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ORIGINAL PAPERS

INR VALUES WITH PATIENTS ON ORAL ANTICOAGULANT THERAPY DURING COVID-19 PANDEMICS

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INTRODUCTION

Anticoagulant therapy is used for treating and preventing arterial and vein thrombosis. Heparin and oral anticoagulant therapy are most commonly used. Warfarin is most commonly used in treating patients with atrial fibrillation (FA), arterial and vein thrombosis, pulmonary embolism (PTE) and mechanical valve (AVR/MVR). The main complication of anticoagulant therapy is bleeding. This is why the laboratory testing of hemostasis is done:

- Before therapy, for making a decision about the type of therapy and the dosage
- During therapy for achieving optimal effect
- In case of bleeding for determining cause and taking adequate measures [1].

Anticoagulant therapy is widely used for treating and preventing arterial and vein thrombosis. It is also very successful for preventing arterial thrombosis and embolism. Therapeutic answer to oral anticoagulant therapy is individual. Therapy is time-consuming; it takes months and with some patients their entire life [1,2]. The mechanism of action is antagonism with vitamin K in carboxylation of glutamine acid in vitamin K molecules of dependent factors (FII, FVII, FIX, FX) and coagulation inhibitors which leads to synthesis of biologically inactive molecules [3]. Due to this fact patients on OAT need regular check-ups and their dosage needs to be adjusted to the results of the check-up. Prothrombin time is most commonly used for check-up and the test sensitivity depends on the type of reagent (thromboplastin). Due to this, the standardization of the OAT check-up has been introduced. Certain types of thromboplastin are marked as reference values and their sensitivity is marked as 1. The sensitivity of commercial thromboplastin is determined according to the reference value and they get the sign ISI (International Sensitivity Index), which marks the sensitivity of the reagent of hemostasis disorder caused by the change of OAT compared to reference thromboplastin. The way of expressing results is also standardized in INR units (International Normalized Ratio) INR is calculated when the relation between PT, patient's plasma and normal plasma is degreed with the value of ISI [3].

The INR value for OAT should be between 2.0-3.5, and if the patient is being prepared for surgical intervention INR should be smaller than 1.6. The COVID-19 pandemics had made it harder or even impossible for patients who use warfarin to come to regular check-ups. The situation is even more complicated by using supplements, antibiotics and other drugs which were used in treating COVID-19.

Warfarin has a narrow therapeutic range and demands careful tracking to make sure its safety and efficiency [4,5]. The appearance of COVID-19 pandemics has set a challenge for patients as well as health workers. Introducing numerous measures in order to prevent the spreading SARS-CoV-2 virus has been very challenging for patients who come regularly on INR check-ups for assessing the efficiency of warfarin/acenocoumarol. These measures included the prohibition of gathering indoors, also infirmaries were mostly used for treating COVID-19 patients, especially in the beginning, public transport was also more complicated [6]. Furthermore, symptomatic presentation of COVID-19 usually includes fever, and earlier it was noticed that fever usually influences the effect of warfarin [7,8].

METHODS

This study includes 89 patients, older than 18, both genders, all age groups who used anticoagulant therapy before the pandemics. The patients were elected by the method of random sample. The information about age, gender, diagnosis and INR control values (International Normalized

Ratio) was taken from the available database from the information system of Polyclinic for Transfusion Medicine UKC Tuzla in the period during 2019 and 2020 and these were compared. INR value is determined on BCS XP System - Siemens Healthineers machine.

