use short and clear sentences. Manuscripts received by the editorial staff are not expected to contain results already published by authors in another journal or similar publication. The original manuscript must be accompanied by the certificate of authorship (you can download the form at: www.tmg.org.rs), scanned signatures of all authors of the article.

The editorial board sends all the papers for peer review - usually two reviewers. Proceedings in supplements are not peer reviewed.

In works where the described patient may be identified, the utmost care should be taken to avoid any details that can identify him/her or obtain written consent for publication from the patient himself or his immediate family. When consent exists, it should be stated in the article.

If the paper receives positive anonymous reviews (2 reviewers) it will be accepted for publication. After receiving a positive review, in order for the paper to be published in electronic version on the website www.tmg.org.rs and printed, it is necessary to pay a fee for the cost of editing the article, proofreading and printing costs for the Timok medical journal **only for the first author**, which amounts to four thousand dinars (4000 RSD) paid to the current account.

Current Account: 205-167929-22
Serbian Medical Association-Zajecar Branch;
purpose: material processing for TMG.

TECHNICAL REQUIREMENTS

The manuscripts are to be submitted exclusively in electronic form, bilingually (starting with volume 45), in Serbian (preferably Cyrillic) and in English. Papers submitted only in Serbian or English only will not be considered. Send the manuscripts in electronic form to: tmglasnik@gmail.com

The electronic format of the manuscript should be in Microsoft Office Word (with a .doc or .docx extension) and should include a final version of the manuscript. All text, references, tables and titles of tables and images and legends of images should be in one document. It is best to form the filename by the first author's last name, one keyword and type of work (for example: paunkovic_tiroidea_originalni.doc).

Use the Times New Roman font, 12p size. Write the paragraph so that only the left alignment is straight. Do not divide words into syllables at the end of the line. Insert only one blank space after the punctuation mark. Allow the titles and subheadings to be aligned with the left edge. Use bold, italic, sub, and superscript and underlined letters only where necessary. **Tables, images and charts should be inserted in the text where they should appear in the paper**. Acceptable formats for tables, charts, illustrations, and photos are doc, xls, jpeg, gif, and npg.

TYPES AND SCOPE OF MANUSCRIPTS

The title of all types of articles is followed by Summary (up to 300 words) and keywords (3 to 8).

The Original Paper (work) is a systematically published research of a problem according to scientific criteria and a clear aim of the research. **The integral parts of the paper are: a) introduction**- (the aim of the paper as the last paragraph of the introduction); **b) material and methods**; **c) results; d) discussion; e) conclusion; f) literature**. The length of the text is limited to 3500 words, with a maximum of 5 tables, charts, or pictures (up to 12 pages of text).

A Review Article covers a systematically addressed specific medical problem, in which the author made some contribution, visible on the basis of self-citations. **Integral parts of the paper are: a) introduction**- (the aim of the review paper as the last paragraph of the introduction); **b) the text of the review of literatureonthe problem , with subtitles**; **c) conclusion; d) literature**. The review article is usually commissioned by the Editorial Board, but non-commissioned manuscripts are also considered. Contact the Editorial Board before writing a review article. Text length can be up to 5000 words (18 pages).

A Case Report (patient presentation**)** sheds light on individual cases ofmedical practice. It usually describes one to three patients, or one family. The integral parts of the paper are: **a) introduction**- (the aim of the paper as the last paragraph of the introduction); **b) presentation of the patient; c) discussion and d) conclusion**. Unlike the original research, omit the section on methodology and results. The text is limited to 2500 words, max 4 tables, or 4 pictures and up to 25 references (up to 6 pages of text in total). Patient names, initials, or medical history numbers should not be used, especially in the illustrations. Casereportsmust not have more than 5 authors

Articles in the history of medicine and health culture shed light on certain aspects of medical practice in the past. Text length can be up to 2500 words (6 pages). These and the articles statedbelow do not have a prescribed structure, such as original papers, case reports, and review articles. Short contributions from the field of medical practice (diagnostics, therapy, remarks, suggestions and opinions on methodological problems, etc.) are published, too, as well as presentations from various medical meetings, symposia and congresses in the country and abroad, book reviews and articles from foreign journals up to 1000 words, 1-2 tables or images, up to 5 references (up to 3 pages of text). Editorial letters have up to 400 words, or 250 words if they contain comments on published articles. By order of the editorial board, or in agreement with the editorial board, works of didactic character are published.

