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C O N T E N T S

ORIGINAL PAPERS

REVIEW ARTICLE

CASE REPORT

THE INCIDENCE OF ADVERSE REACTIONS AMONG VOLUNTARY WHOLE BLOOD DONORS IN VOJVODINA: A FIVE YEAR CROSS-SECTIONAL STUDY

Bežanović Milomir (1), Gulan Zdravko (1), Budakov Obradović Zorana (1,2), Grujić Jasmina (1,2)

(1) BLOOD TRANSFUSION INSTITUTE OF VOJVODINA, HAJDUK VELJKOVA 9A, NOVI SAD.
(2) DEPARTMENT OF INTERNAL MEDICINE, FACULTY OF MEDICINE IN NOVI SAD, HAJDUK VELJKOVA 3, NOVI SAD, UNIVERSITY OF NOVI SAD.

Abstract: Introduction: Blood donors (BDs), in most cases, tolerate the whole blood donation procedure well. However, occasionally adverse reactions (ARs) may occur. ARs often have a negative impact on donors return. Therefore, the staff of transfusion institutions must be educated and properly trained to recognize and take care of BDs who experience ARs before, during or after the procedure. The incidence of ARs is about 1,4%. Aim: To determine the frequency and severity of ARs that occurred among BDs on the territory of Vojvodina, analyze the age and profile of donors in whom they were recognized, indicate possible prevention of ARs. Material and methods: In a retrospective study, the records of ARs among whole BDs at the Blood Transfusion Institute Vojvodina, from January 1 2017, until December 31, 2021 were analyzed. Demographic data of the donors were obtained from the Institute's information system. The data were analyzed according to the time and manner of occurrence and the severity of ARs. Results: During the study period there were 194 425 blood donations. The ARs were identified in 2722 (1,4%) donations. The incidence was 14 in every 1000 donations. BDs who suffered ARs were 28,0 ± 8,3 years old, 1881 (69,1%) were male, 841 (30,9%) were female, while 1908 (70,1%) donated blood for the first time. In 2396 (88,03%) BDs vasovagal reaction occurred, 737 (27,08%) experienced nausea, 363 (13,33%) suffered syncope, 221 (8,13%) developed hyperventilation, 64 (2,34%) gained hematoma. Severe ARs in the form of collapse with convulsions were experienced by 12 (0.44%) donors. In multiple BDs, ARs were significantly less frequent ($p<0,05$). Conclusion: Although the number of donors with ARs in institution is low, it is necessary to monitor them, react promptly in case of their occurrence and minimize the risks of occurrence, primarily through education and preparation of donors for the whole blood donation procedure.

Key words: Blood donors, haemovigilance, fainting, adverse reactions/incidences, vasovagal reaction

INTRODUCTION

Continuous supply of health institutions with sufficient amounts of blood and blood products represents the main task of every transfusion institution. Blood transfusion is one of the most common interventions in medical practice since there is no effective substitute for human blood. Having in mind that blood collection is limited to healthy individuals, ensuring donor's safety without adverse reactions (ARs) is an essential factor that will encourage them to donate blood and come back again in the near future. Blood donation is voluntary, non-remunerated and anonymous. On the territory of Serbia, all needs for blood and blood components are met from one's own sources [1]. In order to ensure sufficient amounts of blood, it is necessary to take measures to retain the old voluntary blood donors (BDs) and recruit new ones. With that in mind, it's important to implement a series of activities to motivate the population and promote blood donation. Although blood donation is considered a safe procedure with low risk rates, every potential BD is thoroughly screened to ensure the safety of both the donor and the recipient. Based on the Ordinance on donors of blood or blood components (Službeni glasnik RS, No. 6/2019-132), any healthy person aged from 18 to 65 years who fulfills the following criteria can be a donor of blood or blood components:

a) good general condition and good venous access;
b) body weight of at least 50 kilograms;
c) adequate hemoglobin and hematocrit values (above 125 g/L and 0,38 L/L for a female; above 135 g/L and 0,40 L/L for a male);
d) body temperature less than 37 °C, pulse 50-100 heartbeats per minute;

e) blood pressure not higher than 180/100 mmHg and not lower than 100/60 mmHg.

After selection and examination of the BDs, blood for transfusion is taken from the cubital vein into disposable bags of 450 mL so that the amount of blood taken is up to 13% of the total volume of the donor's blood. Adverse reactions (ARs) in BDs are defined as any adverse response associated with the collection of blood or blood components and they occurred in about 1% to 5% of blood donations [2]. They must be documented in the donor's records, but also in the records of the quality control system. Analysis of donor adverse reaction reports will definitely help developing approaches to the improvement of the overall safety of blood collection. According to the recommendations of the Council of Europe and the Guide for the preparation, use and quality assurance of blood components, 20th edition, from 2020, a classification of complications related to blood donation was performed [3].

ARs can be classified as:

a) Local complications: hematoma, arterial puncture, nerve injury or compression, tendon injury, thrombophlebitis, local allergic reaction, infection;

b) General complications: vasovagal reaction (VVR) (immediate or delayed; at the venipuncture site or outside);

c) Other complications: generalized allergic reactions, cardiovascular reactions (cardiac arrest, angina pectoris, cerebral ischemia), accident or injury.

According to the severity, ARs can be divided into:

a) ARs which are not significant, classified as mild and moderate:

Hematoma: - local discomfort only during phlebotomy, minor pain or functional impairment (mild)

local discomfort during phlebotomy, but also after the procedure, when performing daily activities (moderate)

Arterial puncture: - without symptoms or local discomfort during venipuncture, without hematoma (mild)

local discomfort that persists after blood collection is completed (moderate)

Pain in the arm: - symptoms lasting less than 2 weeks (mild)

symptoms lasting more than 2 weeks but less than 1 year (moderate)

Vasovagal reactions: - subjective symptoms only (mild)

objective symptoms (moderate)

b) Adverse reactions associated with blood collection that could lead to incapacitation of the donor and result in hospitalization and morbidity are defined as severe reactions such as delayed syncope, cardiac arrest, collapse with convulsions, cerebral ischemia.

AIM

The aim of this study was to determine the frequency and severity of ARs that occurred among BDs on the territory of Vojvodina by analyzing the age and profile of donors in whom they were recognized but also to indicate possible prevention of ARs.

MATERIAL AND METHODS

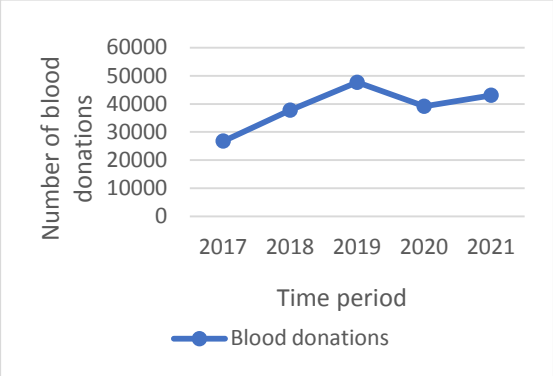
In a retrospective study, the records of ARs among whole BDs at the Blood Transfusion Institute Vojvodina, from January 1, 2017, until December 31, 202 were analyzed. Depending on the number of blood donations, donors are categorized into first-time and multiple donors. Demographic data of the donors related to age, gender, number of donations and place of donation were obtained from the Institute's information system. Depending on the time of occurrence, a classification and analysis of ARs were performed on those that occurred before the beginning of the blood donation procedure, during the procedure and after the procedure is completed. According to the type of occurrence, ARs were divided into local and systemic reactions, while, according to the severity, they were classified and analyzed into mild, moderate, and severe.

The data were analyzed and processed using the methods of descriptive statistics in the Minitab 16 software program. The following descriptive statistical parameters were used: arithmetic mean, standard deviation and median. ANOVA was used to assess the statistical significance of the obtained results with a significance level of less than 0.05. The findings are presented in tabular and graphical form.

RESULTS

During the study period, 194,425 donations were collected and analyzed, in which 108,014 voluntary donors of whole blood participated (Graph 1). Among the blood donors, there were 83.678 (77.47%) men and 24,336 (22.53%) women (the male/female ratio was 3:1). There were 99,524 (92.14%) multiple donors and 8,490 (7.86%) first-time donors.

Graph 1. Number of blood donations in the period from 2017 to 2021



Based on the total number of donations, adverse reactions occurred during 2722 procedures (1.4%). The number of incidence was 14 in every 1000 donations. BDs who experienced ARs were 28,0 ± 8,3 years old, 1881 (69.1%) were male and 841 (30.9%) were female. People who donated blood for the first time were at a higher risk of experiencing an adverse reaction, which happened to 1908 people (70.1%), while multiple donors were less represented, merely 814 of them (29.9%). Donors from urban regions were more represented, 2,349 of them (86.3%), while there were 373 (13.7%) from rural regions.

The chi-square test was used to analyze the occurrence of adverse reactions in men 1811/83678 (2.16%) in regards to women 841/24336 (3.45%) and a highly significant statistical difference was determined ($p<0.001$). Also, the chi-square test was used to analyze the occurrence of adverse reactions in first-time BDs 1908/8490 (22.5%) compared to 814/99524 (0.82%) multiple ones and a statistically significant difference was also determined ($p<0.001$). According to the time of occurrence of the adverse reaction, it was observed that the most ARs occurred during blood donation procedure, 1717 (63.1%). After the blood donation procedure was completed, 893 (32.8%) ARs were identified, while112 ARs (4.1%) were identified before the procedure.

In relation to localization, systemic reactions predominated in 2619 (96.2%) donors, while local reactions occurred in 103 (3.8%). BDs who were younger than 30 years and weighed less than 60 kg had vasovagal reactions, nausea and syncope more often ($p<0.005$). The occurrence of local and systemic ARs in BDs in relation to their donor status is shown in Table 1.

Table 1. Types of adverse reactions during whole blood donation procedure

Adverse reactions		BDs with ARs		Total
		First-time	Multiple	N (%)
Local - associated with venipuncture	Pain, hyperemia and swelling at the puncture site Hematoma	16 28	15 36	31 (1.13%) 64 (2,34%)
	Local phlebitis and thrombophlebitis	14	10	24 (0,89%)
Systemic	Vasovagal reaction	1715	681	2396 (88.02%)
	Syncope	196	167	363 (13.33%)
	Nausea Hyperventilation	553 166	184 55	737 (27,08%) 221 (8,12%)

In relation to the severity of the ARs, 64 (2.34%) BDs had mild reactions in the form of hematoma, and 2396 (88.03%) of them experienced weakness and fainting. Moderate ARs in the form of nausea and sweating occurred in 737 (27.08%) donors. Severe ARs in the form of collapse with convulsions were experienced by 12 (0.44%) donors. Adverse reactions were mostly mild and moderate ($p<0.05$).

DISCUSSION

Caring for donors primarily means protecting their own health. In addition, any inconvenience associated with blood donation procedure may

result in refusing BDs to come again. Conversely, the safe and pleasant experience that BDs have when donating blood can encourage them to come again and be recruited and motivated to become regular blood donors, which consequently leads to a satisfactory supply of blood units. France et al. indicate that donors give up further blood donation after experiencing an adverse reaction [4]. It is very important to analyze ARs related to blood donation, to consider what affects their occurrence so that preventive measures and adequate care can be taken. Several authors dealt with the consideration of the factors that influence the emergence of ARs and the question of which the weakest links in the chain of work processes with BDs are, in order, first of all, to correct them and thereby increase the satisfaction of DDK [5,6]. In case of occurrence of ARs, the most important thing is to provide adequate professional help in a timely manner, determine the cause of the occurrence, and, after analysis, implement corrective and preventive measures. Each adverse reaction with all the measures taken is recorded in the donor's file, while it is a legal obligation to report severe ARs to the hemovigilance system at the national level.

The frequency of ARs certainly depends on several factors, from the preparation of the BD for the blood donation procedure, his/her general condition and hydration, venipuncture, conversation with him/her during the procedure, as well as the provision of post-donation information about behavior after donating blood. In our population of whole blood donors, the incidence of total ARs is 1.4%, while according to published data it ranges from 0.03% to 6% [7,8]. The difference in the mentioned data may be due to the wide range of ARs that were analyzed, as well as the size of the population that was the subject of the research.

On the other hand, most reported ARs are systemic, but even here there are significant differences. While in our study systemic adverse reactions in relation to the total number of donations occurs with an incidence of about 1%, in Greece the frequency is 0.88%, and in Japan 6% [9,10]. Systemic reactions are influenced by many factors, in which the most important are age, gender, stress, fluid intake, proper diet and adequate sleep before donating blood.

Vasovagal reaction is the most common type of AR in our population with a share of about 88% in relation to all other reactions and 1,23% in relation to the total number of donations. The incidence of VVR varies among different populations. Agnihotri et al. published the data that among whole blood donors, 1.6% have VVR, and these are, above all, younger women donating blood for the first time [11]. Dogra et al. came to a similar conclusion, although the incidence was much lower and amounted to 0.365% [12]. VVR represents the reaction of the neurovegetative system to stress, which can also have a cause in acute blood loss. Although it has a low incidence, it can have a long-term negative impact on the return rate of BDs and is often the main reason donors refrain from coming back. The most vulnerable group of BDs for the occurrence of ARs are high school students weighing up to 55 kg who are donating blood for the first time. Since VVR are the most represented, a seasonal variation in their manifestation was also observed because it correlated with periods when there was a higher representation of high school students in organized blood donation actions. Sultan et al. and Tondon et al. indicated a positive correlation between the increase in the age categories of BDs with a decrease in the risk of VVR [10,13]. The reason for this correlation lies in the fact that younger people have a greater sensitivity of the carotid-aortic baroreceptor, which can be the cause of VVR if the receptor is stimulated during or after the donation process. As the age of DDK increases, baroreceptor sensitivity decreases, which explains the decrease in VVR incidence in older age groups. Many studies have indicated that female gender is more associated with the occurrence of ARs, primarily due to the difference in blood pressure. It has been proven that there are gender differences in the renin-angiotensin system and the effects of the bound angiotensin II type 2 receptor on renal vascular resistance, whereby renal sympathetic nervous activity affects the value of blood pressure [14]. The data of our study indicate that in relation to the majority of ARs, the predominant clinical form are mild and moderate adverse reactions, while severe forms occur very rarely. These findings are consistent with data from many other studies, which indicate the fact that blood donation is a safe procedure, mostly without complications [15-17].

It is important to implement all mechanisms that could prevent ARs, especially when it comes to

BDs who are donating blood for the first time. These procedures include: the shortest possible waiting time for BDs, from arrival to the venipuncture itself, in a pleasant environment, good psychological preparation for BDs, pre-donation hydration, performing muscle tension exercises, hiring experienced staff and good puncturers [4,18-20]. Communication with blood donors is extremely important and it is considered that no other prevention measure can replace it.

CONCLUSION

Continuous attention and monitoring of donors during the entire blood donation procedure contribute to a low incidence of adverse reactions. Education of the medical personnel to identify risk factors contributes to the prevention of adverse reactions. Prevention measures of adverse reactions, as well as their quick treatment, are important because of the preservation of donor's health and the negative effects they have on the motivation of the donors and their return.

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Vol. 47 (2022) No. 2-3 TIMOK MEDICAL GAZETTE Review article

A NEW APPROACH TO THE CONSIDERATION OF HYPERTENSION IN CHRONIC KIDNEY DISEASE THROUGH THE PRISM OF THE LAST KDIGO GUIDE 2021

Biserka Tirmenštajn Janković (1), Dušan Bastać (2)

(1)DEPARTMENT OF NEPHROLOGY AND HEMODIALYSIS, HEALTH CENTER "ZAJEČAR", ZAJEČAR; (2) OFFICE FOR INTERNAL MEDICINE „DR BASTAĆ“, ZAJEČAR;

Summary: Hypertension associated with chronic kidney disease (CKD) is related with a high risk of cardiovascular disease (CVD), which is the most common cause of morbidity and mortality in patients with CKD. Control of hypertension is important primarily because it reduces the risk of CVD and all-cause mortality in patients with CKD. The new KDIGO (Kidney Disease: Improving Global Outcomes) guideline for the management of blood pressure in CKD were published in 2021 and represented an updated version of the original guideline from 2012. This guideline covers all topics contained in the original instructions, such as optimal blood pressure targets, lifestyle interventions, choice of antihypertensive drugs, and specific management in kidney transplant recipients and children. Some aspects of general and cardiovascular health, such as lipid control and smoking, are excluded. In addition, this guideline introduces a chapter dedicated to proper blood pressure measurement as all large randomized trials from which the evidence and recommendations of this guide emerged used standardized preparation and measurement protocols adhered to by patients and clinicians. The key recommendation of the KDIGO guideline refers to target systolic blood pressure under120 mmHg in most adults with CKD, provided that the standardized office blood pressure measurement is used. Despite recommendations for lowering target blood pressure, general lack of evidence, especially in patients with diabetes and advanced CKD, still suggests the need to individualize targets according to the characteristics, tolerances, and preferences of each patient. Larger randomized controlled trials are needed to examine the effects of blood pressure targets on major adverse events and mortality in patients with CKD, especially in subpopulations that were not adequately represented in previous studies.

Key words: chronic kidney disease, hypertension, KDIGO, blood pressure measurement, blood pressure targets, lifestyle, physical activity, antihypertensive agents.

INTRODUCTION

High blood pressure (BP) is the leading correctible risk factor for chronic diseases in the world [1]. High BP is not only an important risk factor for chronic kidney disease (CKD) [2], but also an important comorbidity that occurs with a prevalence of 86% in the population of patients with CKD not receiving dialysis [3]. The combination of CKD and hypertension leads to a high risk of cardiovascular disease (CVD), which is the most common cause of morbidity and mortality in patients with CKD [4]. Several clinical studies and meta-analyses have shown that aggressive treatment of hypertension in patients with and without CKD reduces the risk of CVD, as well as all-cause mortality, although the protective effects of BP reduction on renal function remain controversial [5,6]. For these reasons, several different guides/guidelines for the treatment of hypertension in CKD have been published so far, the last few of which are listed in Table 1.