The study includes patients who used anticoagulant therapy. The INR oscillations were investigated with 30 patients with atrial fibrillation, 30 patients with mechanical valve, 29 patients with pulmonary embolism/deep vein thrombosis. The subject of investigation was the change of INR value during 2019 which marks the time before COVID-19 pandemics, and INR values during 2020 at the time of COVID-19 pandemics, with the same patients. Based on anamnesis (change of therapy, self-initiated vitamin supplements and other) we analyzed the information on the disorder of recommended values 3.5< INR <2.0, as well as how many patients had recommended INR values for patients on OAT vitamin K antagonists. It is also to be mentioned that in our facility, it is the transfusion specialist doctor who determines the dosage of the medicine. The period between INR controls in 2019 and 2020 was also investigated as well as the frequency of appearance of hemorrhagic syndrome symptoms in patients who were investigated. These information were collected in Microsoft Excel. For the purpose of statistical analysis we used standard statistical parameters (average value, standard methods (%), MS Excel, Hi square test). Collecting and publishing information was approved by the consent of the Ethical comity UKC Tuzla.

AIM OF THE PAPER

The aim of this research was to check the frequency of disorders in INR values during COVID-19 pandemics. The aim was to investigate whether the oscillations are more common before or during the pandemics as well as which factors might have influenced those. We wanted to portray the percentage of appearance of signs of hemorrhagic syndrome as well as possible causes in INR value disorders. The given information will show the meaning of regular INR controls as well as the need for correcting therapy.

RESULTS

In public healthcare facility, University clinical center Tuzla (UKC TUZLA) at Policlinic for blood transfusion, a retrospective research was conducted on the disorder of INR values in patients on regular oral anticoagulant therapy with vitamin K antagonists. The research included 89 patients divided into three groups based on their primary diagnosis for which they are on anticoagulant therapy. The first group is patients with atrial fibrillation diagnosis, second group is mitral/aortal mechanical valve and the third group is pulmonary thromboembolism and deep vein thrombosis. Figure 1 portrays age and gender structure as well as diagnosis representation.