If the work is part of a master's thesis, or a doctoral dissertation, or is done in the framework of a scientific project, this should be **clearlyindicated in the note after the abstract and before the text**. Also, if the work has been previously announced at a professional meeting, state the official name of the meeting, the venue and time of the event, whether the work has been published and how it has been published (eg the same or a different title or abstract).

ETHICAL CONSENT. Manuscripts on human research should include a statement in the form of a written consent of the persons interviewed in accordance with the WMADeclaration of Helsinki and the approval of the responsible ethics committee that the research can be carried out and is in accordance with legal standards. Experimental research on human material and animal testing should include a statement from the ethics committee of the institution and be in accordance with legal standards. Information on this must be provided in the section

AUTHORSHIP. All persons listed as authors of the work should qualify for authorship. Each author should have participated sufficiently in the work on the manuscript to be able to take responsibility for the entire text and the results presented in the work. Authorship is based solely on: making a significant contribution to the concept of the work, obtaining results or analyzing and interpreting the results; the planning of the manuscript or its critical revision of considerable intellectual importance; the final refinement of the print version of the manuscript. Authors should attach a description of the contributions individually for each co-author within the Submission Letter form. Financing, collecting data or generally overseeing a research team cannot by itself justify authorship. All other contributors who are not the authors of the manuscript should be listed onthe

acknowledgementpage, with a description of their contribution to the work, with written consent, of course.

STATEMENT OF CONFLICT OF INTEREST. The manuscript is accompanied by a signed statement in the form of a Submission Letter stating the authors of each possible conflict of interest or lack thereof. For more information on the different types of conflicts of interest, visit the World Association of Medical Editors' Association (WAME; http://www.wame.org), entitled "Conflict of Interest Statement Policy".At the end of the paper, below the Remarks section, in a separate section Conflict of Interest,each possible conflict of interest or its absence should be declaredfor each author individually (full name of the author or initials) For example Zoran Petrovic: Krka (lecturer) Ljiljana Aleksic: none. Mila Bastac: Pfizer, Sanofi, Bristol-Meyers Squibb (lecturer, honorary consultant, researcher on ascientific project).

PLAGIARISM. As of January 1st, 2019, all manuscripts are subjected to plagiarism / autoplagiarism through the SCIndeks Assistant-Cross Check (iThenticate). Papers containing plagiarism or self-plagiarism will be rejected and the authors sanctioned.

ABBREVIATIONS. Use only when necessary, for very long names of chemical compounds, that is, abbreviations that are already recognizable (standard abbreviations, such as DNA, AIDS, HIV, ATP). For each abbreviation, the full term should be stated when first quoted, unless it is a standard unit of measure. Do not use abbreviations in the title. Avoid using abbreviations in the abstract, but if necessary, explain each abbreviation when first referenced in the text.

ACKNOWLEDGEMENTS. List all contributors who contributed to the creation of the work but did not meet the criteria for authorship, such as those providing technical assistance, writing assistance, or managing a department that provides general support. Financial and material assistance, in the form of sponsorships, scholarships, gifts, equipment, medicines and more, should also be listed

MANUSCRIPT PREPARATION

The text of the paper contains first and foremost the title of the paper, in the following lines: full names of the authors and all co-authors; the name, place and address of the institutions from which the author and co-authors come (in parentheses, associate the names of the authors); possibleacknowledgementfor help with elaborationofthe paper;

It is obligatory to submit:

-proposal of the manuscript category (original work, review article, case report, etc.);

-**first and last name, year of birth of the author and all co-authors**;

-**full address, telephone and fax numbers, as well as the author's e-mail for correspondence**.

The following is a SUMMARY (Abstract), up to 300 words is best. A summary cannot have footnotes, tables, images, or references. A summary of **the original papers** should include: Introduction (state the objective in the last sentence), **Material and methods, Results and Conclusions**. Write each of the segments listed at the beginning of the sentence in bold. Provide the most important results (numerical values) of the statistical analysis and the levelofsignificance. The conclusion must not be general, but must be directly linked to the results of the work. **For case reports, the summary** should have the following parts: **Introduction** (state the objective in the last sentence), **Case report, Conclusion**. For other types of papers the summary has no specific structure.