Table 1. Comparison of several recent hypertension guidelines

	KDIGO[10]	ACC/AHA[15]	ECC/ESH[16]	ISH[63]
Year	2021	2017	2018	2020
Specific population	CKD	NA	NA	NA
Dietary sodium intake	<2 g/day	<1.5 g/day	<2 g/day	Reduce salt intake
Physical activity	Moderate-intensity physical acivity for ≥150 min/wk, or to a level compatible with CV and physical tolerance	Aerobic or resistance exercise 90-150 min/wk; isometric resistance exercise 3 times/wk for 8-10 wk	Moderate-intensity aerobic exercise for ≥30 min 5-7 d/wk; resistance exercises 2-3 d/wk	Moderate-intensity aerobic exercise for 30 min 5-7 d/wk; or high-intensity interval training; resistance/strength exercises 2-3 d/wk
Standardize BP measurement	Yes	Yes	Yes	Yes
Out-of-office BP	Yes	Yes	Yes	Yes
SBP treatment target	<120 mmHg	<130 mmHg	<65 y: <140 mmHg (toward 130); ≥65 y: 130-139 mmHg (could be <130 if tolerated; never <120)	<140/90 mmHg (<65 y: <130/80 but >120/70; ≥65 y: <140/80 in „elderly“)
BP target (CKD)	<120 mmHg	<130/80 mmHg	130-139 mmHg	<130/80 mmHg (<140/80 in elderly)
BP target (DM)	SBP <120 mmHg	<130/80 mmHg	<140 mmHg (toward 130; could be <130 if tolerated; never <120)	<130/80 mmHg (<140/80 in elderly)
BP target (Tx)	SBP <130 mmHg DBP <80 mmHg	<130/80 mmHg	ND	ND
BP target (peds)	Lower MAP by ABPM to ≥50th percentile for age, sex and height	NA	ND	ND
First-line Rx (nonproteinuric CKD)	RASI (ACEI or ARB)	ND	ND	RASI
First-line Rx (proteinuric CKD)	RASI (ACEI or ARB)	ACEI (ARB if ACEI not tolerated)	Combination of RASI with a CCB or a diuretic	RASI
First-line Rx (diabetic CKD)	RASI (ACEI or ARB)	ACEI or ARB in the presence of albuminuria	Combination of RASI with a CCB or a diuretic	RASI

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; MAP, mean arterial pressure; NA, not applicable; ND, not discussed; peds, pediatric; RASI, renin-angiotensin system inhibitors; Rx, prescription; SBP, systolic blood pressure; Tx, transplant;

The original KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline for the management of blood pressure in the population of CKD patients not receiving dialysis was published in 2012. [7]. Since then, several articles have been published reporting on the primary results and important secondary analyses of large, randomized trials of hypertension treatment in various populations, including patients with CKD. Intensive lowering of systolic blood pressure (SBP) to a target of 120 mmHg in SPRINT (Systolic Blood Pressure Intervention Trial) reduced the risk for CVD and all-cause mortality to a similar extent in patients with and without CKD [5].Secondary combined analyzes of SPRINT and ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes-Blood Pressure) trials showed a similar reduction in the primary composite outcome of CVD and all-cause mortality for the SPRINT study and the standard glycemic control arm of the ACCORD-BP trial [8]. In the VA NEPHRON-D study (Veterans Affairs Nephropathy in Diabetes), combination therapy with angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) increased the risk of acute kidney injury (AKI) and hyperkalaemia, and showed no benefit for renal or cardiovascular outcomes. [9]. In 2017, KDIGO undertook a multi-year process of updating its original guideline, and the results of these and many other studies are included in the updated guideline published in 2021. [10].

The 2021 revision of the KDIGO guideline also applies only to the population of patients with CKD not receiving dialysis and it covers topics contained in the original guideline, such as optimal blood pressure targets, lifestyle

interventions, choice of antihypertensive drugs and specific management in kidney transplant recipients and children (Table 2). Some aspects of general and cardiovascular health, such as lipid control and smoking, are excluded. A Work Group of researchers and clinicians working on the revision of the original guideline identified 2 major areas that warrant particular attention due to the emergence of new evidence: BP measurement and BP target in patients with CKD. These 2 problems are closely related, because the target SBP <120 mmHg depends on the proper adherence to standardized preparation and measurement protocols by patients and clinicians. On the other hand, the main objections are also aimed to these 2 focuses: the observed impracticality of standardized BP measurement in clinical practice and the difficulty in achieving new SBP targets [10].

Table 2. Key recommendations from KDIGO 2021 Clinical Practice Guideline for BP Management in CKD.

Blood pressure measurement
✓ A standardized office BP measurement in preference to routine office BP measurement for the management of the high BP in adults is recommended.
✓ It is suggested that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP.
Lifestyle interventions for lowering BP in patients with CKD not receiving dialysis
✓ Targeting a sodium intake <2g of sodium per day (or < 90 mmol sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD is suggested.
✓ It is suggested that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance.
Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis
✓ It is suggested that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mmHg, when tolerated, using standardized office BP measurement.
✓ Starting renin-angiotensin-system inhibitors (RASI) (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1-G4, A3) without diabetes is recommended.
✓ Starting RASI (ACEI or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1-G4, A2) without diabetes is suggested.
✓ Starting RASI (ACEI or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1-G4, A2 and A3) with diabetes is recommended.
✓ Avoiding any combination of ACEI, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes is recommended.
Blood pressure management in kidney transplant recipients
✓ Treat adult kidney transplant recipients with high BP to a target BP of <130 mmHg systolic and <80 mmHg diastolic using standardized office BP measurement.
✓ It is recommended that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as a first-line antihypertensive agent in adult kidney transplant recipients.

BLOOD PRESSURE MEASUREMENT

Sphygmomanometry is the first practical method that Riva Rocci introduced in 1896 for estimation of SBP [11]. Diastolic blood pressure (DBP) readings became feasible in 1905, when Korotkov described his auscultatory method of measurement [20]. It was soon noticed that BP varies dramatically from one reading to another, so attention was focused on standardizing BP measurement methods to avoid errors in estimation. However, despite all the issued guidelines, recommendations and specific approaches to improve the accuracy of measuring BP, a recent meta-analysis documented that the average SBP in routine clinical practice is almost 15 mmHg higher than in research studies [13].

Chapter 1 is a new addition to the original KDIGO BP guideline that highlights the importance of accurate BP measurement in adults. Standardized office BP refers to measurements obtained in accordance with recommended preparations and measurement techniques, regardless of the type of equipment used, as opposed to routine office BP measurements performed without these preparations Standardized BP measurement is an integral part of BP target and the BP target guideline cannot rely on routine BP measurements, because large randomized trials

that examined target BP, including SPRINT and ACCORD, have consistently used standardized BP measurements [10]. Furthermore, strong evidence shows that routine office BP and standardized office BP measurements do not give the same values, and the relationships between these 2 techniques are highly variable, so it is not possible to use some correction factor to convert routine values to standardized BP values [14]. The KDIGO recommendations for measuring standardized BP are in line with other recent guidelines [15-18], but what makes a critical distinction is the insistence on widespread adoption of standardized BP measurement in patients with CKD, because it allows the use of lower target SBP with proven efficacy in clinical trials.

Key elements for successful BP measurement in the office include proper patient preparation, use of a validated measuring device, correct techniques, and average BP values from at least 2 measurements (Table 3). Patients should be instructed to empty their bladder and avoid smoking, caffeine, and physical activity for at least 30 minutes before measuring their BP. They should be seated comfortably with their back supported and feet on the ground > 5 minutes before the readings. The patient and the observer should refrain from talking during the rest period and during BP measurement. The patient's arm should be supported, and all clothing covering the location of cuff placement should be removed. Cuff size should correspond to the circumference of the patient's arm, and the cuff should be placed at heart level (the midpoint of the sternum). The guidelines recommend using an average 2 or more readings obtained on 2 or more occasions to estimate the individual's level of BP. Patients should be informed of their BP values [10,15-18].

Table 3. Checklist for standardized measurement of blood pressure in the office

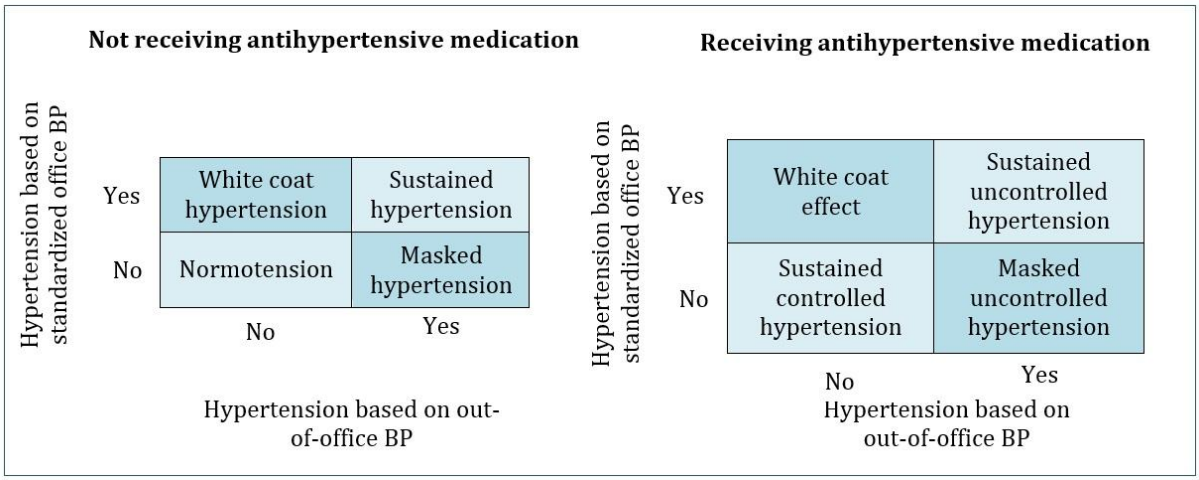
Key steps	Special instructions
1. Properly prepare the patient	1. Have the patient relax, sitting in a chair (feet on floor, back supported) for >5 min. 2. The patient should avoid caffeine, exercise, and smoking for at least 30 min before measurement. 3. Ensure patient has emptied his/her bladder. 4. Neither the patient nor the observer should talk during the rest period or during the measurement. 5. Remove all clothing covering the location of cuff placement. 6. Measurements made while the patient is sitting or lying on an examining table do not fulfill these criteria.
2. Use proper technique for BP measurements	1. Use a BP measurement device that has been validated, and ensure that the device is calibrated periodically. 2. Support the patient's arm (e.g., resting on a desk). 3. Position the middle of the cuff on the patient's upper arm at the level of the right atrium (the midpoint of the sternum). 4. Use the correct cuff size, such as the bladder encircles 80% of the arm, and note if a larger- or smaller-than-normal cuff size is used. 5. Either the stethoscope diaphragm or bell may be used for auscultatory readings.
3. Take the proper measurements needed for diagnosis and treatment of elevated BP	1. At the first visit, record BP in both arms. Use the arm that gives the higher reading for subsequent readings. 2. Separate repeated measurements by 1-2 min. 3. For auscultatory determinations, use a palpated estimate of radial pulse obliteration pressure to estimate SBP. Inflate the cuff 20-30 mmHg above this level for an auscultatory determination of the BP level. 4. For auscultatory readings, deflate the cuff pressure 2 mmHg per second, and listen for Korotkoff sounds.
4. Properly document accurate BP readings	1. Record SBP and DBP. If using the auscultatory technique, record SBP and DBP as onset of the first Korotkoff sound and disappearance of all Korotkoff sounds, respectively, using the nearest even number. 2. Note the time of most recent BP medication taken before measurements.
5. Average the readings	Use an average of ≥2 readings obtained on ≥2 occasions to estimate the individual's level of BP.
6. Provide BP readings to patient	Provide patients with the SBP/DBP readings verbally and in writing.

A variety of BP measurement devices can be used for standardized office BP measurement, because the emphasis of standardization is on adequate preparation of patients for BP measurement, and not on the type of equipment [10]. However, there are several reasons why oscillometric devices are now considered a clinical standard for BP measurement [15, 18]: environmental concerns about mercury toxicity, the need for frequent calibration with aneroid sphygmomanometers, errors due to auscultation and inappropriately rapid deflation of the cuff, and greater

convenience and cost savings associated with use of oscillometric devices [18]. Oscillometric devices can be used to measure BP in patients with atrial fibrillation [10]. Given that large randomized studies have not found significant differences between standardized BP values measured using oscillometric and manual devices, manual BP devices are also considered acceptable when oscillometric devices are unavailable [19, 20]. Automated office BP devices may be the preferred method for standardized office BP measurement. They may increase the likelihood of adherence to proper preparation because they can be programmed to include a rest period, and they can also take multiple BP measurements and provide an average. Automated devices can measure BP either with or without a health worker in the room. The results of the SPRINT trial indicate attended or unattended automated office BP measurements result in similar BP values when the recommendations for accurate BP measurement are followed [21,22].

Out-of-office BP measurement techniques include home BP monitoring (HBPM) and 24-hour ambulatory BP monitoring (ABPM). In patients not taking BP-lowering medications, the following 4 groups can be categorized based on in-office and out-of-office BP measurements (Figure 1): normotension, white coat hypertension, sustained hypertension, and masked hypertension. In those taking BP lowering medications, 4 similar groups can be categorized: white coat effect, sustained controlled hypertension, sustained uncontrolled hypertension, and masked uncontrolled hypertension. [10].Approximately 30% of patients have discordant BP values in-office and out-of-office [23].Masked uncontrolled hypertension is more common in people with CKD compared to people without CKD [24]. Masked hypertension is associated with an increased risk of CVD and renal failure. In contrast, white coat hypertension is associated with a lower risk of adverse events than masked and sustained hypertension, but patients with untreated white coat hypertension have a higher risk of adverse events than patients with controlled office and out-of-office BP [25]. The high prevalence of white coat hypertension and masked hypertension, as well as the increased risk of adverse outcomes identified in observational studies, have resulted in the recommendation that ABPM and HBPM be used to complement standardized office BP for the management of high BP [10,15-17].

Figure 1. BP patterns based on out-of-office BP measurements in addition to standardized office BP measurements.



The KDIGO BP guideline recommends that ABPM be used initially to supplement standardized office BP measurement, while HBPM is further used for ongoing BP management. In areas where ABPM service is not available, HBPM may be used instead of ABPM as the initial procedure. Out-of-office BP measurement additionally burdens patients and clinic staff. For example, ABPM requires patients to wear a monitor for 24 hours, with the obligation to visit the clinic on 2 consecutive days for placement and removal of the monitor. On the other hand, HBPM is a more accessible method and can be particularly important for

the management of BP when a visit to the clinic is impossible or difficult for some reason. As with all BP measurements, out-of-office readings should be obtained using the standardized technique and a validated upper arm device.Notwithstanding the recommendations made, the KDIGO work group recognized the lack of randomized controlled trials comparing the effect of ABPM/HBPM to office-based BP management on cardiovascular or kidney disease outcomes, and therefore supports further research in this area [10].

LIFESTYLE INTERVENTIONS

According to the KDIGO guideline, the suggested sodium intake should be<2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD [10]. Interventional studies in the general population have shown a gradual benefit in reducing of both BP and CVD risk with reduced dietary sodium intake [26]. Although the majority of the world's population consumes more than 2 g of sodium per day, even modest reductions in sodium intake that do not reach this goal are associated with BP and CVD benefits in the general population. However, there are no large and long-term randomized controlled trials evaluating the effects of dietary sodium restriction on clinical outcomes in CKD population.A recent meta-analysis that included only studies with CKD patients found that salt reduction in patients with CKD significantly reduced BP, and if such an effect were maintained in the long term it would result in a clinically significant reduction in CKD progression and CV events [28]. Finally, ACEI and ARB medications are commonly used in CKD population, and their kidney and cardiovascular benefits may be improved if accompanied by a low-sodium diet [29].

Considering that data on specific targets of sodium intake in CKD population with high BP are not firmly established, the KDIGO work group has adopted the recommended target for dietary sodium intake in the general population from the World Health Organization [30], which is in line with the recommendations of several recently published guides to hypertension [16, 17], but also consistent with KDIGO 2020 Guideline for Diabetes Management in CKD [31]. The WG also noted that there are circumstances in which recommendations from the general population cannot be applied to CKD population. The warnings relate to patients with CKD and salt-wasting nephropathy, for whom reduction in sodium intake may be inappropriate. The second warning relates to the dietary approach to the treatment of hypertension, taking into account that diets employed to lower BP are usually rich in potassium, and salt substitutes also contain potassium as the primary cation. These approaches may increase the risk of hyperkalemia, especially in advanced CKD [10].

As part of lifestyle changes, patients with high BP and CKD are advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance. Studies in the general population have clearly demonstrated the beneficial effects of physical activity on BP-lowering, physical fitness and strength, weight loss and reducing the risk of dysglycemia and diabetes [10]. In the CKD population, the evidence is much more limited, but it also suggests that physical activity reduces BP and body weight and improves quality of life [32,33]. Observational data have shown a dose-response relationship between higher levels of physical activity and lower risk of mortality in patients with CKD [34]. On the other hand, the KDIGO work group recognizes a higher prevalence of comorbidities and frailty in the CKD population that might limit the level of physical activity by CKD patients and increase the risk of adverse events. Therefore, the degree of physical activity should be individualized in accordance with the patient's cognitive and physical conditions , which may change over time. Significant health benefits can be gained even if the level of physical activity falls below the proposed targets [10].

BLOOD PRESSURE TARGETS

In adults with high BP and CKD, the KDIGO guideline suggests a target SBP of <120 mmHg when tolerated, provided that a standardized office BP measurement is used. This recommendation pertains to patients with diabetes and without diabetes, and does not apply to patients with a kidney transplant or to those receiving dialysis [10].

For most patients with CKD, particularly those who are older, with low levels of albuminuria or are in the earlier stages of CKD, the risks for CVD and CV mortality are much

higher than those for kidney failure [35]. Therefore, this KDIGO recommendation relies heavily on the results of a high-quality and randomized SPRINT, that showed beneficial effects on CV and mortality outcomes in a study cohort of hypertensive subjects randomized to a target SBP <120 mmHg versus 140 mmHg [5].In this study, 90% of participants were receiving antihypertensive therapy at baseline, and beneficial effects were demonstrated in the group of patients with CKD [36], in the elderly [37] and in those with prediabetes [38]. Two meta-analyses also reported a risk reduction for CV events with intensive BP lowering in the CKD population, regardless of whether the reduction was equal to [39] or lower than in the general population [40].

The effects of intensive BP lowering on CKD progression toward kidney failure are less certain. There is a common perception that BP lowering is renoprotective, but only secondary analyses of some earlier randomized trials have shown that more intensive BP lowering reduces the rate of CKD progression among patients with greater baseline proteinuria [41,42]. However, the results of the two most frequently cited recent randomized trials, SPRINT and ACCORD, indicate that intense BP lowering leads to a small but consistent reduction in estimated glomerular filtration rate (eGFR) shortly after initiation, compared to less intensive controls (may be explained by hemodynamic effects), while the effects of intensive BP lowering on eGFR in the long term remain uncertain [36,43].

The original KDIGO 2012 BP guideline recommended a more intensive BP lowering for patients with albuminuria than those without [7]. With the adoption of an SBP target bellow 120 mmHg for all CKD patients in the revised guideline, separate targets for patients with and without albuminuria were no longer considered necessary. The KDIGO work group considered that the cardiovascular and survival benefits of intensive SBP control outweighed the observed increases in the risks for hyperkalaemia, hypokalaemia and acute renal injury [36].However, evidence supporting the SBP target <120 mmHg is less certain in some subpopulations, including patients with diabetes, advanced CKD (G4 and G5), significant proteinuria (> 1 g/day), baseline SBP 120-129 mmHg, in younger than 50 years or very old (age> 90 years), as well as those with "white coat" or severe hypertension [10], table 4. For example, the ACCORD trial studied exclusively patients with diabetes and randomized them to the same SBP targets as in SPRINT (<120mmHg, vs<140mmHg), but excluded those with a serum creatinine levels >132.6 umol/L and those with proteinuria >1g/day. Intensive BP control resulted in a lower risk for stroke, but without a statistically significant reduction in overall CV events. The analyses of ACCORD suggest a CV benefit of the lower BP target in the group with standard glucose control, but not in the group with intensive glucose control [8,43,44].However, for a similar SBP lowering, there was a greater risk of eGFR decline in patients with diabetes in ACCORD-BP than in patients without diabetes in SPRINT [45]. Therefore, the KDOQI (Kidney Disease Outcomes Quality Initiative) work group commented that the risk-benefit ratio of lower SBP target in patients with CKD and diabetes requires further research in randomized controlled trials, and currently considers an SBP target of <130 mmHg to be a more reasonable target in this subpopulation [46].

Table 4. Certainty of evidence supporting an SBP target of <120 mmHg for patients with CKD

More certain
Age >50 y
High risk for cardiovascular disease
Less certain
Age <50 or >80 y
Diabetes with CKD
CKD G4 or G5*
Proteinuria >1 g/d
White coat hypertension
Pretreatment SBP of 120-129 mmHg
Prior stroke
Very low DBP
Polycystic kidney disease
Severe hypertension – e.g., SBP >180 mmHg while receiving no treatment or ≥150 mmHg despite >4 antihypertensive agents

Abbreviations: CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure;
*CKD G4-G5 indicates estimated glomerular filtration rate <30 ml/min/1.73m^2.