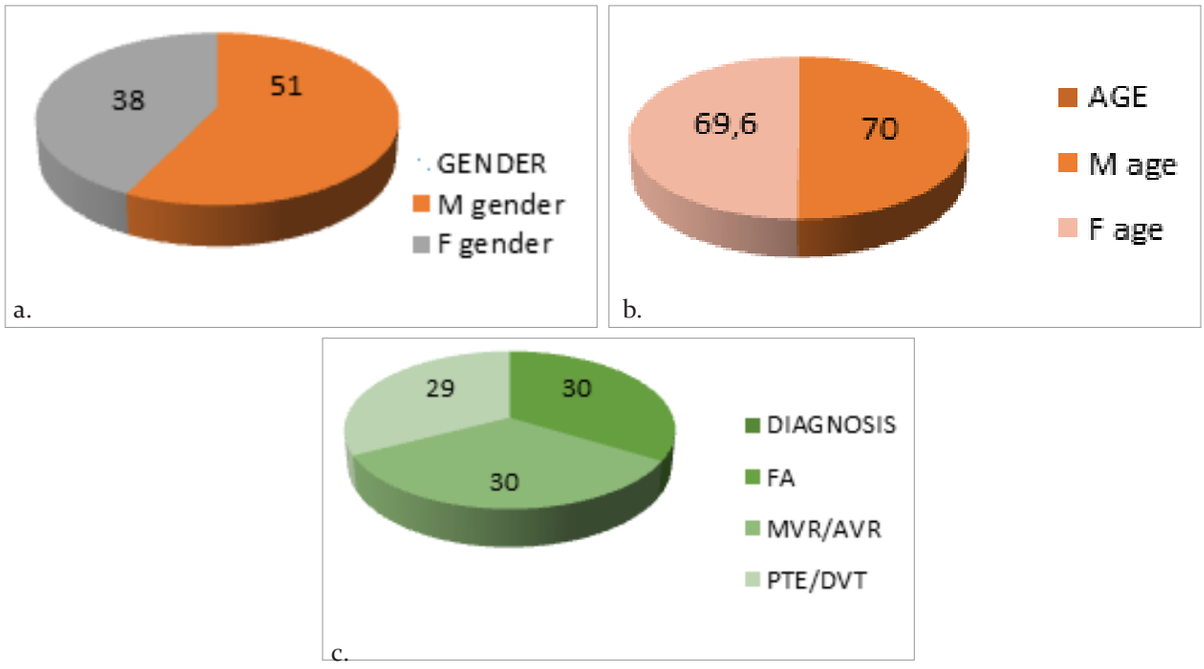

Figure 1. a. Gender structure of the examinees (M-men, F-women); b. Age structure (M-men, F-women); c. Diagnosis representation (FA-atrial fibrillation, MVR/AVR-mitral/aortal mechanical valve, PTE/DVT-pulmonary embolism/deep vein thrombosis)

As far as the gender representation is concerned, from the examinees there are 57.3% (51) men and 42.7% (38) women, and the total average age of the patients is 69.8 years. All patients on oral anticoagulant therapy by vitamin K antagonists must regularly control their INR values for determining the dosage of the medicine. The frequency of controls and the check-ups of INR values during 2019 and 2020 are shown on table 1.

Table 1. Average INR controls expressed in weeks

Year	FA/Week	MVR/AVR/ Week	PTE/DVT/ Week	Total	Average value/ year
2019	4.0	5.2	5.5	14.6	4.9
2020	6.1	7.1	10.8	24	8

FA-atrial fibrillation, MVR/AVR-mitral/aortal mechanical valve, PTE/DVT-pulmonary embolism/deep vein thrombosis

As it was previously stated it is visible that patients prolonged the time period between regular controls in comparison to recommended controls (every 4 weeks). When it comes to comparing periods before and during COVID pandemics we see that the control period is prolonged for 3.1 week in average in relation to the total number of patients who were investigated. Most common breaks that the patients made between controls were in the period February-May 2020, 45 patients (50.6%), and 41 patients (46.1%) in the period February-June/July. Only three patients (3.3%) came to regular controls even though it was in the period of restrictive measures for preventing the spreading of SARS-Cov2 virus. The percentage of the patients who had recommended INR therapeutic values (2.0-3.5) in relation to their diagnosis in 2019 and 2020 are shown on figure 2.

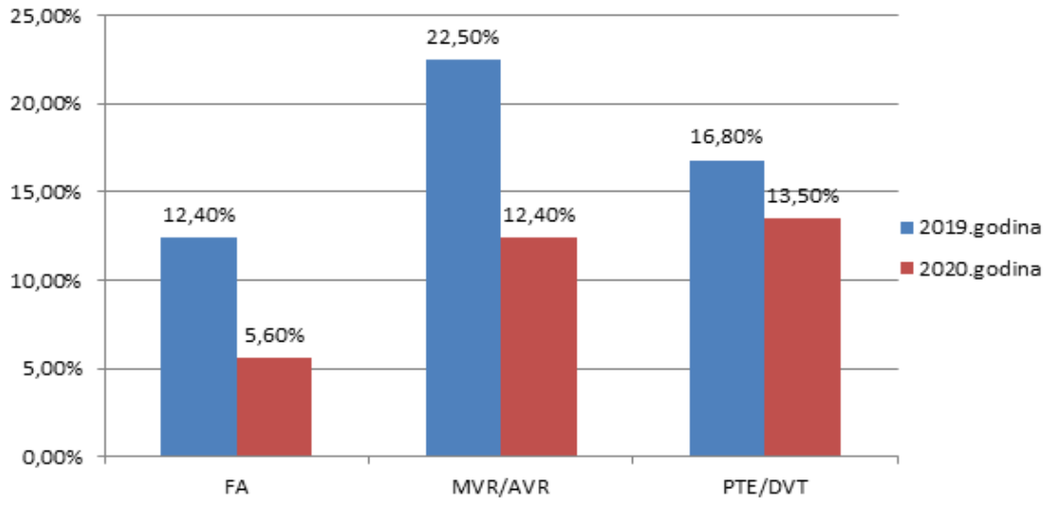

Figure 2. Percentage of patients with therapeutic values of INR in 2019 and 2020. FA-atrial fibrillation, MVR/AVR-mitral/aortal mechanical valve, PTE/DVT-pulmonary embolism/deep vein thrombosis

Average INR values in relation to diagnosis is shown in table 2 where it is evident that there is no statistically relevant difference in INR values from 2019 compared to 2020 (p=0.05).