The summary must not contain any claims that are not contained in the text of the article. It must be written in such a way that even an educated nonexpert can understand the content of the article. After the summary, write 3 to 8 keywords. The words in the title should not be repeated and the keywords should be relevant or descriptive and in accordance with MESH rules (available at https://www.nlm.nih.gov/mesh).

The next part of all the papers is an **INTRODUCTION** (with a subtitle of the same name), which must be brief, with a brief overview of the literature on the problem in question, and with a clear statement of **the purpose of the article** in a separate paragraph at the end of the introduction.

MATERIALS AND METHODS (with the same subtitle) must contain sufficient information to enable other researchers to repeat similar research without further information. Patient names and medical history numbers should not be used nor other details to help identify patients. The names of the apparatuses, software and statistical methods used must be indicated.

Show the **results** (with the subtitle of the same name in BOLD) clearly and concisely. You should not display the same data both in tables and charts.

DISCUSSION (with the subtitle of the same name) should discuss the interpretation of the results, their meaning in comparison with other, similar research and in accordance with the hypotheses of the research. The results already written should not be repeated.

CONCLUSION (with the subtitle of the same name) should be given in a separate chapter.

Each table, chart, or illustration must be self-explanatory, i.e. even without reading the text in the manuscript. Above the table, chart, orimage,there should be a serial number and a title. Put the legend in a footnote below the table, chart, or image and explain any non-standard abbreviations there. Illustrations (images) should be sharp and contrasting, no larger than 1024x768 pixels. The number of images should be limited to the most necessary (generally no more than 4-5). If the image, table, or chart is downloaded from the Internet or another source, the source must be indicated.

REFERENCES

LITERATURE. At the end of the paper, write a list of cited literature, which should be as current as possible and most references should not be older than 5 years. References are numbered in the order they appear in the text. Mark the references in the text with an Arabic number in square brackets [...]. The literature lists the first 3 to 6 authors of the article cited, followed by "et al". Journal titles can only be abbreviated as in Index Medicus. The journal abbreviation can be found at: http://www.nlm.nih.gov/. If the abbreviation is not known, give the name of the journal as a whole. The literature is cited as follows:

Journal articles

Standard journal article:

Gao SR, McGarry M, Ferrier TL, Pallante B, Gasparrini B, Fletcher JR, et al. Effect of cell confluence on production of cloned mice using an inbred embryonic stem cell line. Biol Reprod. 2003; 68 (2): 595-603.

Organization as author:

WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. Lancet. 2000; 355: 451–5.

No authors listed:
Coffe drinking and cancer of the pancreas [editorial]. BMJ. 1981; 283 628.

A volume with a supplement:
Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig heart anaphylaxis. Pharmacol Res Commun. 1988; 20 Suppl 5: 75–8.

Books and other monographs

The author is a person (s):
Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.

Editor (s) as authors:
Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

Chapter in a book:
Blaxter PS, Farnsworth TP. Social health and class inequalities. In: Carter C, Peel JR, editors. Equalities and inequalities in health. 2nd ed. London: Academic Press; 1976. p. 165–78.

Meeting announcements: Harris AH, editor. Economics and Health: 1997: Proceedings of the 19th Australian Conference of Health Economists; 1997 Sep 13-14; Sydney, Australia. Kensington, N.S.W.: School of Health Services Management, University of New South Wales; 1998.

Conference Articles:
Anderson JC. Current status of chorion villus biopsy. In: Tudenhope D, Chenoweth J, editors. Proceedings of the 4th Congress of the Australian Perinatal Society; 1986: Brisbane, Queensland: Australian Perinatal Society; 1987. p. 190-6.

Dissertation:
Cairns RB. Infrared spectroscopy studies of solid oxygen. Dissertation. Berkley, California: University of California, 1965.

Electronic material

Article in aninternetmagazine:
Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002; 102 (6). Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Article published electronically before the printed version:
Yu WM, Hawley TS, Hawley RG, Qu CK. Immortalization of yolk sac-derived precursor cells. Blood. 2002-Nov-15; 100 (10): 3828-31. Epub 2002 Jul 5.