Uncertainty about benefits and risks of intensive BP lowering in different subpopulations does not mean that intensive BP lowering is not warranted, but suggests that the potential adverse effects should be taken into consideration when deciding on the BP target for individual patients. Inconsistency in recommendations for treatment target SBP may contribute to physician confusion: ACC/AHA (American College of Cardiology/American Heart Association) BP guideline offers a target of<130/80 mmHg for patients with CKD, which is more aggressive than that recommended by the European Society of Cardiology/European Society of Hypertension (ESC/ESH; SBP target 130-139 mmHg), and different from that recommended by the National Institute of Health and Care Excellence (NICE; SBP target 120-139 mmHg) [15,16,47]. ESC also published a 2021 Clinical Guideline on Cardiovascular Disease Prevention in Clinical Practice that recommend office BP targets for people with CKD<140–130 mmHg SBP (lower SBP is acceptable if tolerated) and <80 mmHg DBP [48]. In practice, it should be borne in mind that it would be potentially hazardous to apply the recommended SBP target of <120 mmHg to BP measurements obtained in a non-standardized manner. It is also reasonable to use less intensive therapy for BP lowering in patients with very limited life expectancy or symptomatic orthostatic hypotension [10].

CHOICE OF ANTIHYPERTENSIVE DRUGS

Recommendations for the choice of antihypertensive therapy in CKD are based on evidence that renin-angiotensin system inhibitors (RASI), ACEI and ARB, reduce both CV events rates and kidney end points among patients with CKD. The strength of the evidence varies from strong in the CKD subpopulation with low eGFR and severely increased albuminuria to weak or absent in the subpopulation with normal eGFR without albuminuria. Many patients with CKD will need a combination of 2 or more antihypertensive drugs, but there are no randomized controlled trials comparing different combination therapies in CKD. Therefore, any algorithm for antihypertensive treatment in CKD is based on expert opinion, pathophysiological or pharmacodynamic considerations, or extrapolation from findings in the general population [10].

In patients with high BP, CKD(G1-G4) and severely increased albuminuria (A3) without diabetes, it is recommended to start RASI therapy (ACEI or ARB) [10]. Evidence supporting this view is based on the results of several placebo-controlled randomized trials, which confirmed the effects of this therapy on reducing the risks for both adverse renal outcomes and CV events [49-51].

In patients with high BP, CKD (G1-G4) and moderately increased albuminuria (A2) without diabetes, it is recommended to start

RASI therapy (ACEI or ARB) [10]. This is a weak recommendation, because there is no high-quality evidence from randomized controlled trials evaluating kidney outcomes in this subpopulation. The recommendation relies heavily on the results of the HOPE (Heart Outcomes and Prevention Evaluation) trial, which showed a CV benefit of ramipril compared to placebo, independent of BP, in patients with moderately increased albuminuria [52].

In patients with high BP, CKD (G1-G4) and moderate to severe albuminuria (A2 and A3) with diabetes, it is recommended to start RASI therapy (ACEI or ARB) [10]. Strong evidence from IDNT (Irbesartan Diabetic Nephropathy Trial) and RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) indicates that RASI, compared with placebo or calcium channel blockers (CCBs), reduces risk for kidney events in diabetics with severely increased albuminuria [53,54]. MICROHOPE (Microalbuminuria, Cardiovascular, and Renal Outcomes Substudy of Heart Outcomes Prevention Evaluation) found a reduction in CV risk in patients with diabetes and moderate albuminuria who were randomized to ramipril [55,56]. Meta-analysis by the KDIGO ERT (Evidence Review Team) showed that ACEIs compared with placebo had no effect on all-cause mortality but significantly reduced the risk for doubling of serum creatinine and progression of albuminuria from category A2 to A3 [10].

The KDIGO guideline highlights several practical points to pay attention to. The first point suggests that RASI (ACEI or ARB) would be a reasonable choice of therapy for people with high BP, CKD, and no albuminuria, with or without diabetes.Based on some research [57], the KDOQI work group believes that a diuretic or CCB would be equally reasonable choice as a first-line treatment for high BP in patients with CKD and without diabetes and no albuminuria [46], which is also recommended by the ACC/AHA guideline [15]. The need to use RASI (ACEI or ARB) in the highest approved dose that is tolerated is further emphasized, because the described benefits were achieved in trials using these doses. Changes in BP, serum creatinine, and serum potassium should be checked within 2-4 weeks of initiation or increase in the dose of a RASI, depending on the current eGFR and serum potassium. Hyperkalaemia associated with use of RASI can often be managed by measures to reduce serum potassium levels, rather than decreasing the dose or discontinuing RASI. ACEI or ARB therapy should be continued unless serum creatinine rises by more than 30% within 4 weeks of starting treatment or increasing the dose. Dose reduction or discontinuation of ACEI or ARB should be considered in the setting of either symptomatic hypotension or uncontrolled hyperkalaemia despite medical treatment, or to reduce uremic symptoms during treatment of kidney failure (eGFR <15 ml/min/1.73 m^2). Mineralocorticoid receptor antagonists (MRA) are effective for treatment of refractory hypertension, but may cause hyperkalaemia or reversible decline in kidney function, particularly in patients with low eGFR [10].

Special recommendation is to avoid any combination of ACEI, ARB, or direct renin inhibitors (DRI) in patients with CKD, with or without diabetes. This is a strong recommendation based on evidence from randomized controlled trials of sufficient duration to evaluate kidney and CV protection.There is growing evidence that dual RAS blockade does not lead to long-term CV or kidney benefit despite lowering proteinuria in the short term, and on the other hand increases the risks of hyperkalemia and AKI [10]. A large meta-analysis comparing the effects of monotherapy and dual RAS blockade in patients with CKD, with and without diabetes, found no significant differences in all-cause mortality, progression to end-stage CKD, and CV events between two groups [58]. In contrast, there is evidence that dual blockade of RAS in patients with CKD, with and without diabetes, increases the incidence of AKI by 40% compared to monotherapy [9,59]. Therefore, it can be considered justified that this recommendation places a higher importance on preventing hyperkalemia and AKI than on the potential benefits in reduction of albuminuria [46].

Most patients with CKD will require multiple antihypertensive therapy with ACEI or ARB in addition to CCB and diuretics to achieve target BP values. An instrumental variable analysis by Markovitz et al demonstrated an incremental reduction in SBP and cardiovascular risk with the addition of each additional antihypertensive agent in SPRINT [60]. Diuretics are often used in CKD patients with high BP due to pre-existing hypervolemia, but the literature on the effects of diuretics on major clinical

outcomes in this population is limited. Limited data have shown that the addition of an MRA, such as spironolactone, eplerenone, or finerenone, to an ACEI or ARB for renoprotection in CKD patients reduces blood pressure and urinary protein/albumin excretion with a quantifiable risk of hyperkalaemia [61]. The recent FIDELIO-DKD trial (The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) in CKD patients with diabetes showed a kidney and cardiovascular protection by finerenone, despite its modest effect on SBP and higher incidence of hyperkalemia-related events [62].

CONCLUSION

The updated 2021 KDIGO BP clinical practice guideline insists on standardized office BP measurement and recommends a target SBP <120 mm Hg in most subpopulations of CKD patients, provided this technique is used. The implementation of standardized BP measurement in a busy clinical practice is recognized as a challenge, but is fundamental to the practice of evidence-based medicine, because the available evidence for treatment recommendations is derived from the studies in which BP was measured in this way. That means the adoption of a target SBP <120 mmHg is inextricably linked to the technique of standardized office BP measurement, and kidney and cardiovascular benefits that would result from long-term intensive BP reduction in patients with CKD depend on it. Given the importance of these goals and the existing resistance to standardization of the method, it is possible that the new measures will require the regulatory enforcement of standardized BP measurement protocols in routine clinical practice.

Regardless of the recommended target SBP, the KDIGO work group warns of caution in certain subpopulations of CKD patients, pointing out that it is reasonable to apply less intensive BP targets in people with very limited life expectancy or symptomatic orthostatic hypotension. This suggestion supports physician autonomy and shared decision making, depending on patient characteristics, tolerability, and preferences, in order to select patients who are most likely to benefit from more intensive BP lowering. Large randomized controlled trials on the effects of intensive BP lowering for cardiovascular, kidney, and cognitive outcomes and/or survival in CKD patients are needed, particularly in subpopulations that were not adequately represented in previous studies. There is also an urgent need for randomized trials comparing the effects of different combinations of antihypertensive drugs on outcomes, which would contribute to the development of evidence-based algorithms for hypertension treatment in CKD.

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Vol. 47 (2022) No. 2-3 TIMOK MEDICAL GAZETTE Review article

PROTON PUMP INHIBITORS: ASSESSMENT OF SIDE EFFECTS AND APPLICATION IN COVID-19 INFECTION

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

(1) OFFICE FOR INTERNAL MEDICINE „DR BASTAĆ“, ZAJEČAR; (2) SPECIALIST OFFICE FOR INTERNAL MEDICINE "DR PAVLOVIĆ CARDIOLOGIA" BELGRADE

Summary: Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs. Their use is probably even higher than estimated due to the increase in the number of PPIs available over the counter. These medications are often prescribed for inappropriate indications or unnecessarily long treatment. The increased use of PPIs in the last two decades has called into question the long-term effects of these drugs. There are data from observational studies that indicate that long-term use of PPIs increases the risk of chronic kidney disease, dementia, osteoporosis, pneumonia, gastrointestinal tract infections, malabsorption of minerals and vitamin B12, as well as the risk of infection and a more severe course of the disease, COVID-19. However, the aforementioned suspicions do not yet have enough evidence to confirm a causal link between the disorder and PPI use, and even when there is a perceived risk, it is generally small. There is a need for better quality studies investigating this relationship. Proton pump inhibitors prescribed for the appropriate indication and for the appropriate duration of treatment are still safe drugs that bring more benefits to patients than risks.
Keywords: proton pump inhibitors, side effects, COVID-19

INTRODUCTION

Proton pump inhibitors (PPIs) are the most potent group of drugs used to suppress gastric acid secretion. With the appearance of these drugs at the end of the eighties of the last century, the treatment of acid peptic disorders has radically changed. PPIs are becoming one of the most prescribed drug groups in the world. In the pharmacotherapy of gastrointestinal disorders, they significantly suppressed the use of histamine H2 blockers, as another important or older group of antisecretory drugs.

The benzimidazole derivative - omeprazole was the first PPI introduced in 1988, and today there are others on the market: lansoprazole, rabeprazole, pantoprazole and esomeprazole (the active C-isomer of omeprazole). Their use in the world is growing year by year. PPIs are the second group of drugs in the number of prescribed and issued prescriptions in the USA in 2008, right after statins. The results of three different studies showed that 40-71.4% of patients treated in hospitals received PPIs, of which even 65-70% of patients had no real indication for their use [1]. In 2016, 839,548 PPI prescriptions were issued in Slovenia (4.7% of all prescriptions), and their representative drug pantoprazole is the second most commonly prescribed active ingredient after paracetamol. As PPIs are also available without a prescription, the actual consumption is probably even higher [2].

There are many indications for PPI treatment. Among them we include: peptic ulcer of the stomach and duodenum, dyspepsia, bleeding and prevention of bleeding from the upper parts of the gastrointestinal tract (due to non-steroidal anti-inflammatory drugs, antiplatelet, anticoagulant and corticosteroid therapy), prevention of bleeding in critically ill patients, eradication of Helicobacter pylori infection, gastroesophageal reflux disease, Barrett's esophagus, eosinophilic esophagitis and Zollinger-Ellison syndrome. Because of their exceptional efficacy and absence of serious side effects, the number of "indications" for PPIs gradually expanded to include various, even ill-defined problems without a convincing causal link to stomach acid. Regardless of the specialty of the doctor who prescribed the PPI, the proportion of inappropriately prescribed PPIs is alarmingly high, as it often exceeds 50% [3]. The following is a brief critical review of the possible side effects of long-term PPI use.

KIDNEY DISEASE

PPIs are a known trigger of acute interstitial nephritis, and recent research suggests an association between PPI treatment and the onset of chronic nephritis. In studies from 2014 and 2016, 72 cases of acute interstitial nephritis were diagnosed in a cohort of 572,661 patients with newly prescribed PPIs. The risk was fivefold higher in patients taking PPIs, the highest in patients older than 60 years [4,5]. A 2015 study involving 290,592 patients over 65 years of age taking PPIs and the same number of controls identified 40 cases of acute interstitial nephritis. The risk of acute kidney damage in patients treated with PPIs was 2.5 times higher [6]. Acute interstitial nephritis can be overlooked, and further treatment with the active substance that triggered the inflammation leads to the development of chronic kidney disease [5]. The relationship between PPI treatment and chronic kidney disease has been studied in four large studies [7–10].

In a study published in 2016, 10,482 patients were treated; PPIs were given to 3% of patients. Compared to patients who did not use PPIs, they had a statistically significantly higher body mass index and an increased prevalence of arterial hypertension. The absolute risk of chronic kidney disease in patients on PPIs was higher by 3.3% [7]. Xie et al. found a 1.22 times higher risk for chronic kidney disease when using PPIs [8]. A slightly higher risk was shown in PPI dosing twice a day, while no increased risk was observed in patients treated with histamine H2 receptor antagonists [9]. A 2017 study by Klatta et al showed that in patients treated with PPIs, prolonged duration of this therapy was associated with an increased risk of adverse renal outcomes, and that the risk of doubling serum creatinine concentration was 1.26 times higher than in users of histamine antagonists. H2 receptors [10]. Given the design of the mentioned research (retrospective, observational studies), we cannot unequivocally conclude about a cause-and-effect relationship between PPI treatment and the development of chronic kidney disease. These shortcomings can only be avoided by planning prospective randomized studies.

DEMENTIA

Research conducted on a population of mice showed that PPIs accelerate the formation of beta amyloid, and at the same time, by acting on the proton pumps of lysosomes, prevent its degradation [11]. In a German cohort study on a sample of 3,327 elderly people, during an 18-month follow-up with a structured neurological assessment, 431 cases of dementia were identified, including 260 cases of Alzheimer's disease [12]. Patients treated with PPIs had a 1.38 times higher score of any form of dementia and a 1.44 times higher risk of Alzheimer's disease. In an extended German cohort study with 73,679 elderly people, 29,510 cases of dementia were identified based on coded diagnoses in the insurance database, and PPI users were found to be 1.44 times more likely to have dementia [13]. Differences between groups in age, sex, number of regularly prescribed drugs and history of stroke, ischemic heart disease and diabetes were equalized using statistical methods. A similarly high risk was found in an Asian retrospective study, which was also based on insurance data [14]. The above findings are in contrast to the findings of the Finnish case-control study. The study included 70,718 patients diagnosed with Alzheimer's disease between 2005 and 2011 [15]. They found that PPI use was not associated with a higher incidence of Alzheimer's disease, and no higher risk was identified in patients taking higher doses of PPIs or taking them for longer periods of time.

A 2020 study from Great Britain based on a population of 3,765,744 people, using health data from multiple centers in Wales, could not confirm an association between PPI use and an increased risk of dementia. Previously reported associations may be related to uncertain data on PPI use or medications used for cardiovascular disease or depression. The results of two smaller studies with approximately 10,000 subjects also do not show a conclusive link between PPI use and dementia [17,18]. Although the mentioned studies indicate a possible safety risk when using PPIs in the elderly, the findings of the Finnish study with the most and most accurately diagnosed cases of Alzheimer's disease question the described causal relationship - the risk did not depend on the dose of PPIs or the duration of treatment.

OSTEOPOROSIS AND BONE FRACTURES

The mechanisms of bone damage associated with PPIs are still unclear, but impaired micronutrient absorption,

hypergastrinemia, and increased histamine secretion may play a role. During PPI treatment, the pH in the stomach increases (the acidity of the gastric fluid decreases), therefore the secretion of gastrin is compensatory increased.

Animal studies may indicate that hypergastrinemia is caused by hyperparathyroidism, if at the same time there is a disorder of vitamin B12 absorption, and at higher pH values of the stomach contents, the concentration of homocysteine increases, all of which can affect bone density [11]. In a study published in 2022, it was shown that long-term administration of lansoprazole caused symptoms of osteoporosis in mice, and lansoprazole triggered an increase in calcium in osteoblasts. Intracellular calcium persisted in high concentration, thus causing endoplasmic reticulum stress and inducing osteoblast apoptosis [19]. In a meta-analysis of 10 studies on a sample of 223,210 fracture cases, a slightly increased risk of hip and vertebral fractures was revealed (1.25 times) and (1.50 times), respectively, while the difference in cases of wrist fractures was not statistically significant [20]. In three of the four included cohort studies, no increased risk of fracture was demonstrated, while in five of the six case-control studies, an increased risk was found (up to 1.62 times). A difference in the level of risk regarding the duration of treatment was not determined in the meta-analysis [2]. A recent meta-analysis confirmed an increased risk of hip and vertebral fractures also taking into account only cohort studies, but the duration of PPI treatment did not affect the level of risk - namely, the increased risk was recognized already in the first year of use and it did not change over time [21]. In previous research, a convincing association between PPI treatment and reduction of bone density has not been proven [22,23]. Therefore, it was not possible to assess a causal relationship between taking PPIs and the effect on bone density, as the risk was only slightly increased. However, clinicians should exercise caution when prescribing PPIs to subjects with a pre-existing high fracture risk and consider the use of anti-osteoporotic drugs to control this additional effect of PPIs on bone.

GASTROINTESTINAL INFECTIONS

Gastric acid has a bactericidal effect on the ingested microbiome, and the intestinal microbiota changes during PPI treatment [24]. The effect of both mechanisms can increase the likelihood of Clostridium difficile infection and other gastrointestinal infections. The association between PPI treatment and C. difficile infection was discussed in three meta-analyses, which found that patients treated with PPIs were 1.7 times more at risk of developing C. difficile infection than those not using PPIs [23– 25]. The risk is further increased in patients receiving antibiotics at the same time as PPIs. The studies were mostly retrospective and differed from each other in terms of criteria within the groups. The duration of therapy and the dose were registered in only one study, so with the mentioned remarks, no conclusion can be drawn about the causal relationship between the frequency of C.difficile infection and the use of PPIs. In a recent retrospective cohort study on a sample of 18,134 intensive care unit patients at particular risk of C.difficile infection, no additional risk of C.difficile infection from PPI therapy was identified [26]. As expected, the most important risk factor for C. difficile infection was the use of antibiotics.

Research on the incidence of bacterial infections from the genera Salmonella and Campylobacter are significantly less frequent than studies on C.difficile infection. In two studies, they found that infection with these strains was 6 times higher when PPIs were used [27,28]. A large retrospective cohort study of 1,913,925 patients and nearly 7,000 cases of Salmonella and Campylobacter infections showed a slight increase in the risk of these infections in the PPI group, but infections with these bacteria were more common in these patients even before PPI administration [29].

INFECTIONS OF THE LOWER RESPIRATORY TRACT

An elevated pH value in gastric juice can allow bacterial growth, and microaspiration of gastric contents can lead to pneumonia [11]. An association between PPI use and the development of host lower respiratory tract infection has been identified in several observational studies. In two older meta-analyses, no differences were found [30,31]. In a recent meta-analysis, the risk of developing pneumonia in people using PPIs is 1.5 times higher [32]. According to the vast majority of research, when using PPIs, the risk of lower respiratory tract infection is higher in the first month, most pronounced in the first week of use.