CD-ROM:
Anderson SC, Poulsen KB. Anderson's Electronic Atlas of Hematology [CD-ROM]. Philadelphia: Lippincott Williams & Wilkins; 2002.

Online monograph:
Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/.

Website:
Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

Part of awebsite:
American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2screens]. Available from: http: //www.ama-assn.org/ama/pub/category/1736.html

NOTE. A paper that does not meet the requirements of this guide cannot be referred for review and will be returned to the authors for completion and correction. Adhering to the preparation instructions will significantly shorten the time of the entire process until the paper is published, which will positively affect the quality of the articles and the regularity of the publication of the journal.

For any additional information, please contact the address and email below.

EDITORIAL ADDRESS

Timočki Medicinski Glasnik
(Timok Medical Journal)
Zdravstveni centar Zaječar
(Zaječar Health Center)
Pedijatrijska služba Pediatric Service
Rasadnička bb, 19000 Zaječar,
Serbia (Republic of Serbia-RS)

Ordinacija "Dr Bastać",
Kosančićev venac 16 19000 Zaječar
Serbia (Republic of Serbia-RS)
063402396, 019432333
dusanbastac@gmail.com

Email: tmglasnik@gmail.com
Website: http://www.tmg.org.rs/

Milorad Mile Antić

Pejzaži

Milorad Mile Antić svoj umetnički rad započeo je u turbulentnim vremenima između dva svetska rata u malom gradu na jugu Srbije. Vranje, kao i jug Srbije uopšte, kroz istoriju bio je izvor inspiracije različitim umetnicima od kojih je svakako najpoznatiji književnik Bora Stanković čija su dela gotovo u celini smeštena u vranjski kraj.

Za razliku od Bore Stankovića koji se nije vratio u rodni grad, Milorad Antić je svoj životni i radni vek proveo upravo u Vranju. Slikarstvo i vajarstvo učio je na Kraljevskoj umetničkoj školi u Beogradu koju je sa uspehom završio 1937. godine. Akvarel, i slikarstvo uopšte, učio je kod Bete Vukanović, impresionističke slikarske i jedne od najznačajnijih predstavnica plenerizma u Srbiji. Plenerizam – slikanje u otvorenom prostoru – postao je veoma popularan sredinom 19. veka posebno kod impresionista kao što su Mone i Renoar. Beta Vukanović je rad u pleneru donela u Srbiju i prenela ga svojim učenicima i drugim umetnicima. Slikala je portrete, mrtve prirode i pejzaže pre svega sa motivima iz vardarske Makedonije, Srbije i Bosne, ali i karikature od kojih je većina rađena u akvarelu.

Tehnika akvarela svakako nije rezervisana samo za karikature, ilustracije ili slikarske studije tj. skice. Iako je veoma stara tehnika čije početke možemo tražiti čak u pećinskom slikarstvu, umetnosti drevnog Egipta i evropskoj srednjovekovnoj umetnosti ili Kini, kao samostalan umetnički medij počela je da se razvija tek u Renesansi, a značajan razvoj doživela je u 18. veku u Engleskoj gde posebno mesto zauzimaju pejzaži. Izuzetna sposobnost akvarela da izrazi transparentnost, da predstavi svetlost i boju činilo ga je, kao što je to i dalje slučaj, idealnim medijem za slikanje pejzaža i mnogi umetnici i danas preferiraju upravo akvarel u svojim delima.

Pejzaže u akvarelu slikao je i Milorad Antić po povratku u Vranje. Visoki jablani dominiraju delom, dok male kuće koje se naziru u pozadini sugerišu da je pejzaž nastao ili inspirsan upravo Južnom Srbijom, možda baš Vranjem ili manjim mestom u njegovoj okolini. U Vranju je Milorad Antić radio kao slobodni umetnik odmah nakon Drugog svetskog rata i jedno kratko vreme bio je direktor Gimnazije, a kasnije je radio kao scenograf u pozorištu Bora Stanković. Takođe, mnoge đake učio je crtanju i slikanju i pripremao ih za upis na umetničke akademije. Nakon smrti, ostala je mala kolekcija slika i skulptura koja svedoči o delu prvog vranjanskog školovanog slikara i vajara.

Ada Vlajić
Istoričar umetnosti