The results of a double-blind, randomized controlled trial with esomeprazole that included more than 9,000 patients showed no association between PPI use and respiratory infections [33]. Based on the time interval between PPI prescriptions, it appears that the onset of respiratory infection symptoms is most likely attributable to gastroesophageal reflux disease (GERD) [34]. Despite the undeniable shortcomings of study randomization, it is unlikely that lower respiratory tract infections have any proven clinically relevant causal relationship with PPI use.

CLOPIDOGREL AND PROTON PUMP INHIBITORS

Clopidogrel is a prodrug that is activated in the liver by the action of cytochromes (mainly CIP2C19). These enzymes also metabolize PPIs, especially omeprazole, esomeprazole, and lansoprazole. Due to competition for enzyme binding sites, it is therefore theoretically possible that concurrently prescribed PPIs reduce the efficacy of clopidogrel and thereby increase the risk of cardiovascular events [11]. In a meta-analysis, which included research results up to February 2014 (39 studies with 214,851 patients, of which 73,731 received clopidogrel and PPIs simultaneously) [35,36] in patients who received both drugs simultaneously, an increased risk for death, myocardial infarction, blood vessel thrombosis and cerebrovascular event. If we consider only randomized trials and cohort studies with statistical equalization of initial differences between groups of patients, increased CV risk is not observed. However, whatever the study criteria included, it is evident that the risk of gastrointestinal bleeding in patients receiving clopidogrel and PPIs was significantly lower. Most authors conclude that the difference in conclusions between the randomized and nonrandomized studies is likely due to the underlying increase in cardiovascular risk in patients receiving PPIs in the nonrandomized studies. There is no convincing evidence to challenge the use of PPIs in combination with clopidogrel, but it may make sense to use pantoprazole or rabeprazole, which are metabolized by other pathways [37].

There is not much work to conclude on the interaction between PPIs and the newer antiplatelet agents, ticagrelor and prasugrel.

TUMORS OF THE GASTROINTESTINAL TRACT

Proton pump inhibitors cause compensatory hypergastrinemia and at the same time interfere with mucus secretion from the gland in the fundus of the stomach [11]. Long-term PPI treatment with concurrent H. pylori infection can worsen gastritis (caused by H. pylori infection) and lead to atrophy of the gastric mucosa, which is a possible pathophysiological mechanism of gastric carcinogenesis. In vitro studies have shown the trophic effect of gastrin on colon adenocarcinoma cells. A meta-analysis showed that long-term, at least one-year use of PPIs was associated with a 2.45-fold increased risk (range 1.03 to 10.7-fold) for the formation of gastric fundic gland polyps [38]. Fundic gastric polyps associated with PPI use are clinically insignificant and do not pose a risk of malignancy. The appearance of dysplasia in these polyps is extremely rare, therefore there is no need for endoscopic monitoring and polypectomy. Data on the association between PPIs and gastric adenocarcinoma are not consistent [39]. Two meta-analyses found that the risk of gastric cancer with PPI use was up to 1.5 times higher, but the possibility that PPIs were actually prescribed to treat early unrecognized symptoms of gastric cancer in these studies could not be excluded. Likewise, several studies did not provide data on the presence of H. pylori infection. Also, there is no convincing evidence of gastric neuroendocrine tumors as a consequence of PPI therapy, although moderate hypergastrinemia has been demonstrated with their use [40,41]. Individual examples of findings of neuroendocrine tumors when using PPIs are most likely coincidental without a proven cause-and-effect relationship with PPIs [41]. The link between long-term PPI use and colorectal cancer has not been proven either. An extensive post-marketing analysis at the request of the Food and Drug Administration (FDA) did not show a higher risk of developing tumors of the digestive organs in people who used PPIs [42,43].

Although the authors of the latest retrospective study of 973,000 new users of PPIs and 198,000 new users of histamine-2 receptor antagonists suggest that the absolute increase in gastric cancer risk with PPI use is very small, they support the need to avoid long-term PPI use when not medically indicated. [44]

VITAMIN AND MINERAL ABSORPTION DISORDERS

An elevated pH value in the stomach can reduce the absorption of iron and vitamin B12, while the pathophysiological mechanism of hypomagnesemia is unclear [11]. A retrospective cohort study [45] and a case-control study [46] identified an increased risk of iron deficiency depending on the dose and duration of PPI treatment. A risk for reduced iron absorption was also observed in a controlled study with histamine H2 receptor antagonist therapy. In the extended phase of two randomized trials (12 and 5 years, respectively) comparing the efficacy of PPIs and antireflux surgery, it was found that there were no differences in iron stores between these groups of subjects [47].

Although the cause-and-effect relationship and the influence of other variables on the reduction of iron levels in such designed studies cannot be reliably assessed, the influence of PPIs should also be considered if there is iron deficiency in people who use PPIs for a long time and regularly.

Data on hypovitaminosis B12 in people using PPIs are conflicting.

In a case-controlled study involving 25,956 patients with vitamin B12 deficiency and 184,199 controls, a 1.65-fold increased risk for hypovitaminosis B12 was found in patients receiving PPIs for more than two years [48]. In the previously mentioned randomized trials on the effectiveness of antireflux surgery or PPIs, there were no differences between groups regarding vitamin B12 deficiency [47].

There are completely different data on hypomagnesemia. The results of a meta-analysis of nine observational studies showed a 1.43-fold increased risk of hypomagnesemia [49], while a later prospective cohort study on a sample of 9,818 patients with long-term PPI use reported a clinically insignificant decrease in serum magnesium levels. At the same time, the risk of hypomagnesemia was highest in patients who simultaneously used a loop of Henle diuretic [48]. In a study of a sample of 414 patients who received PPIs for at least 6 months and were followed for an average of 5.7 years, 57 cases of hypomagnesemia were found. At least one additional causative factor of hypomagnesemia was present in 44 of them. In addition, hypomagnesemia was mild and asymptomatic in most cases [49].

Hypomagnesemia is probably an idiosyncratic effect of PPIs that we should consider in the absence of another clear cause of said electrolyte disturbance.

COVID-19 AND PROTON PUMP INHIBITORS

In early 2020, there were reports that PPIs could have a beneficial effect on the course of SARS-CoV-2 viral infection [50,51]. At the same time, there were reports of more severe disease progression in patients taking PPIs simultaneously, due to more frequent secondary infections and acute respiratory distress syndrome (ARDS) [52]. Reduced secretion in the stomach is "blamed" for that. Namely, the hypoacidic environment reduces the probability of eradication of introduced pathogens or allows them to grow in the intestines. Later published data from a meta-analysis of 5 studies suggested that there is a relationship between taking PPIs and a higher risk of severe disease from COVID-19 [53], as well as an increased likelihood of SARS-CoV-2 infection [54]. A pooled analysis of data from three of the five mentioned studies showed an almost 50% higher risk of a severe form of the disease, that is, of a fatal outcome of COVID-19 in patients receiving PPIs. [55–57]. Another pooled analysis showed a significantly increased risk of secondary infections in patients receiving PPIs [52,58].

A large meta-analysis published in February 2022 aimed to address the relationship between PPI use and severity of COVID-19 infection. A systematic literature search was conducted from December 2019 to January 2022. 14 studies were included. Susceptibility to infection with COVID-19, severity of COVID-19 (defined as a composite of adverse outcomes: admission to intensive care, need for oxygen therapy, need for ventilatory support, or death) and mortality from COVID-19 were assessed. It was concluded that PPI use was marginally associated with a nominal but statistically significant increase in the risk of infection with COVID-19. PPI use also increased the risk of complications and poor outcomes in patients with COVID-19. The study also concludes that the increased risk of COVID-19 infection in PPI users is only marginal and therefore does not merit prophylactic discontinuation of PPIs in patients for whom this drug is indicated. This study suggests that PPIs increase the risk of poor clinical outcomes in patients with COVID-19; therefore, PPIs should

be initiated with caution in this population. All patients with COVID-19 using PPIs should be closely monitored for severe or co-morbidities. Current evidence is insufficient to recommend discontinuation of PPIs in patients with COVID-19. Further studies are needed to consolidate the findings. Furthermore, future studies should investigate whether the variant of COVID-19 influences the association of PPI use with the susceptibility and prognosis of COVID-19 [59].

CONCLUSION

PPIs have an excellent safety profile marred by frequent prescribing for the wrong indication, or inappropriate and unnecessarily long duration of treatment. Despite the widespread use of PPIs, data on adverse effects are based almost exclusively on the results of observational studies, which are, however, unsuitable for defining causality. The identified levels of associated risk with the use of PPIs are generally small and insufficient to rule out the possibility of research bias. It is unrealistic to expect that randomized studies can be conducted for all potential side effects of PPIs, although only in this way can we reasonably conclude about possible causality.

Proton pump inhibitors are very effective if they are indicated for peptic ulcer, dyspepsia, prevention of bleeding from the upper gastrointestinal tract due to non-steroidal anti-inflammatory drugs, antiplatelet and anticoagulant drugs, in the prevention of bleeding in critical patients, eradication of Helicobacter pylori infection, gastroesophageal reflux disease, treatment of Barrett's esophagus, eosinophilic esophagitis and Zollinger-Ellison syndrome. For now, until we get the results of new qualitative research, which would show different results, and with a sober consideration of indications, doses and duration of treatment, we consider PPIs to be safe drugs where the benefits of the treatment outweigh the potential risks.

In patients with COVID-19, an individual assessment of the benefits and risks of taking PPIs is required or a regular check of the indications for taking PPIs in the lowest, still effective doses or substitution for otherwise less potent histamine-2 receptor inhibitors.

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Vol. 47 (2022) No. 2-3 TIMOK MEDICAL GAZETTE Review article

DAMAGE TO THE CARDIOVASCULAR SYSTEM AND COMPLICATIONS IN COVID-19 INFECTION WITH A FOCUS ON THE POST-ACUTE COVID19 SYNDROME

Mila Bastać (1), Dušan Bastać (2), Anastasija Rašanin (2), Zoran Joksimović (2), Vojkan Čvorović (3), Biserka Tirmenštajn Janković (4), Stanislav Tadić (1), Jasna Strajnić (4), Maja Mladenović (4), Igor Đorđioski (4)

(1) MEDSCAN TADIĆ DIAGNOSIS, ZAJEČAR; (2) "DR BASTAĆ" INTERNIST'S OFFICE, ZAEČAR; (3) BEL-MEDIC, BELGRADE; (4) ZC ZAJEČAR

ABSTRACT: The causative agent of severe acute respiratory syndrome, corona virus 2 (SARS-CoV-2), the etiological agent of the COVID-19 disease, can infect the heart, vascular tissues and circulating cells via angiotensin-converting enzyme 2 (ACE-2), a cell receptor host for the viral spike protein. The focus of this review article is on the prevalence, risk factors, pathogenesis, clinical course and sequelae of myocardial damage caused by the disease COVID-19. Emphasis is also placed on the interactions of platelets with the vascular endothelium, which includes consideration of the role of the SARS-CoV-2 virus protein in triggering the development of generalized endothelitis, which further in a circle triggers more intense activation of platelets. Acute cardiac lesion is a common extrapulmonary manifestation of COVID-19 with potential chronic consequences. Clinical manifestations include direct cardiac damage and indirect immune response mechanisms that affect the cardiovascular (CV) system and have implications for the treatment of patients after recovery from acute COVID-19 infection. **The most common direct cardiovascular lesion** is an acute heart lesion, present in more than 12% of all infected patients and defined by a significant increase in cardiac troponins in the serum and echocardiographic signs of damage to the myocardial texture due to inflammation, impairment of segmental mobility or global systolic and diastolic function of the left ventricle and sometimes inflammation of the pericardium. Arrhythmias, venous thromboembolism and cardiomyopathy are predominant KV manifestations described in the patient with COVID- 19. An analysis of 72,314 confirmed cases of COVID - 19 (Wuhan) showed total mortality of 1663 patients or 2.3%, with presence of a previous KV disease in 10.5%, diabetes Mellitus in 7.3% and arterial hypertension in 6%. Cardiovascular complications because of COVID-19 associated with comorbidities were: myocardial lesion (20 %), cardiac arrhythmias (16%), myocarditis and fulminant myocarditis with lowered ejection fraction (10%), non-occlusive myocardial infarction and venous thromboembolism and acute‘ cardiac insufficiency and cardiogenic shock. Hypertension and diabetes are the most frequent_comorbidities in those infected with COVID-19, for whom hospitalization was necessary. A Denmark study based on the national register of over 5000 patients with hospitalized COVID-19 revealed that the risk from the acute myocardial infarction and ischemic stroke was 5 and even 10 times higher , respectively , during the first 14 days after COVID- 19 infections in comparison with the period which preceded the known infection. Numerous individual cases point to extremely high values and troponin T dynamics typicalfor non-occlusive myocardial infarction with normal coronary arteries. **Mechanisms of indirect cardiovascular lesions** are: dysregulation of inflammatory or immune responses of hyperinflammation, vascular thrombosis and activation of platelets, autoimmune phenomena and adaptive immunological dysfunction in vascular thrombosis associated with COVID- 19. Cardiovascular dysfunction and disease are often fatal complications of a severe COVID- 19 virus infection. Cardiac complications can occur even canin patients without basic cardiac insufficiency, as a part of acute infections and they are associated with a more severe form of COVID 19 disease and increased mortality. Of COVID-19 patients treated in the intensive care unit 61% died because they had acute respiratory distress syndrome (ARDS), 44% of them had severe cardiac arrhythmias and 31% percent of them experienced a shock syndrome. Elevated troponin levels were rare in survivors of uncomplicated COVID-19 (1%–20%), common in critically ill patients (46%–100%), and almost universally elevated in critically ill (ie, those requiring intensive care or mechanical ventilation) and those who did not survive. Some autopsy findings suggested myocardial infiltration by mononuclear leukocytes and revealed some cases of severe myocarditis with a dilated phenotype. Among patients hospitalized with COVID-19, evidence about

acute damage of cardiac functions are frequent _ and include the following: acute cardiac insufficiency (3%-33%), cardiogenic shock (9%-17%), ischemia or myocardial infarction (0.9%–11%), left ventricular dysfunction (10%–41%), right ventricular dysfunction (33%–47%), biventricular dysfunction (3%–15%), stress cardiomyopathy (2%–5.6%), arrhythmias (9%–17%), venous thromboembolism (23%–27%) and arterial thrombosis as secondary viral mediated coagulopathy. COVID - 19 is associated with abnormalities of cardiac structures and functions including echocardiographic evidence of left ventricular dysfunction, regional wall movement abnormalities and mild reduction of right ventricular function. Involvement of myocardial lesion because of SARS - CoV -2- infection was very much widespread even in patients with mild symptoms.

Key words: COVID-19, ACE 2 receptor, acute myocardial lesion, venous thromboembolism, non-occlusive myocardial infarction, myocarditis, cardiovascular diseases, corona virus, post-acute COVID- 19

INTRODUCTION

Corona Virus Disease 2019 (COVID-19) has brought the life of the whole humanity to a standstill. Catastrophic loss of life, a confusion in healthcare and the vulnerability of the global economy are some of the outcomes of this pandemic. COVID-19 infection affects global population regardless of age and gender, and with comorbidities present, COVID-19 and its complications escalate at an alarming rate. Cardiovascular (CVD) diseases per se are the leading cause of death globally with an estimated 31% of deaths worldwide of which nearly 85% are due to heart attack and stroke. Scientific researchers have noted that individuals with pre-existing CV diseases and conditions are relatively more susceptible to infection with COVID-19 [1,2]. Moreover, it was shown in the comparison between subgroups: milder and more severe cases, survivors and non-survivors, patients from intensive care units and those who were not in intensive care [2]. The impact of the COVID-19 preventive measures of isolation and quarantine (lockdown) on CVD patients in Denmark showed that at that time, compared to the pre-Covid 19 era, there was no difference in the mortality of CVD patients. However, an increased out-of-hospital mortality and decreased in-hospital mortality were found. In contrast, in Germany and France, there was a significant increase in mortality, even by 12-20% in CV patients in April 2021.

Strategies for the diagnosis of SARS-CoV-2

The diagnosis of COVID-19 is based on a combination of epidemiological criteria (contact within the incubation period), the presence of clinical symptoms, laboratory tests (PCR tests) and tests based on clinical imaging. Antibody-based tests and SARS-CoV-2 antigen enzyme-linked immunosorbent assay (ELISA) are under development and not yet fully validated. Widespread testing has proven effective in the containment phase of the epidemic. The quality of sample collection (deep nasal swab) and transport (time) to the laboratory is necessary to avoid false negative results. Lung computed tomography (MSCT) can be used as a diagnostic test for COVID 19 [3] .

We know that the penetration of the SARS COV-2 virus and the cause of the COVID-19 infection, after a short incubation and various respiratory symptoms, loss of the sense of smell and general symptoms: elevated body temperature, malaise, myalgia and arthralgia, most often affect the lung parenchyma . At the beginning lung damage manifests like flu syndrome (cough and fever), which is progressing to the pneumonia (dyspnea, hypoxemia , tachypnea) and , in some cases , to _ acute respiratory distress syndrome or non-cardiogenic pulmonary edema (ARDS).

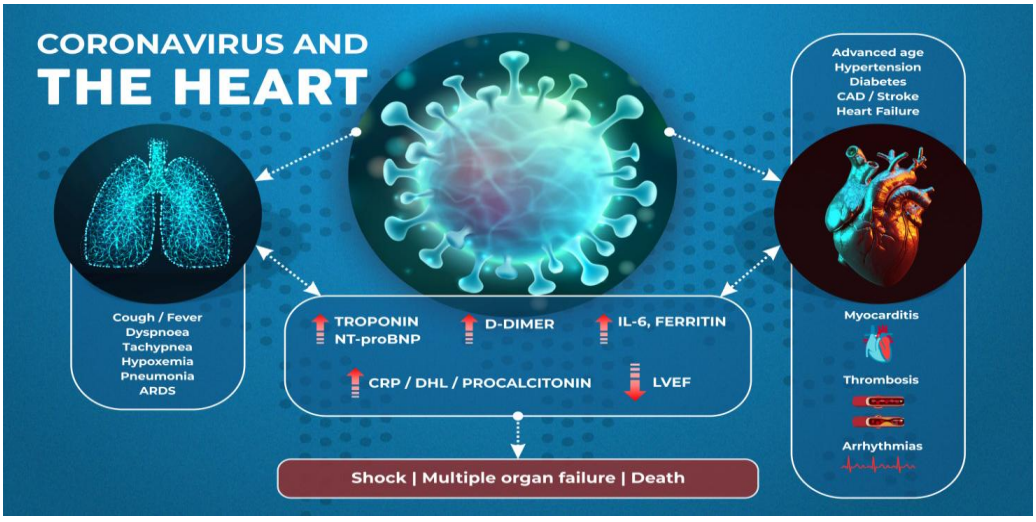
Acute cardiac lesion is an ordinary extrapulmonary manifestation of COVID- 19 with potential chronic consequences. Clinical manifestations include directcardiac involvement and mechanisms of indirect immune response which affect the cardiovascular system and implications on the treatment of patients after the recovery from the acute COVID- 19 infections [4]. Early radiography of the lungs and the heart and the most reliable MSCT (multilayer, multidetector computer-tomographic scan) of the thorax show detectable changes in the lung parenchyma in up to 85% of patients, which can be both oligosymptomatic and asymptomatic [5].

PATHOGENESIS OF ACUTE COVID-19 MYOCARDIAL LESIONS

Acute COVID-19 myocardial lesion whose marker is elevated high-sensitivity troponin T is

present in > 12% of infected patients [6]. Hence, cardiac lesions in patients infected with the SARS COV-2 virus become associated with higher morbidity and mortality. [6]. Severe acute respiratory distress syndrome-caused by coronavirus 2 (SARS-CoV-2) is manifested by the dominance of excessive production of inflammatory cytokines (IL-6 and TNF-α), which leads to systemic inflammation and syndrome of multiple dysfunction of organ systems, acutely involving the cardiovascular system. Hypertension (56.6%) and diabetes (33.8%) are the most common comorbidities in those infected with COVID-19 who require hospitalization. Cardiac lesion, defined as elevated high-sensitivity troponins T and I, is significantly correlated with inflammatory biomarkers: interleukins 6 and 2 (IL-6, IL- 2) and C-reactive protein (hsCRP), hyperferritinemia and leukocytosis, and reflects a significant association of the myocardial lesion and inflammatory hyperactivity caused by viral infection [6]. In addition, mechanisms by which activated platelets intensify pre-existing endothelial activation and dysfunction, most likely caused by the release of platelet-derived calcium-binding proteins (SA 100A8 and SA 100A9), have been described. Coronavirus 2 (SARS-CoV-2), the etiological agent of COVID-19, can infect the heart, vascular tissues and circulating cells via ACE2 (angiotensin-converting enzyme 2), the host cell receptor for the viral spike protein. Endotheliitis caused by SARS-CoV-2 [1] involves the interaction of the viral spike (S-protein part of the virus, the so-called spike) protein with the endothelial enzyme that converts angiotensin 2 (ACE2 convertase) together with alternative mechanisms via nucleocapsids and viroporins. These events create a cycle of intravascular inflammation and coagulation driven by the SARS-CoV-2 virus, which significantly contributes to poor clinical outcome in patients with more severe forms of infection. Patients with risk factors and/or cardiovascular diseases are prone to developing severe forms of COVID-19 and its complications (FIGURE 1). The host's response to the virus leads to signs of systemic inflammation, with increases in markers of inflammation (hsCRP, procalcitonin, d-dimer, IL-6, ferritin, LDH) and myocardial lesions and/or cardiac dysfunction (troponin and/or NT-proBNP), which predisposes to acute heart failure, myocarditis, thrombosis and arrhythmias. These CV complications interfere with the host's response to the virus, which can lead to shock syndrome, multiple organ failure, and death [7]. (FIGURE 1)

FIGURE 1. Corona virus and the heart.



LEGEND: CAD: coronary artery disease; LDH: lactate dehydrogenase; LVEF: left ventricular ejection fraction; CRP: C-reactive protein; IL-6: interleukin-6; ARDS: acute respiratory distress syndrome [7]. *retrieved from https://abccardiol.org/wp-content/uploads/articles_xml/0066-782X-abc-20200279/0066-782X-abc-20200279-en.pdf*

COVID-19 AND CARDIOVASCULAR COMORBIDITIES

A meta-analysis of 6 studies from China with 72314 COVID-19 patients shows a high prevalence of arterial hypertension (17 ± 7%), diabetes mellitus (8 ± 6%) and cardiovascular disease (CVD) (5 ± 4%) as comorbidities [7, 8]. In 138 hospitalized patients with COVID-19 and pneumonia, Wang et al found a high prevalence of hypertension (31.2%), CVD (19.6%), and diabetes (10.1%), and these comorbidities lead to the most severe forms of COVID 19 which usually requires hospitalization (hypoxemia, need for treatment in intensive care), especially in the elderly (median 42-64 years old) [9]. Another meta-analysis of 7 studies, on 1576 out-of-hospital infected patients, shows the highest prevalence of comorbidities: hypertension (21.1%), diabetes (9.7%), cardiovascular diseases (CVD) (8.4%) and chronic respiratory diseases (1 .5%). By comparing severe forms of COVID-19 with moderate and mild ones, a statistical parameter was obtained: **ODDS** ratio **(OR)** - odds ratio for a bad outcome: for hypertension - 2.36 (95% CI: 1.46–3.83), for respiratory diseases – 2.46 (95% CI: 1.76–3.44) and the highest for cardiovascular diseases - 3.42 (95% CI: 1.88–6.22)/respectively [10].

MORTALITY IN RELATION TO PREVIOUSLY RELEVANT CHRONIC DISEASES

An analysis of 72314 confirmed cases of COVID-19 (Wuhan) found a total mortality of 1663 patients or 2.3%, with the presence of a previous disease: 10.5% with CV disease, 7.3% with diabetes mellitus and 6% with arterial hypertension. Cardiovascular complications due to COVID-19 associated with comorbidities were: myocardial lesion (20%), cardiac arrhythmias (16%), myocarditis (10%) and acute heart failure and cardiogenic shock (about 5%) [8,9,11, 12]. Guo et al, evaluating a cohort of 187 patients, found that those with myocardial lesions had a higher prevalence of hypertension (63% vs 28%), diabetes (30.8% vs 8.9%), coronary disease (32.7% vs 3%) and heart failure (15.4% vs 0%) and these are of older age (median 71.4 years) [9]. In a group of 191 patients, Zhou et al. compared those discharged from the hospital with those who died and those who died had a higher prevalence of hypertension (48%), diabetes (31%) and CVD (24%) [13].

CARDIOVASCULAR DISEASE IN PATIENTS WITH COVID-19

COVID-19 patients treated in the intensive care unit had the following diagnoses from which they died: acute respiratory distress syndrome (ARDS) in 61%, severe cardiac arrhythmias in 44% and shock syndrome in 31%. Some autopsy findings suggested myocardial infiltration by mononuclear leukocytes and revealed some cases of severe myocarditis with a dilated phenotype [14,15]. COVID-19, as well as earlier coronaviruses and influenza epidemics, suggest an association with acute coronary events, arrhythmias and exacerbation of chronic heart failure, but the data also suggest the development of DE NOVO cases of cardiovascular diseases and worsening of the existing ones [14]. Cardiac lesion in patients infected by SARS COV -2 virus (COVID - 19) is associated with higher risk from: myocardial infarction, fulminant myocarditis which quickly develops with lowered EF left ventricular function, arrhythmias, venous thromboembolism, cardiomyopathy which reminds of the acute heart attack with ST elevation - STEMI the so-called Takotzubo cardiomyopathy. In addition, SARS-CoV-2 tropism and interaction with the rennin-angiotensin-aldosterone system (RAAS), through the ACE2 receptor, enhances the inflammatory response and aggression to the heart, leading to the imperative position on the use of ACE inhibitors and angiotensin receptor blockers (ARBs, sartans) in infected patients. CV consequences lead to a poor prognosis, emphasizing the importance of their early detection and the introduction of an optimal treatment strategy [6]. Among hospitalized patients with COVID-19, evidence of acute impairment of cardiac function is common and includes the following: acute heart failure (3%–33%), cardiogenic shock (9%–17%), myocardial ischemia or infarction (0.9% -11%), ventricular dysfunction (left ventricular [10%–41%], right

ventricular [33%–47%], biventricular [3%–15%]), stress cardiomyopathy (2%–5.6%), arrhythmias (9%–17%), venous thromboembolism (23%–27%) and arterial thrombosis secondary to viral-mediated coagulopathy [4]. A Danish study based on a national registry of over 5000 hospitalized patients with COVID-19 found that the risk of acute MI and ischemic stroke was 5-fold and 10-fold higher, respectively, during the first 14 days after infection with COVID-19 compared with the period which preceded the known infection [16].

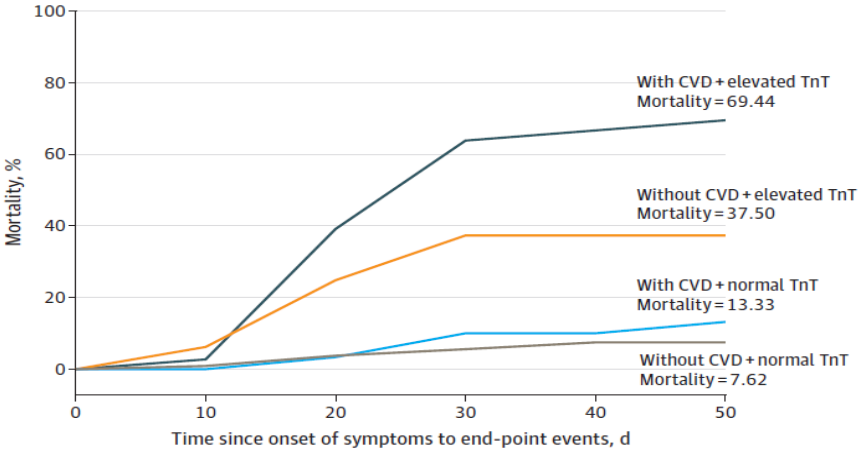
PROGNOSIS OF CVS DAMAGE IN COVID-19 AND PREDICTORS OF MORTALITY

The prognosis depends on the presence of CV risk factors (e.g. male gender, older age, population, hypertension, diabetes), comorbidities (e.g. coronary disease and other cardiac diseases, chronic obstructive pulmonary disease, chronic renal failure and malignancies) that predispose patients with COVID-19 to more severe forms of diseases and increased mortality [4]. Racial and ethnic disparities in the outcomes of COVID -19 are also evident [4]. Advanced age is an independent predictor of mortality in COVID-19 infection. The mortality rate increases with age as follows: 1.3% in patients aged 50-59 years; 3.6% in patients aged 60-69; 8% in patients aged 70-79 years; and 14.8% in patients older than 80 years. Population studies have reported an overall mortality rate of 6% in patients with hypertension, 7.3% in patients with diabetes, and 10.5% in patients with CVD. Patients with malignant tumors have a higher risk of COVID-19 due to impaired immune defenses and the consequences of antineoplastic treatment. In China, among confirmed cases of COVID-19, the prevalence of cancer ranged from 1% to 7%, which is higher than the total incidence of cancer in that country (0.2%). Patients with cancer were more likely to develop a severe form of COVID-19 compared to those without cancer (39% vs. 8%). Of cancer patients who had undergone recent chemotherapy or surgery, 75% developed severe disease compared with 3% of those who had not received recent treatment [17].

Biomarker evidence of cardiac lesion is strongly associated with worse outcomes in COVID-19. Elevation of cardiac biomarkers, such as NT-proBNP, Troponin(Tn) T and I or D-dimer, predicts poor clinical outcomes. In hospitalized patients with COVID-19, the prevalence of elevated hs-TnT (high-sensitivity troponin-T) is 20% to 30%. Based on such elevated Tn levels, acute myocardial lesions range from 8% to 62% according to various data, and more severe forms of the disease are associated with higher levels of cardiac biomarkers. Elevated Tn levels were rare in survivors of uncomplicated COVID-19 (1%–20%), common in critically ill patients (46%–100%), and almost universally elevated in critically ill (ie, requiring intensive care or mechanical ventilation and those who did not survive) [11].

Among 2736 hospitalized patients with COVID-19 in New York, even small elevations of Troponin I (>0.03–0.09 ng/mL) were associated with higher mortality.

DAMAGE to the myocardium and earlier CVD



Data of a retrospective study, of COVID-19 patients hospitalized in 7 hospitals in Wuhan in the period 23.01.-23.02.2020 [18].

Moreover, the greater the increase in TnT, the greater the risk of mortality [18]. Compared with those without elevated TnI, COVID-19 patients with elevated Tn have a higher risk of acute respiratory distress syndrome (58%–59% vs. 12%–15%), need for mechanical ventilation (22%–60% vs. 4% – 10%), malignant arrhythmias (17% vs 2% VT/VF) and death (51%–95% vs 5%–27%). Tn and NT-proBNP levels increased during hospitalization in non-survivors but not in survivors [11,13].

VISUALIZATION METHODS IN PROVING MYOCARDIAL LESIONS

COVID-19 is associated with abnormalities of cardiac structure and function including echocardiographic evidence of left ventricular dysfunction, regional wall motion abnormalities, and mild reduction in right ventricular function [19] . Several cardiovascular magnetic resonance (CMR) studies have documented myocardial abnormalities that persist after acute infection. In a study of 100 patients with COVID-19, imaging was performed an average of 71 days after the diagnosis of COVID-19. Pericardial effusion (>10 mm) was detected in 20% (20/100) of patients. Late gadolinium enhancement (LGE), reflecting fibrosis and cicatrix, was observed in 32% and was significantly more common in patients with COVID-19 than in healthy or risk-factor-matched controls. In addition, other studies have noted a high prevalence of myocardial edema following COVID-19 infection. Whether the abnormal CMR imaging findings observed after COVID-19 reflect a permanent cardiac lesion is unknown at this time due to the lack of long-term studies.

RADIOGRAPHY AND MSCT OF THE CHEST

Early MSCT (multislice, multidetector computed tomography scan) of the thorax shows detectable changes in the lung parenchyma in as many as 85% of patients, which can be both oligosymptomatic and asymptomatic. Also, in as many as 75%, there are COVID-19 bilateral lung changes with subpleural and peripheral distribution [5]. In addition to other viral pneumonias, COVID-19 pneumonia on the Rtg manifests as peripherally located ground glass opacity. Perihilar or diffuse widespread ground-glass opacification and ‘‘crazy paving" are present in MSCT findings in COVID- 19 and are difficult to distinguish from the others diseases only on the basis CT findings (other viral pneumonia, acute respiratory distress syndrome - ARDS, acute hypersensitive pneumonitis, sarcoidosis, pulmonary hemorrhage, alveolar proteinosis) [20,21].

By appearance, peripherally located consolidations with marginal zone ground glass opacity do not differ from the findings in Cryptogenic organizing C organizing_ pneumonia (COP), Eosinophilic pneumonia , Vasculitis , Invasive aspergillosis and should be interpreted within the whole clinical picture. The organizing pneumonia (pulmonary tissue consolidation) in COVID- 19 has the same characteristics as the organizing pneumonias of other causes . Nodules with a halo sign, apart from COVID-19, are also a common finding in numerous other diseases. [20,21].

Even in less severe, ambulatory-treated COVID-19 patients, signs of incipient lung congestion can be detected on a chest radiograph: Kerley B lines and redistribution of the pulmonary vascular pattern. In patients who are treated in intensive care units, enlargement of the cardiac shadow-cardiomegaly, bilateral pleural effusion as part of cardiac decompensation and pronounced lung congestion can be detected. MSCT is sovereign in the detection of thrombus in the branches of the pulmonary artery and the diagnosis of pulmonary thromboembolism [16]

ABNORMALITIES INDICATING A HEART LESION ON ECHOCARDIOGRAPHY

Echocardiography - (ultrasound of the heart) is the most accessible method that can also be performed as an emergency at the patient's bedside (point of care-POC approach). Echocardiographic abnormalities commonly registered in hospitalized patients with COVID-19 include right ventricular (RV) dysfunction (26.3%), left ventricular (LV) wall motion abnormalities (23.7%), global left ventricular dysfunction with reduced LV EF (18.4%), grade II or III diastolic dysfunction (13.2%) and pericardial effusion (7.2%) [22]. Biomarker evidence of myocardial lesion associated with echocardiographic abnormalities correlates with a higher risk of in-hospital mortality. Myocardial

involvement caused by SARS-CoV-2 infection may be important for long-term prognosis. Myocardial effects during SARS-CoV-2 infections can be characterized with advanced echocardiographic techniques. Strain imaging was performed in 18 patients with SARS CoV-2 infection assessing longitudinal, radial, and circumferential strain or left ventricular (LV) strain including rotation, torsion, and twisting [17]. LV deformation (strain) was also analyzed in a control group of healthy individuals of the appropriate age (n = 20). The dominant finding was the finding: reduced longitudinal strain observed predominantly in more than one basal segment of the LV (n = 10/14 patients, 71%). This pattern resembles a "reverse Tako-tsubo" morphology, which is not typical of other viral myocarditis. Additional findings included a biphasic pattern with maximal postsystolic thickening or negative regional radial strain predominantly in the basal segments (n = 5/14 patients, 36%); absence or dispersion of left ventricular basal rotation (n = 6/14 patients, 43%); decreased or positive regional circumferential strain in more than one segment (n = 7/14 patients, 50%); net rotation showing late post-systolic twist or biphasic pattern (n = 8/14 patients, 57%); cardiac rotation showing a polyphasic pattern and/or higher peak values during diastole (n = 8/14 patients, 57%). Descriptive myocardial damage due to SARS-CoV-2-infection was highly prevalent in the presented cohort, even in patients with mild symptoms. COVID-19 myocardial damage appears to be characterized by specific deformation (strain) abnormalities in the basal segments of the LV. These data raise an idea for prospective testing: whether these parameters are useful for risk stratification and for long-term follow-up of these patients [17].

It is important to present a large meta - analysis by Ogungbe O. et al [23] on 41013 patients, where the aim was to quantify the relationship between myocardial lesion biomarkers, coagulation and severe COVID-19 and death in hospitalized patients. Individual study effect estimates of the association of markers of myocardial lesion (troponins), myocardial dysfunction (N-terminal-prohormone BNP, NT-proBNP) and coagulopathy (D-dimer) and death or severe/critical COVID-19 were pooled using the statistical parameter Odds ratio (odds ratios for adverse events-OR) by outcomes of critical/severe COVID-19 and death. Comorbidities of hypertension - 39% (95% CI: 34–44%); diabetes, - 21% (95% CI: 18%–24%); coronary artery disease, 13% (95% CI: 10–16%); chronic obstructive pulmonary disease, 7% (95% CI: 5–8%); and history of malignancy, 5% (95% CI: 4–7%). Elevated troponin was associated with higher pooled odds of critical/severe COVID-19 and death [OR: 1.76, 95% (CI: 1.42–2.16)]; By separate OR analysis, the odds ratio for death was OR: 1.72, 95% (CI: 1.32–2.25) and for critical/severe COVID-19, OR: 1.93, 95% (CI: 1 ,45–2,40). Elevations of NT-proBNP were also associated with more severe COVID-19 and death (OR: 3.00, 95% CI: 1.58–5.70). Increased D-dimer levels were significantly associated with critical/severe COVID-19 and death (pooled OR: 1.38, 95% CI: 1.07–1.79). This meta-analysis synthesizes the existing evidence that myocardial injury and coagulopathy are significant complications of COVID-19. The reversibility and functional significance of these complications and their contribution to long-term cardiac disease outcomes are still being investigated. Patients who have recovered from COVID-19 may benefit from assessment of markers of myocardial injury, heart dysfunction-failure, and coagulopathy for early risk stratification [23].

An important aspect of COVID-19 pandemic is the associated collateral damage in the treatment of many other diseases. This includes diagnostic difficulty and treatment of all forms of cardiac and other serious chronic diseases of other organ systems and not only the treatment of infarctions and acute cardiac diseases during the COVID-19 pandemic, which has consequences for our daily cardiology practice. [24,25]

ABNORMALITIES INDICATING A LESION ON CARDIAC MAGNETIC RESONANCE (CMR)

CMR findings include: T1 mapping abnormalities (suggesting diffuse myocardial changes such as diffuse fibrosis and/or edema); T2 mapping abnormalities (more specific to myocardial inflammation, as occurs in acute myocarditis); the presence of late gadolinium enhancement (LGE), which indicates an acute myocardial lesion and/or myocardial fibrosis); or pericardial involvement – all of which may indicate cardiac lesions associated with COVID-19. In a systematic review of 199 patients, post-recovery CMR studies in patients with COVID-19, CMR diagnosed myocarditis in 40.2%,

myopericarditis in 1.5%, Takotsubo in 1.5%, ischemia in 2.5% and a double lesion: ischemia and non-ischemic changes in 2.0%. Regional wall motion abnormalities were reported in 40.6%, edema (on T2 or short tau inversion recovery) in 51.1%, LGE in 42.7%, and T1 and T2 mapping abnormalities in 73% and 63%, respectively. Additionally, perfusion and extracellular volume mapping abnormalities were described in 85% and 52% of patients, respectively. Pericardial involvement included pericardial effusion in 24% and pericardial LGE in 22%. In summary, the most common CMR diagnosis in COVID-19 patients is myocarditis, and imaging findings included evidence of diffuse myocardial edema and myocardial fibrosis. However, it is important to note that most of the reported findings were mild increases in T1 and T2 signal intensity, and the clinical significance of isolated T1/T2 abnormalities associated with COVID-19 still remains unknown [26,27].

CARDIAC INVOLVEMENT AFTER RECOVERY FROM ACUTE COVID 19 DISEASE - POST-ACUTE COVID 19 (PASC) or LONG COVID-19 SYNDROME

Certain patients infected with SARS-CoV-2 continue to have symptoms for weeks to months after apparent recovery from the acute phase of the disease. Early reports suggest that up to 10% of patients with COVID-19 may experience "PROLONGED OR LONG COVID SYNDROME" or POST-ACUTE COVID 19 (PASC). Symptoms of PASC vary widely in variety, severity, and duration [16]. **Preliminary studies suggest that up to 30% of patients may report symptoms as late as 9 months after acute infection** [28]. The most common symptoms include fatigue, decreased functional capacity and exercise tolerance, shortness of breath, sleep problems, and palpitations. Some patients describe difficulty thinking clearly ("brain fog"), anxiety and/or depression. The exact predictors, duration, extent of cardiac (or other organ) involvement, and potential effects of different treatments for PASC require extensive research, which has already begun [16].

The potential for long-term cardiac sequelae of myocardial damage associated with COVID-19 has been highlighted in CMR studies of recovered patients with evidence of myocardial fibrosis or myocarditis reported in a wide range of **9% to 78% of patients recovered from acute COVID-19.** Among 100 post-COVID-19 patients who underwent CMR 2 to 3 months after diagnosis, Puntmann et al reported **cardiac involvement in 78% with evidence of ongoing inflammation in 60%.** On the day of imaging, 71% had elevated hs-TnT. Cardiac symptoms were common and included atypical chest pain (17%), palpitations (20%), and dyspnea and fatigue (36%). Recovered patients had lower left ventricular (LV) ejection fractions and larger LV volumes compared with risk factor-matched controls. These CMR findings of myocarditis and myocardial fibrosis raise concerns about potential long-term cardiac consequences, including increased risk of heart failure and arrhythmia based on previous experience with myocarditis. The presence of late gadolinium accumulation (LGE) subepicardially and medially in the left ventricular wall associated with myocarditis often implies myocardial necrosis in addition to myocardial edema and has previously been associated with adverse outcomes in multiple CMR studies of non-Covid-related myocarditis [27]. Post-acute sequelae of SARS-CoV-2 infection, often called post-acute COVID-19 syndrome or long-lasting-LONG COVID-19, can occur in patients who are slow to recover. Of 143 patients who were treated as outpatients after infection with COVID-19, only 12.6% were asymptomatic. (Carfe A) [28]. Symptoms included fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%), and chest pain (21.7%); 44.1% reported deterioration in quality of life. Among 1,733 discharged patients with COVID-19 followed for an average of 6 months after symptom onset, the most common symptoms were fatigue or muscle weakness (63%), difficulty sleeping (26%), and anxiety or depression (23%). Greater disease severity during hospitalization was associated with reduced pulmonary diffusion capacities and abnormal chest radiography. (Huang C. 2021). The contribution of cardiac changes after COVID and acute myocardial injury to the symptoms of post-acute COVID-19 syndrome is unclear [29].

PROOF OF DIRECT VIRAL HEART INFECTION BY PATHOHISTOLOGY

Cardiac autopsies showed cardiomegaly, right ventricular enlargement, lymphocytic myocarditis (14%–40%), focal pericarditis (19%), endocardial thrombosis (14%), or endotheliitis and thrombosis of small coronary

vessels (19%). The cardiac tropism of SARS-CoV-2 was initially established by quantitative RT-PCR detection of viral RNA in postmortem hearts of patients with COVID-19 and then in endomyocardial biopsies of patients with suspected myocarditis. The cardiac cellular tropism of SARS-CoV-2 has now been demonstrated by in situ labeling of SARS-CoV-2 RNA and electron microscopic detection of virus-like particles within cardiomyocytes, interstitial cells, and cardiac endothelial cells post mortem [30,31]. Autopsies in patients with acute myocarditis have recently shown evidence of viral infection, and replication within cardiomyocytes. The preponderance of evidence suggests that SARS-CoV-2 can readily infect human cardiac myocytes and can be detected in myocytes at autopsy or endomyocardial biopsy in patients with and without clinical evidence of cardiac involvement. There are pathohistological findings of clear myocarditis in individual cases where all elements strongly suggest COVID-19 myocarditis or direct cardiomyocyte damage in an extremely strong inflammatory reaction (cytokine storm) caused by viremia rather than a microvascular myocardial lesion [14,32]

Of 277 hearts in 22 autopsy studies of COVID-19, only 20 cases of myocarditis (7.2%) were reported. In contrast to the low prevalence of myocarditis, interstitial macrophage infiltration without cardiomyocyte degeneration was common in a multicenter COVID-19 autopsy series (18 of 21 cases, 86%) [33]. Other more common histologic findings reported in the COVID-19 autopsy series include perivascular and inflammatory myocardial infiltrates, endocardial and small vessel thrombosis, endotheliitis, and myocyte degeneration. One study of 39 autopsied hearts detected SARS-CoV-2 by qRT-PCR in 24 (61.5%) cases, with 16 hearts showing high viral loads (>1000 genomic copies per mg of total RNA) [34,35]. It remains to be determined whether the heterogeneity of cardiac histopathology in COVID-19 signifies different endophenotypes of the myocardial lesion of COVID-19 or the continuity of a single pathological process.[16] .

PROLONGED EXERCISE INTOLERANCE AND DYSAUTONOMY

There is increasing evidence of prolonged symptoms of COVID-19 after a period of acute infection (post-acute covid, long covid) with prolonged exercise intolerance (failure to exert effort) which is becoming a common finding not only in competitive athletes and active individuals, but also in many young and elderly people survivors of COVID-19 [3,16]. Common symptoms associated with myocarditis and post-COVID syndrome include chest pain, dyspnea, and palpitations. CMR findings of a cardiac lesion, small nerve fiber neuropathy caused by the COVID-19 virus, and dysautonomia are likely causes. Postural orthostatic tachycardia syndrome associated with COVID-19 is common. The relative poor cardiac fitness during periods of exercise and training limitations is often confounding in situations when trying to delineate the cause of failure to exercise [3,16].

The potential for increased risk of sudden cardiac death in post-COVID fibrosis or myocardial inflammation is of concern to athletes or active individuals returning to exercise. The wide range of LGE prevalence after COVID-19 has led to controversy over the routine practice versus targeted use of CMR. Risk stratification with noninvasive biomarkers, ECG, or echocardiography may be insensitive for detecting CMR abnormalities. Conversely, ECG changes considered abnormal in non-athletes may represent normal variants in athletes. According to the American College of Cardiology, Sports, and Exercise, athletes who have recovered from COVID-19 can return to sports based on biomarkers and noninvasive cardiac imaging, including ECG and echocardiogram [3,16]. Athletes are advised to limit exercise to 5 days a week, minimally at first with a gradual increase in exercise intensity. Cardiovascular risk assessment is recommended for mild symptoms lasting longer than 10 days; for moderate or severe symptoms, including hospitalization, further cardiac testing depends on symptoms and abnormal findings on baseline testing. The uncertainty of long-term consequences and the potential for long-term evolution into chronic myocardial disease, cardiomyopathy, and other cardiovascular complications, including heart failure, chronic sinus tachycardia, autonomic dysfunction, and arrhythmias, await further definition. In addition, studies are needed to determine whether therapeutic interventions to moderate the inflammatory response can also limit the extent of intermediate- to long-term myocardial injury associated with COVID-19. Evaluation of post-acute COVID-19 syndrome (long-COVID-19) and recommendations for long-

term surveillance, monitoring, and return to exercise or sport remain areas for further evaluation [3,16].

PRINCIPLES OF THE THERAPEUTIC APPROACH TO COVID-19 INFECTION WITH A FOCUS ON THE CARDIOVASCULAR SYSTEM

The most important principles in the therapeutic approach to COVID-19 patients [16]: A) optimal supportive measures and treatment of complications; B) treatment of existing chronic cardiovascular diseases and conditions developed as part of COVID-19 according to the current guidelines of professional societies and associations (ESC, AHA/ACC) including inhibitors of the renin-angiotensin-aldosterone system [14]; C) in cases of cytokine storm associated with the development of ARDS and myocarditis, consider the introduction of immunomodulatory therapy; D) individual risk stratification for development of KV complications in COVID-19 infection, prevention of these, early recognition and treatment [14]. Treatment of COVID- 19 and complications associated with COVID-19 [16] continues to develop rapidly as more treatments complete testing in randomized trials. Treatment in early phase includes antiviral medicines and monoclonal antibodies against SARS - CoV- 2.

Antiviral medicines . Remdesivir is nucleoside analog which inhibits RNA dependent RNA polymerase and is the only antiviral medicine approved by US Food and Drug Administration (FDA) for treatment of COVID-19 [16]. It is currently recommended to patients hospitalized with moderate COVID-19 who need extra oxygen, but its benefit has not been established in patients who require high flow oxygen , non-invasive ventilation or mechanical ventilation . Treatment lasts about 5 days, it can be prolongedto 10 days if there are no clinical improvements [36] .

Monoclonal antibodies against SARS - CoV -2 which have been approved by FDA for emergency use : Bamlanivimab plus etesevimab (applied together) have been approved for treatment of mild to moderate COVID- 19 in adults and pediatric outpatients [37]. Besides, FDA has issued permission for kasirivimab and imdevimab applied together) for treatment of mild to moderate variant of COVID-19 in adults and pediatric patients [38]. Potential cardioprotective effects of treatment by anticytokines haven't been determined yet due to inconsistencies in the results of clinical trials[16].

Corticosteroids have showed benefit in a patient subgroup with moderate COVID-19 whoneeded extra oxygen . In a randomized evaluation trial of therapy for COVID-19, dexamethasone (6 mg one time daily up to 10 days) reduced the 28 -day mortality, but patients who didn't need oxygen did not experience any benefits [16**,** 39]. In meta - analysis of 7 randomized controlled studies (CT) which included 1703 critically sick patients (including those who needed mechanical ventilation) with COVID-19, the use of systemic dexamethasone , hydrocortisone or methylprednisolone resulted in the reduction of risks of mortality from all causes by 34% after 28 days [16,40].

"A "storm" of cytokine release", which comes from T cell activation imbalance with unregulated interleukin release (IL)-6, IL -17 and other cytokines , can contribute to CVD in COVID- 19. Anti-IL-6 antibody therapy trial is ongoing. Activation of the immune system together with the changes in immunometabolism can lead to the instability of atherosclerotic plaques, contributing to the development of acute coronary events [16].

The role of anticoagulation in COVID- 19. Many observational or smaller studies have investigated which patients with COVID- 19 could benefit from anticoagulants or antiaggregation therapy, in which dose and in which phase of the disease with different results . While waiting for sufficiently strong, properly designed and performed blinded randomized trials, many institutions have adopted the prophylaxis of escalated doses in all or specific _ groups of hospitalized patients with COVID-19. Documents about consensus generally recommend tracking the available medical recommendations based on the evidence in order to avoid a widespread use higher than the prophylactic dose of anticoagulants , except if it is not used as a part of a research study [16,41]. In general , risk from venous thromboembolism (VTE) in hospitalized patients reached its climax in the early stage of the pandemic, but later the incidence decreased thanks to the adoption of prophylactic anticoagulation. A big study of Danish registers based on the national population suggests that the risk from the VTE in hospitalized patients with COVID -19 is low to

moderate and that it's not significantly higher than the risks from the VTE in hospitalized SARS - CoV -2- negative patients and patients with flu [42]. VTE Risk in the period after dismissal and in ambulatory cases of COVID - 19 can be slightly elevated, but it is much smaller than the risks in acutely ill and hospitalized patients.

Antagonists of the renin-angiotensin-aldosterone system (RAAS antagonists)

Following the discovery that SARS-CoV-2 uses ACE2 to enter the host cell, concerns have been raised about the potential for ACE inhibitors and ARBs to cause a compensatory increase in ACE2 expression and worsen prognosis among those with COVID-19. Observational studies evaluating outcomes associated with the use of ACE inhibitors and ARBs among patients with confirmed COVID-19 [43,44] and RCTs comparing continuation or withdrawal of these agents among those hospitalized with COVID-19 have shown no adverse effects on survival and other clinical outcomes [45,46] . Therefore, continuation of ACE inhibitors and ARBs during the course of COVID-19 disease is recommended for patients treated with these drugs. It also appears that in experimental models, ARBs may have a potentially protective effect. A recent observational study of over 8910 patients from 169 hospitals in Asia, Europe, and North America showed no adverse association of ACEIs or ARBs with in-hospital mortality, while a study in Wuhan showed that in 1128 hospitalized patients, ACEI/ARB use was associated with a lower risk from infection with COVID-19 or serious complications or death from infection with COVID-19. This is consistent with previous guidelines from the major cardiovascular associations, which state that patients on ACEIs or ARBs should not discontinue these medications [16].

ORGANIZATION OF CARE AND SPECIFICITY OF THE MOST IMPORTANT CVD DURING THE COVID-19 PANDEMIC

Non-ST elevation acute coronary syndromes (NSTEMI)

Management of patients with NSTE ACS should be guided by risk stratification [3]. Testing for SARS-CoV-2 should be performed as soon as possible after the first medical contact, regardless of the treatment strategy, so that the healthcare professional can implement adequate protective measures and care pathways. Patients should be categorized into 4 risk groups (ie, very high risk, high risk, intermediate risk, and low risk) and managed accordingly. Patients with an increase in troponin and without acute clinical signs of instability (ECG changes, recurrence of pain, hemodynamically stable) can be treated with a primarily conservative approach. Non-invasive imaging with CCTA can speed up risk stratification, avoid an invasive approach and allow early discharge. For high-risk patients, the medical strategy aims at stabilization while planning an early (< 24 hours) invasive strategy. In the case of a positive SARSCoV-2 test, patients should be transferred for invasive treatment to a COVID-19 hospital equipped to treat the patients positive for COVID-19. Intermediate-risk patients should be carefully evaluated considering alternative diagnoses of T1MI, such as type II MI, myocarditis or myocardial lesion due to respiratory distress or multiorgan failure, or Takotsubo. In case any of the differential diagnoses seems plausible, a non-invasive strategy should be considered and CT scan coronary angiography (CCTA) should be preferred [3].

ST segment elevation myocardial infarction (STEMI)

The COVID-19 pandemic should not compromise timely reperfusion via percutaneous balloon angioplasty with stent placement (PCI) or thrombolytic therapy in patients with STEMI [3] .

According to current guidelines, reperfusion therapy remains indicated in patients with symptoms of ischemia lasting less than 12 hours with permanent ST-segment elevation on ECG in at least two adjacent leads. At the same time, there must be safety for healthcare workers and in the absence of testing for SARS-CoV-2, all patients should be treated as if they were Covid-19 positive. The safety of healthcare professionals is of utmost importance to avoid healthcare worker infections and further spread of infection.

Chronic coronary syndromes (CCS)

Patients with Chronic Coronary Syndrome **(**CCS) with a clinical scenario of stable angina pectoris are generally at low risk of CV events, which allows delaying diagnostic and/or interventional procedures in most cases [3] **.**

Medical therapy should be optimized and/or intensified depending on the clinical status. Clinical monitoring of a patient via telemedicine is justified for the early detection of unstable angina or changes in clinical status that may require hospital admission in high-risk patients.

Acute heart failure (AHF)

Bilateral COVID-19 pneumonia often leads to worsening hemodynamic status due to hypoxemia, dehydration, and hypoperfusion. The main mechanisms of AHF in COVID-19 are acute myocardial ischemia, myocardial infarction or inflammation (myocarditis), acute respiratory distress syndrome (ARDS), acute kidney damage and hypervolemia, stress-induced cardiomyopathy, and tachyarrhythmias [3] **.**

Clinical presentation, the presence of existing CV comorbidities and the findings of X-ray thorax (cardiomegaly and/or bilateral pleural effusion, congestion of the lung wings at the bases) are of utmost importance. Significantly elevated levels of BNP and not NT-proBNP also suggest acute HF. Careful use of point-of-care (POC) transthoracic echocardiography (TTE) is recommended to prevent contamination of personnel and/or equipment from the patient. The same treatment strategy for acute HF can be applied in patients with and without COVID-19 [3,47]. Regarding prognosis, in a recent report 23% of all hospitalized patients developed AHF, while the prevalence of HF was significantly higher in fatal cases compared with survivors (52% vs. 12%, $P < 0.0001$). [3].

Chronic heart failure (CHF)

The risk of infection with COVID-19 may be higher in chronic heart failure HF patients due to age and the presence of multiple comorbidities. In ambulatory stable patients with HF, without urgent cardiac conditions, the prescribing physician should refrain from hospital treatment. Medical therapy according to the guidelines (including the five parallel pillars of therapy according to the new ESC guideline [3,47] Beta-blockers, SGLPT-2 inhibitors, mineralocorticoid receptor antagonists (MRA), loop of Henle diuretics for congestion and one of the RAAS inhibitors, preferably sacubitril/valsartan or ACEI, OR ARBa), should be continued in patients with chronic HF, regardless of COVID-19. The implementation of telemedicine to provide medical advice and follow-up of stable patients with COVID-19 is important.

Arterial Hypertension

An association between hypertension and risk of severe complications or death from COVID-19 infection was found, with a confounding lack of effect of age and comorbidities associated with aging and hypertension. However, there is currently no evidence to suggest that hypertension per se is an independent risk factor for severe complications or death from COVID-19 infection [3]**.** Despite much speculation, evidence from a recently published series of observational cohort studies suggests that previous or current treatment with an ACEI or ARB does not increase the risk of infection with COVID-19 or the risk of developing severe complications from infection with COVID-19 compared to the risk in patients taking other antihypertensive drugs. Treatment of hypertension should follow the existing recommendations in the ESC-ESH Guidelines. No changes to these treatment recommendations are necessary during the COVID-19 pandemic [3] **.**

COVID 19 Myocarditis

Limited clinical experience indicates that SARS-CoV-2 can lead to all forms of myocarditis from subclinical to fulminant myocarditis. Myocarditis should be suspected in patients with COVID-19 and acute chest pain, ST segment changes, cardiac arrhythmia, and hemodynamic instability. In addition, dilatation of the left ventricle (LV) with reduced ejection fraction (EF), global or multisegmental hypocontractility of the LV with a significant increase in cardiotroponin T and I and the level of both or only one natriuretic peptide (BNP I / or NTproBNP) with the exclusion of significant chronic coronary disease are elements for establishing a working clinical diagnosis. In particular, myocarditis should be suspected in COVID-19 patients with acute heart failure: pulmonary edema or cardiogenic shock and

without anamnestic data on previous CV disease. Echocardiography, as the first and routine imaging method, often shows diastolic dysfunction, multisegmental hypocontractility, dilatation of both ventricles and a significant decrease in systolic function - a drop in LV ejection fraction (LVEF) and sometimes a small pericardial effusion. Advanced echocardiographic methods, such as myocardial deformation imaging (strain-strain imaging) Myocardial damage due to SARS-CoV-2-infection, specific deformation (strain) abnormalities in the basal segments of the left ventricle were highly prevalent even in patients with mild symptoms [17]. MSCT of the coronary arteries (CCTA) is suggested as the best approach to rule out concomitant coronary disease and cardiomagnetic resonance (CMR), if available, can be used for further diagnostic evaluation. Endomyocardial biopsy is not recommended in patients with COVID-19 with suspected myocarditis [3].

Efficacy of anticovid vaccination and post-vaccination myocarditis

Vaccines have shown efficacy in reducing morbidity and mortality from COVID-19 in randomized clinical trials and real-world studies, which also reduce cardiovascular complications. Their widespread use has led to a significant reduction in the incidence of COVID-19.

As of July 2021, the CDC's Adverse Event Reporting System (VAERS) has received over 1,100 reports of myocarditis or pericarditis after receiving a COVID-19 vaccination (primarily mRNA vaccine) and confirmed about 70% of them. In Europe (EEA), cases of myocarditis have also been reported with mRNA vaccines and with AstraZeneca vaccine, mostly in young adults, more often in men and usually after the second dose of the vaccine. Myocarditis, which can be detected by cardiac magnetic resonance imaging, usually occurs within 3 to 5 days after vaccination and presents with chest discomfort, an abnormal EKG, and elevated troponin. Although the exact mechanism is unknown, it is probably immunologically mediated. The possible incidence of asymptomatic cases, risk factors and long-term effects remain to be determined. Overall, myocarditis following COVID-19 immunization appears to be rare (~24 doses per million vaccines), often mild, and probably self-limiting in most cases. Treatment is primarily supportive [48,49].

CONCLUSION

Acute cardiac lesion is a common extrapulmonary manifestation of COVID-19 with potential chronic consequences. Clinical manifestations include direct cardiac damage and indirect immune response mechanisms that affect the cardiovascular system and have implications for the treatment of patients after recovery from acute COVID-19 infection. Hypertension (56.6%) and diabetes (33.8%) are the most common comorbidities in those infected with COVID-19, requiring hospitalization.

Cardiovascular manifestations of COVID-19 vary, and acute infection is associated with a wide range of cardiovascular complications, including acute coronary syndromes, stroke, acute-onset heart failure, arrhythmias, myocarditis, venous thromboembolism, and cardiac arrest.

The most common direct damage to the heart is an acute heart lesion, defined by a significant increase in cardiac troponins in the serum in >12% of infected and echocardiographic signs of damage to the texture of the myocardium due to inflammation, impairment of segmental mobility, global systolic and diastolic function of the left ventricle and inflammation of the pericardium. Among hospitalized patients with COVID- 19, the evidence about acute damage of heart function is common: acute heart insufficiency (3%-33%), cardiogenic shock (9%-17%), ischemia or myocardial infarction (0.9%–11%), ventricular dysfunction (left ventricular [10%–41%], right ventricular [33%–47%], biventricular [3%–15%]), stress cardiomyopathy (2%–5.6%), arrhythmias (9%–17%), venous thromboembolism (23%–27%).

Elevated troponin T is associated with more frequent development of severe complications: adult respiratory distress syndrome (ARDS), malignant arrhythmias (VT, VF), acute coagulopathy and acute kidney damage. Numerous individual cases indicate extremely high values and dynamics of troponin T typical for non-occlusive myocardial infarction with normal coronary arteries. Pathohistological findings of myocarditis strongly suggest COVID-19 myocarditis or direct damage to cardiomyocytes in an extremely strong

inflammatory reaction, a cytokine storm, caused by viremia.

About 10% of patients with COVID-19 may experience "LONG COVID SYNDROME" or POST-ACUTE COVID 19 (PASC). The symptoms of PASC vary widely in variety, severity, and duration.

Theoretically, the predicted increases in Angiotensin II levels by COVID-19 infection can be curbed by administration of maximal doses of ACE inhibitors and AT1 receptor blockers.

Cardiovascular dysfunction and disease are often fatal complications of severe infection with the COVID-19 virus, and cardiac complications can occur, even in patients without underlying heart disease, as part of an acute infection and are associated with a more severe form of COVID-19 disease and increased mortality.

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DISCONNECTION OF ARTERIAL COLLATERAL AS THE CAUSE OF LOWER LEG AMPUTATION AFTER CONQUASSATION CONQUASSATIONCAUSED BY PETROL TILLER. A CASE REPORT

Ivan Golubović (1), Predrag Stojiljković (1), Mihailo Ille (2), Milan Radojković (3), Nemanja Jovanović (3), Milan Lazarević, Ivana Golubović (3), Ivan Milošević (2), Zoran Baščarević (4), Dejan Tabaković (5), Nebojša Mitić

(1)CLINIC FOR ORTHOPAEDIC SURGERY AND TRAUMATOLOGY, CLINICAL CENTER NIS, SERBIA; (2)CLINIC FOR ORTHOPAEDIC SURGERY AND TRAUMATOLOGY, CLINICAL CENTER BELGRADE, SERBIA; (3)FACULTY OF MEDICINE, UNIVERSITY OF NIS, SERBIA; (4)INSTITUTE OF ORTHOPAEDIC SURGERY "BANJICA", BELGRADE, SERBIA; (5)CLINIC FOR ORTHOPAEDIC SURGERY AND TRAUMATOLOGY, CLINICAL CENTER KOSOVSKA MITROVICA, SERBIA

Abstract: Introduction. Leg conquassationconquassation caused by petrol tiller is one of the most severe injuries in bone and joint traumatology. Firm strokes by sharp tiller blades produce strong force that easily damages both soft tissues and bones. Since tillers are used in soil processing, the wounds are highly contaminated with dirt and fertilizers, hence the anaerobic spore-forming bacilli, such as tetanus and gas gangrene pathogens. Casereport. This paper presents the treatment of a 69 years old man with chronic arterial insufficiency of the lower extremities who suffered severe injury of the lower leg (IIIB open tibial fracture according to Gustillo) by petrol tiller while performing agricultural work. Due to the absence of pulsations, Multislice CT angiography and arteriography were performed. Arteriography of the injured leg confirmed chronic occlusion of the anterior tibial artery and numerous stenotic lesions of the peroneal and posterior tibial arteries. Posterior tibial artery was chronically occluded in its distal part and connected to the foot with moderately developed collateral arteries which provided the viability of the injured leg. Despite undertaken basic principles of treatment of this serious injury (primary surgical treatment of wounds, external fixation, reconstruction of soft tissue, antibiotic and anti-tetanus prophylaxis) due to infection and gangrene the treatment ended with lower leg amputation. Conclusion. Leg amputation can be expected in this type of injuries in cases of extensive destruction of tissue in the field of existing chronic arterial insufficiency in elderly patients, even in the absence of injury of main blood vessels due to traumatic disconnection of collateral in such patients.

Keywords: leg conquassationconquassation, IIIB open tibial fracture, external fixation, chronic arterial insufficiency, amputation of the lower leg

INTRODUCTION

Farmer is one of the most frequent professions in Serbia. Leg conquassation caused by engine tiller is among the most severe injuries in bone and joint traumatology. Firm strokes produced by sharp tiller blades produce strong force that easily damages both soft tissues and bones. Since tillers are used in soil processing, the wounds are highly contaminated with dirt and fertilizers, hence the anaerobic spore-forming bacilli, such as tetanus and gas gangrene pathogens. Skin and soft tissue destruction, comminution and bone defect, high level of both anaerobic and aerobic contamination and threatening infection make the treatment of these injuries, particularly open lower leg fracture, complex and challenging (1).

Meticulous irrigation of these wounds, removal of all foreign bodies and dirt and thorough surgical debridement of damaged tissue are crucial for successful prevention of infection, both non-specific and specific (tetanus and gas-gangrene). Also, fracture stabilization with external skeletal fixation, antibiotic therapy and anti-tetanus protection are mandatory. High-quality physical therapy following successful healing of soft tissue wounds and bone fractures is necessary for patient's early recovery and faster return to everyday activities (2).

The most common complications of leg conquassation include soft tissue and bone infection, gas-gangrene, fracture malunion and finally amputation (3,4). Healing may be compromised and prognosis worsened by vascular insufficiency due to magistral vessels injury. Open Gustilo type IIIC fractures are among the most severe lower leg injuries.

These injuries often occur in older people over 60 who have co-morbidities. Chronic arterial insufficiency of lower extremity greatly complicates surgical treatment of this injury.

Aim of the study is to present a patient treated for severe lower leg and foot conquassation caused by petrol tiller during agricultural labor. We aimed to depict the specificities of such injury, the problems that may arise and the complications that may occur during the treatment of this severe trauma.

CASE REPORT

A 69-year old male patient was injured during soil processing by an engine tiller when the machine hit the hurdle in the ground, changed the direction and caused him severe both right and left lower legs and feet trauma with its sharp blades. Injuries included open left lower leg fracture Gustilo type IIIB with soft tissue defect, severe laceration of the left foot dorsum also with soft tissue defect and right lower leg laceration. He was initially admitted to the regional hospital emergency unit where his injuries were assessed and left leg plaster immobilization was done. Subsequently, the patient was referred to Orthopaedics and Traumatology Clinic, Clinical Center Nis where resuscitation and preoperative preparation were immediately performed. On examination, there was large skin and subcutaneous tissue defect on the front left lower leg with lacerated and ruptured tibialis anterior muscle tendon. X-rays revealed comminuted fracture of the left lower leg proximal third and left medial malleolus fracture. Left lower leg was deformed in the proximal third with complete functional impairment. There were crepitations during the movements and palpation of the fracture site. Both anterior and posterior tibial pulses were absent.

Multislice CT angiography revealed multiple stenoses in popliteal and tibioperoneal arteries of the injured leg, and also significant lesions in crural arteries (Figure 1). After preoperative preparation, surgery is done 9 hours after the injury, along with primary treatment of the wounds, fracture reduction and external fixation (Figure 2). In the absence of a pronounced bleeding, as well as violations of main blood vessels, there was no need for vascular reconstruction. Postoperatively angiography confirmed chronic occlusion of the anterior tibial artery and numerous stenotic lesions of the peroneal and posterior tibial arteries. Posterior tibial artery was chronically occluded in its distal part and connected to the foot with moderately developed collateral arteries which provided the viability of the injured leg (Figure 3). Also, additional multiple multilevel stenoses and occlusions were detected in the proximal arterial segments of our patient.

Figure1. Multislice CT angiography of injured lower leg

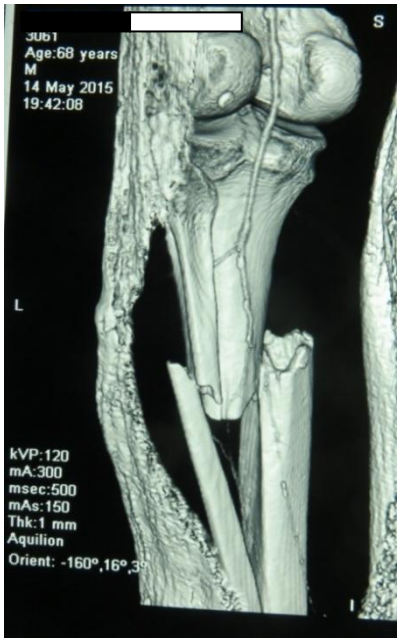


Figure 2. Left lower leg after the primary wound care and external skeletal fixation.

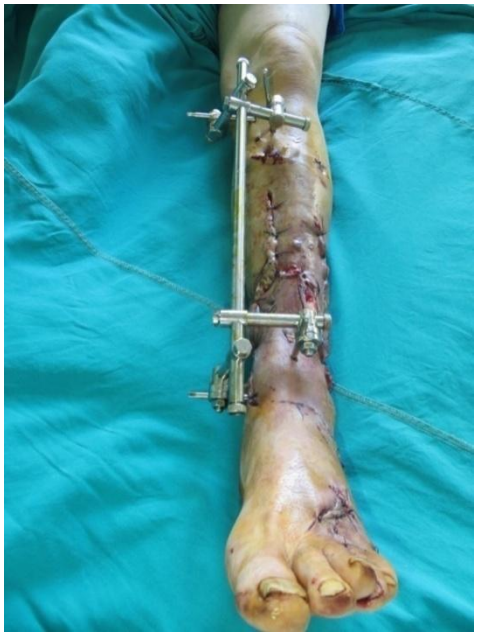
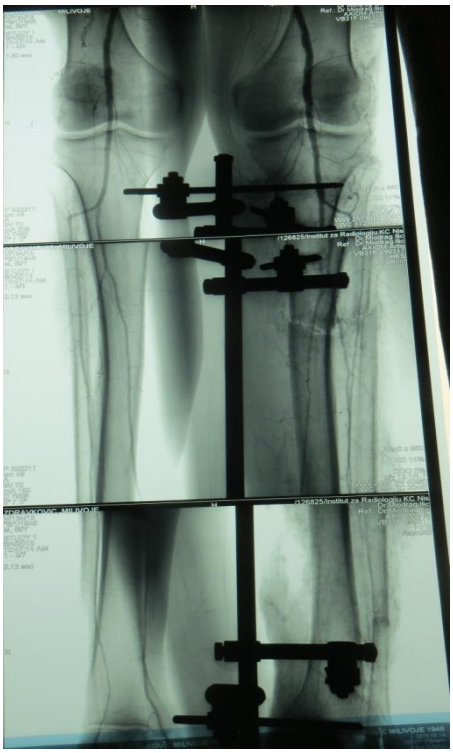


Figure 3. Postoperatively angiography of the lower leg.



The patient was administered anti-tetanus protection and anticoagulant prophylaxis of deep vein thrombosis and pulmonary thromboembolism (nadroparin 0,6mL/24hr). The patient received postoperative intravenous antibiotic therapy (ceftriaxone 2gr daily, amikacin 500mg/12hr and metronidazole 500mg/8hr). Vascular surgeon administered the medication therapy for chronic arterial insufficiency of the lower extremities.

Subsequently, front lower leg and foot dorsum soft tissue necrosis occurred with the dry gangrene of the third toe (Figure 4).

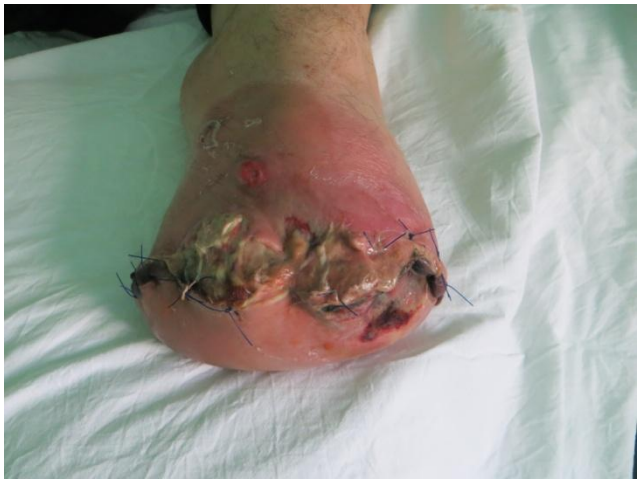
Figure 4. Front left lower leg and foot dorsum soft tissue necrosis with the dry gangrene of the third finger.

Secondary wound debridement including necrosectomy and gangrenous third finger of the left foot amputation was performed in spinal anesthesia (Figure 5).

Figure 5. Left lower leg and foot after secondary wound debridement including necrosectomy and gangrenous third finger amputation

It was followed by general aggravation, severe wound infection, infection around the skeletal fixator nails and critical lower leg ischemia. A multidisciplinary team of orthopedist, vascular and plastic surgeons made a decision to amputate the lower leg for vital indication (Figure 6).

Figure 6. Severe infection of the amputation stump.



Perioperatively, the patient was administered 1750mL whole blood transfusion and 1500mL fresh frozen plasma. Postoperatively it was continued with antibiotics (ceftriaxone 2gr daily, clindamycin 600mg/12hr and vancomycin 1gr/12hr) and subcutaneous anticoagulant (nadroparin 0,6mL/24hr). Meticulous everyday wound cleaning and dressing was performed. However, infection and necrosis of the amputation stump developed. All the sutures were removed, debridement of the stump was done and it was left wide open. Thorough everyday wound care was continued. Seven days after the amputation secondary debridement of the stump and wound closure were performed (Figure 7). Postoperative course was uneventful. The stump healed and the sutures were removed. The patient was referred to physical therapy and limb prosthesis specialist.

Figure 7. Amputation stump after repeated debridement and secondary wound closure

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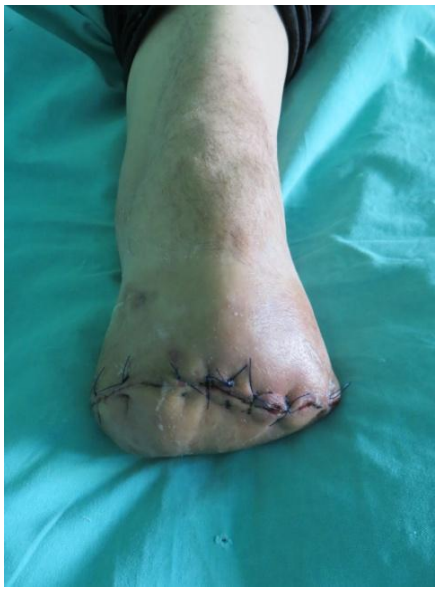

DISCUSSION

Agriculture is one of the most important economy braches in Serbia. Limb injuries caused by petrol tiller almost always include sever skin and soft tissue destruction, magistral blood vessels injury, severe comminuted fracture and often traumatic amputation. These injuries are highly mutilating and may lead to death. Possibilities of tissue reconstruction are small and require multidisciplinary approach that includes orthopedist, vascular and plastic surgeons.

Lower leg conquassation caused by petrol tiller requires urgent surgical treatment providing patient's satisfactory general condition. The management of the open lower leg fracture contaminated with soil includes meticulous wound irrigation, removal of all foreign bodies and dirt, thorough surgical debridement of damaged tissue, fracture stabilization with external skeletal fixation, antibiotic therapy, anti-tetanus protection and delayed wound closure (5).

Primary surgical care – debridement of the open fracture wound is crucial for prevention or successful treatment of infection. If possible, it has to be done within six hours after injury in order to prevent progressive wound contamination and infection, including gas gangrene, tetanus and osteitis. Wound smear, microbiological examination for contaminating microorganisms' identification and their sensitivity to antibiotics (biogram and antibiogram) are necessary before primary treatment. First step is meticulous wound irrigation using saline and hydrogen peroxide (sometimes more than 10L) followed by detailed cleaning and removal of all foreign bodies – dirt, pieces of clothing and cellular debris. Debridement must include extensive surgical removal of devitalized soft tissue (skin, fat, fascia, muscle and bone) (6). Since necrotic muscle tissue represents the environment susceptible for both aerobic and anaerobic bacteria, special care has to be made during muscle debridement regarding adequate assessment of its color, consistence, contractility and bleeding. The surgical removal of a muscle tissue that does not bleed and tightens when touched, does not have natural roseate healthy color and does not look vital is mandatory. If necessary, open fracture wound debridement may be repeated after 24 or 48 hours (secondary debridement) after demarcation and exposure of further (new) tissue devitalization. Adequate primary surgical care is most important for the successful prevention of deep osteitis and leg salvation (7,8).

Further treatment includes bones reposition and external skeletal fixation which is the method of choice for lower leg open fracture stabilization except for Gustilo type I fractures when internal fixation is possible. External skeletal fixation provides optimal biomechanical conditions for successful fracture healing, good approach for wound care and does not interrupt knee and ankle joint movements. Postoperatively, patients are being mobilized early, start with knee and ankle movements and walking (9).

Problems related to external skeletal fixation include common soft tissue and bone infection around the device nails, especially if applied for more than six months. Edwards and al. reported 50 (29,24%) patients with soft tissue infection and 4 (2,33%) with local osteitis around the nails in a study of 171 patients with open fracture treated with external skeletal fixation (10). Marsh et al. reported the incidence of 39 (38,61%) patients with complications related to device nails among 101 patients with open tibia fracture treated with external skeletal fixation and 10 of them required device replacement. However, in the same study low incidence of deep bone infection around fracture (6%) was observed (11).

Early aggressive soft tissue reconstruction during the first 7 days after the injury, in order to cover the fractured bone segments in patients with grade III open fractures, significantly reduces the risk of infection, fracture malunion/nonunion and amputation (12). Delayed wound closure is preferable and is performed after infection is definitely ruled out, using suturing or plastic and reconstructive surgery procedures (fasciocutaneous or microvascular flap), depending on the soft tissue defect size (1).

Early intravenous antibiotic therapy in patients with lower leg open fractures should be initiated immediately on admission. 3 antibiotics are usually administered for a period of 5 days to cover the entire bacterial flora as there is a massive contamination of the soil. After completed microbiological examination, further antimicrobial treatment should be administered according to antibiogram results and continued for additional 48-72 hours for types I and II open

fractures and 120 hours for type III (6). Anti-tetanus protection is mandatory for all patients with open fractures.

Treatment outcome in such patient depends, among other factors, on the residual perfusion of the injured leg which can be diminished due to both injury of the magistral vessel and pre-existent chronic arterial insufficiency. Since our patient had marked advanced asymptomatic occlusive arteriosclerosis of the leg confirmed angiographically, the absence of clinically significant critical ischemia could only be explained with the functional collateral circulation that compensated serious perfusion deficit. Extreme trauma such as presented in our patient including the injury and exclusion of collateral arterial blood supply may lead to the critical leg ischemia and gangrene. The experience with our patient developing posttraumatic limb gangrene and amputation demonstrates the severity of the consequences of collateral circulation damage which is often inevitable in such injuries. Considering that the leg viability in patients with chronic arterial insufficiency may depend on the patency of no more than one sole seemingly insignificant collateral vessel 1-2mm in diameter, its damage due to trauma or surgical ligation may reduce the perfusion to the critical ischemia and gangrene.

Amputation of the lower leg on account of contaminated environment requires delayed closure of the stump when there are no signs of infection.

CONCLUSION

Leg amputation, can be expected in conquassant lower leg injuries in cases of extensive destruction of tissue in the field of existing chronic arterial insufficiency in elderly patients, even in the absence of injury of main blood vessels due to traumatic disconnection of collateral.

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THE SIGNIFICANCE OF ORAL ANTICOAGULANT THERAPY IN THE PREVENTION OF THROMBOEMBOLIC COMPLICATIONS IN PATIENTS WITH ATRIAL FIBRILLATION DURING A 14-YEAR FOLLOW-UP - CASE REPORT

Anastasija Raščanin (1), Dušan Bastać (1), Mila Bastać (2)

(1)OFFICE OF INTERNAL MEDICINE "DR BASTAĆ", KOSANČIĆEV VENAC NO. 16, ZAJEČAR; (2) MEDSCAN TADIĆ DIAGNOSIS, ZAJEČAR;

Summary: INTRODUCTION. Atrial fibrillation (AF) is the most common long-term arrhythmia and represents one of the main public health problems primarily due to the aging of the general population, in which this arrhythmia occurs more often and causes thromboembolic stroke. Cardioembolic stroke associated with AF is usually severe, highly recurrent, and often fatal or with permanent disability of specific stroke risk factors/modifiers. Common risk factors are summarized in a risk factor-based clinical score called the CHA2DS2-VASc Score. Poor INR control increases the risk of both thromboembolic and hemorrhagic complications, and the optimal balance between the benefits and risks of using oral VKAs is achieved when the TTR, or time in the therapeutic range, is ≥ 70% [9]. We present the case of a female patient that confirms the importance of oral anticoagulant therapy when the INR is in the therapeutic range between 2-3, in the largest number of measurements in the successful prevention of recurrent thromboembolic complications during a 14-year follow-up. CASE REPORT: We present a 60-year-old MD patient who first came to the Office of Internal Medicine "Dr. Bastać" in 2008 due to a feeling of instability and heart palpitations. Due to grade II hypertension, which is not well regulated, she has been taking antihypertensive therapy for the past two years, treats elevated cholesterol with statins, and states that in two years and a year before her first examination at the Office of Internal Medicine "Dr. Bastać", she had two minor strokes verified by MSCT of the endocranium. In our patient, a high CHA2DS2-VASc score of 4 was calculated (hypertension, female gender and previous stroke) and the estimated annual risk for stroke is 9.27% (TABLE 2). Her bleeding risk - HAS BLED Score is moderate and is 2 (hypertension, CVI). Based on CHA2DS2-VASc, the risk of adverse thromboembolic events is high and requires the introduction of oral anticoagulant therapy. The patient in therapy receives acenocoumarol according to the scheme so that the value of PT/INR is between 2.0 and 3.0. Good anticoagulation is defined as having 3 to 4 PT/INR values in the therapeutic range (similar to TTR 50 to 60% of the time), while poor anticoagulation is: 0-2 measured INR values in the therapeutic range (TTR <50%) [3]. In our patient, the TTR is about 70%, which represents excellent anticoagulation. During 14 years of monitoring for three months, as well as at the recent control on 04/29/2022. the patient feels well, with no new thromboembolic complications and no bleeding episodes. CONCLUSION. Antithrombotic therapy with vitamin K antagonists can achieve good anticoagulation and long-term successful prevention of repeated cardioembolic strokes in patients with atrial fibrillation. We emphasize the need for highly motivated patients to regularly monitor the level of anticoagulation via INR and the full engagement of the prescribing physician. In this case, we emphasize the frequent problem of delays in the introduction of anticoagulation therapy in atrial fibrillation. Stroke prevention is the cornerstone of care for patients with atrial fibrillation.

Key words: atrial fibrillation, stroke prevention, thromboembolic stroke, vitamin K antagonists, non-vitamin K anticoagulant drugs, INR, TTR,.

INTRODUCTION

AF is the most common long-term arrhythmia and represents a major public health problem. It is estimated that the number of patients will progressively increase in the next few decades, primarily due to the aging of the general population, in which this arrhythmia occurs more often [1]. Atrial fibrillation (AF) is characterized by disorganized, rapid, and irregular activation of the atria, with a lack of atrial contraction and irregular ventricular rate. Absolutely irregular RR intervals (which is why it

is also called absolute arrhythmia), lack of P waves, and atrial frequency higher than 300/min, are registered electrocardiographically. Risk factors for developing AF, in addition to age, include hypertension, diabetes mellitus, heart disease, and sleep apnea. AF increases the risk of ischemic stroke fivefold. Cardioembolic stroke associated with AF is usually severe, highly recurrent, and often fatal or with permanent disability [2]. Ischemic stroke in patients with AF is most often caused by the dissemination of a thrombus formed in the auricle of the left atrium [3]. The risk for stroke associated with AF is not homogeneous, considering that it depends on the presence of specific stroke risk factors/modifiers. Common risk factors are summarized in a risk factor-based clinical score called the CHA2DS2-VASc Score, in which congestive heart failure, hypertension, age 65-74 years, diabetes, peripheral vascular disease, and female gender contribute 1 point each, while previous ischemic stroke or transient ischemic attack (TIA) as well as age ≥ 75 years carry 2 points (TABLE 1). Lifelong anticoagulant therapy is always recommended in patients with atrial fibrillation for stroke prevention when the CHA2DS2-VASc score is > 2 in men and > 3 in women (recommendation class I, level of evidence A), and may be considered in CHA2DS2-VASc score = 1 in men or = 2 in women (recommendation class IIa, level of evidence B) [4].

TABLE 1 CHA2DS2-VASc Score: Clinical Risk Factors for Stroke, Transient Ischemic Attack

CHA2DS2-VASc Risk Factor Score		Score
C	Congestive heart failure	1
H	Hypertension	1
A2	Age >75 years	2
D	Diabetes	1
S	Stroke/transient ischemic attack	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Females	1
Maximum score		9

TABLE 2 One-year frequency of stroke (%) in AF according to CHA2DS2-VASc score

CHA2DS2-VASc score	One-year incidence of stroke %
0	0.78
1	2.01
2	3.71
3	5.92
4	9.27
5	15.26
6	19.74
7	21.50
8	22.38
9	23.64

Before initiating oral anticoagulant therapy, the risk of bleeding should be assessed using the HAS-BLED score (hypertension, abnormal kidney/renal function, stroke, bleeding history or predisposition, labile INR, age over 65 years, drug/alcohol use) and if it is high, i.e. over 3, the correction of modifiable risk factors should be considered and those patients should be monitored more often, but certainly a high score is not a reason to stop anticoagulant therapy (recommendation class IIa, level of evidence B) (TABLE 3) [5].

TABLE 3. HAS-BLED Score: assessment of bleeding risk for patients with AF

Risk factors		Score
H	Hypertension	1
A	Abnormal liver or kidney function (1 point for each)	1 or 2
S	A punchline	1
B	Bleeding	1
L	Labile INR values	1
E	Older than 65 years	1
D	Drugs or alcohol (1 point for each)	1 or 2
Maximum score 9		

For more than 60 years, vitamin K antagonists (VKA) have been used to prevent stroke in patients with AF [6]. Oral VKAs are coumarin derivatives that inhibit the synthesis of vitamin K-dependent coagulation factors (II, VII, IX and X) in the liver. Representatives of this group of drugs are acenocoumarol, warfarin, and rarely phenprocoumon [7]. The safe and effective use of these drugs implies regular control of indicators of the intensity of the anticoagulant effect of vitamin K antagonists, the INR (international normalized ratio of prothrombin times), which should be in the range of 2.0 to 3.0 [8] .

Poor INR control increases the risk of both thromboembolic and hemorrhagic complications, and the optimal balance between the benefits and risks of using oral VKAs is achieved when the TTR or time in the therapeutic range is ≥ 70% [9] .

In the last few years, several phase III randomized clinical trials comparing the effect of new oral anticoagulant drugs with warfarin in the prevention of thromboembolism in AF have been completed. The new drugs are divided into two groups: oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban and apixaban). The advantage of the new drugs lies in the smaller number of clinically significant interactions with food and other drugs and the absence of the need for regular laboratory monitoring of the anticoagulant effect, with equal effectiveness in the prevention of thromboembolism and a lower frequency of significant bleeding compared to VKA (10,11).

We present the case of a female patient, which confirms the importance of oral anticoagulant therapy when the INR is in the therapeutic range between 2-3 for most of the time in the prevention of recurrent thromboembolic complications during the 14-year follow-up.

Material and methods

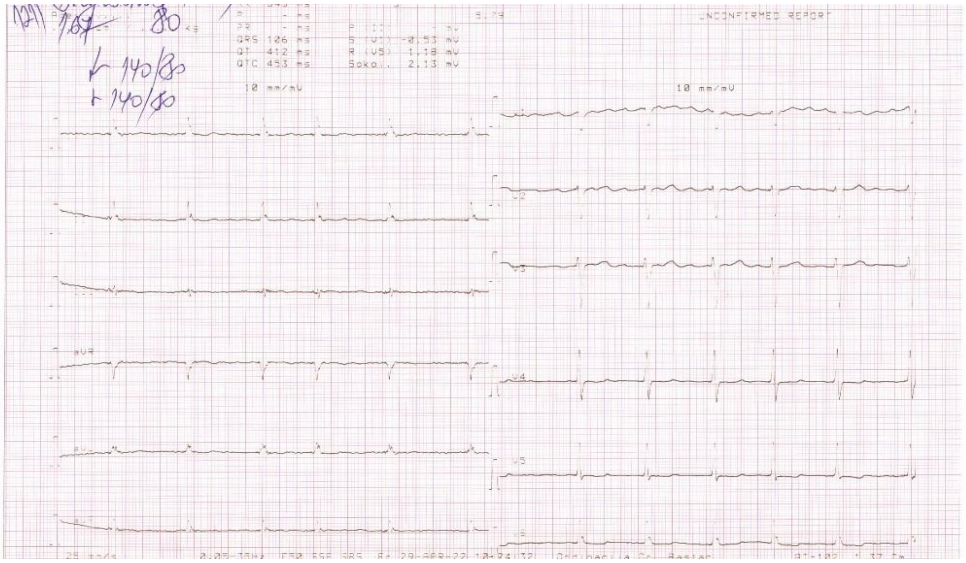
The material used for the preparation of this paper was the patient's electronic health record as well as his personal medical documentation (laboratory analysis findings, specialist doctor's reports and discharge list). The method of retrospective analysis of medical records was applied.

Case presentation

The case is about a 60-year-old MD patient who came to the Office of Internal Medicine "Dr. Bastać" for the first time in 2008 due to a feeling of instability and heart palpitations. Due to grade II hypertension, which is not well regulated, she has been taking antihypertensive therapy for the past two years, treating elevated cholesterol with a statin. She has had palpitations and arrhythmia for the last 2 years, two years ago and a year before her first examination at the Office of Internal Medicine"Dr. Bastać" office, she had two minor strokes verified by MSCT of the endocranium. The patient is a non-smoker, pre-obese BMI 29.0 with pronounced abdominal obesity (waist circumference 104 cm). During the physical examination, we determined that the patient was cardiopulmonarily compensated and hemodynamically stable. Heart rhythm was irregular, tones were clear, murmurs were not registered. Blood pressure on arrival, measured

brachially bilaterally, was 170/100 mmHg. Auscultation of the lungs revealed a normal respiratory murmur. The liver was not enlarged and there was no pretibial edema. Hematological and biochemical analyzes were within normal limits. ECG on arrival: atrial fibrillation, fr 85/min, normogram, incomplete left bundle branch block, horizontal depression ST -0.5 in V5-V6 (Figure 1).

Figure 1. ECG on arrival from 2008



Echocardiographic findings from 2008 indicate that the left ventricle was of normal dimensions without myocardial hypertrophy and with preserved global systolic function. There were no segmental outbursts in the contractility of the left ventricular walls. Mitral cusps were slightly more voluminous with minor mitral regurgitation. Left sternum dilated, 39 mm measured in a standard parasternal section. Right ventricle of normal dimensions.

After the completed physical examination and additional diagnostics, the CHA2DS2-VASc Score and the HAS BLED Score were calculated. In this patient, CHA2DS2-VASc was 4 (hypertension, female gender and previous stroke) and the estimated annual risk for stroke is 9.27% (TABLE 2). The calculated HAS BLED Score is 2 (hypertension, CVI). Based on CHA2DS2-VASc, the risk of adverse thromboembolic events is high and requires the introduction of oral anticoagulant therapy. The patient in therapy receives acenocoumarol according to the scheme that the value of PT/INR should be between 2.0 and 3.0 with the note that if a serious bleeding episode occurs, she should stop taking acenocoumarol , check the value of PT/INR and contact the doctor. After this first examination, the patient regularly came for follow-up examinations. PT/INR was done initially for 2 weeks and later for a month. When INR stability was achieved, INR control for 2 months was sufficient, which is optimal for these patients.

The time in the therapeutic range (TTR) could not be calculated by the most commonly used Rosendaal method due to the lack of a sufficiently large number of INR measurements over the years (12, ie once a month). That is why the method used in their study " One -year monitoring of the quality of oral anticoagulant therapy in patients with atrial fibrillation and analysis of the impact on the quality of anticoagulation" was used by Dr. D. Bastać and colleagues, where the criterion for excellent anticoagulation was that within a year 5 to 7 measured values of PT/INR will be ≥ 2 .-TTR >60-85% of the time). Good anticoagulation is defined as having 3 to 4 PT/INR values in the therapeutic range (analogous to TTR 50 to 60% of the time), while poor anticoagulation is: 0-2 measured INR values in the therapeutic range

(TTR <50%) [3]. In this patient, TTR is about 70%, which represents excellent anticoagulation.

During 14 years of regular follow-up every three months, as well as telephone consultations to achieve optimal INR, as well as at the recent check-up on 04/29/2022., the patient felt well, with no new thromboembolic complications and no bleeding episodes.

DISCUSSION

In the last few years, several phase III randomized clinical trials comparing the effect of new oral anticoagulant drugs with warfarin in the prevention of thromboembolism in AF have been completed. The new drugs are divided into two groups: oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban and apixaban). The advantage of the new drugs lies in the smaller number of clinically significant interactions with food and other drugs and the absence of the need for regular laboratory monitoring of the anticoagulant effect, with equal effectiveness in the prevention of thromboembolism and a lower frequency of significant bleeding compared to VKA (10,11). But the presented case shows that long-term successful prevention of repeated cardioembolic strokes in patients with permanent atrial fibrillation can also be achieved with classic antithrombotic therapy with VK antagonists.

A high CHA2DS2-VASc score of 4 (hypertension, female gender and previous stroke) with an estimated annual risk for stroke of 9.27% was an absolute indication for the introduction of anticoagulant therapy. Her bleeding risk - HAS BLED Score is moderate and is 2 (hypertension, CVI). Based on CHA2DS2-VASc, the risk of adverse thromboembolic events is high, and oral anticoagulant therapy was immediately introduced, with acenocoumarol according to the scheme that the value of PT/INR should be between 2.0 and 3.0 Unfortunately, due to the delay in the therapeutic sense, 2 years were missed by the prescribing doctors and only after 2 strokes we introduced anticoagulant therapy

A high CHA2DS2-VASc score of 4 (hypertension, female sex, and previous stroke) with an estimated annual risk for stroke of 9.27% was an absolute indication for the initiation of anticoagulant therapy before strokes occurred. The problem of delay in the introduction of anticoagulant therapy in particularly asymptomatic AF is great in practical work. An effort is needed in medical practice to introduce early oral anticoagulant therapy in AF and avoid well-preventable events such as cardioembolic complications, especially stroke.

People who do not have the financial ability to take NOAKA can be adequately treated with high-quality anticoagulation with dicoumar preparations with the involvement of the prescribing physician and the patient's motivation. However, clear indications for switching from vitamin K antagonists to NOAC regardless of the patient's financial burden are: labile INR, frequent bleeding, thromboembolic attacks despite a relatively good time spent in the therapeutic range (TTR).

On the other hand, vitamin K antagonists have an advantage in AF in the prevention of stroke when new anticoagulant drugs, non-VK antagonists are contraindicated in AF as part of mitral stenosis and mechanical artificial valves. Also, in severe renal insufficiency, when the glomerular filtration rate is less than 30 ml/min, and in all hemodialysis patients, NOAKA must be switched to dicoumarol preparations.

CONCLUSION

The presented case confirms the view that, even in the era of new anticoagulant drugs NON-VK antagonists (NOACs), classic antithrombotic therapy with Vitamin K antagonists can achieve good anticoagulation and long-term successful prevention of repeated cardioembolic strokes in patients with permanent as well as paroxysmal atrial fibrillation based on CHA2DS2-VASc score without significant hemorrhagic complications, the risk of which we assess HAS BLED Score

During 14 years of monitoring for three months, as well as at the recent control on 04/29/2022., our patient has had no new thromboembolic complications and no bleeding episodes. This proves that patients with atrial fibrillation can be adequately treated with high-quality anticoagulation with dicoumarol preparations with great involvement of the prescribing physician and good motivation of the patient even when they do not have the financial means to switch to non-vitamin k anticoagulant drugs.

In connection with this case, we highlight the frequent problem of delay in the introduction of anticoagulant therapy in atrial fibrillation. An effort is needed in medical practice to introduce early oral anticoagulant

therapy in AF and avoid well-preventable events such as cardioembolic complications, especially stroke. Stroke prevention is the cornerstone of care for patients with atrial fibrillation.

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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;

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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.

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Standard journal article:

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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.

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

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Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

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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.

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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.

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Electronic material

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

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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/.

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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

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Kosančićev venac 16 19000 Zaječar
Serbia (Republic of Serbia-RS)
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dusanbastac@gmail.com

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