Table 2. Average INR value in relation to diagnosis

Dg/average INR	2019 year	2020 year
FA	2.5	1.6
MVR/AVR	2.8	1.9
PTE/DVT	2.6	1.7

FA-atrial fibrillation, MVR/AVR-mitral/aortal mechanical valve, PTE/DVT-pulmonary embolism/deep vein thrombosis

Average INR value in 2019 was 2.6 and in 2020 it was 1.7. Vitamin K antagonists are drugs on which other substances as well as diet have a huge synergistic/antagonistic impact. Most common possible causes of reducing INR values INR<2.0, in examinees, and on the basis of available anamnestic data from the database at the Policlinic for blood transfusion, are shown in table 3, as well as on figure 3 in percentages.

Table 3. Causes of INR disorders INR<2,0.

Causes of INR disorders	2019		2020	
INR<2.0	Number	Percentage%	Number	Percentage%
Tooth extraction	5	5.6	3	3.4
Irregular medicine taking	10	11.2	28	31.5
Preparation for surgery	4	4.5	4	4.5
Diet	9	10.1	21	23.6
Change of therapy	4	4.5	1	1.1

The data was processed by Chi square test on MedCalc's statistical free calculator (Chi=9.3, p=0.05). There is no significant statistical difference on the causes of INR reduction in value under therapeutic range in the period during COVID pandemics, in relation to the period before the pandemics (p<0.05). The most common cause in reduction of INR values during the pandemics was that the patients haven't regularly taken their recommended medicine dosage, and that they have reduced their dosage on their own initiative, 28 patients (31.5%), who were scared of bleeding and were unable to come to regular controls due to the measures of preventing COVID pandemics (movement prohibition, indoor gatherings...).

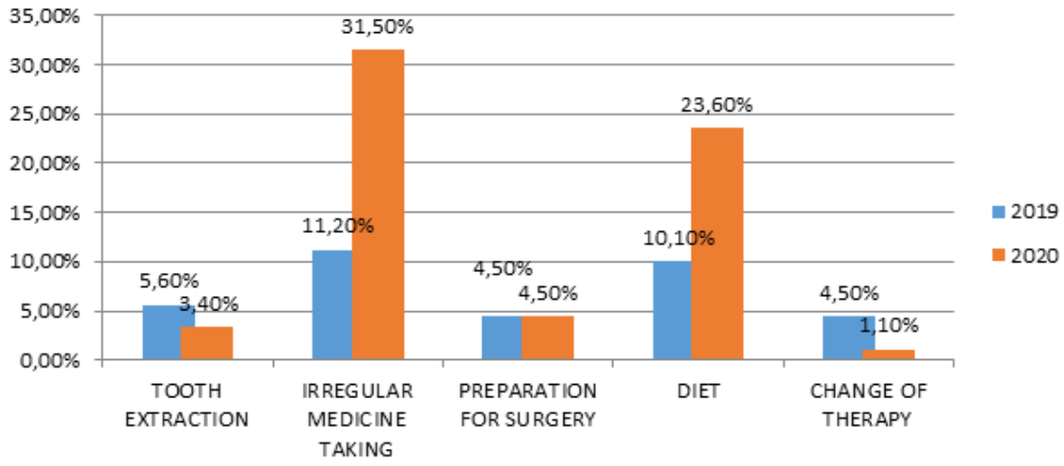

Figure 3. INR values <2.0 2019/2020 year

The most common cause of increase in INR values during the pandemics was the use of antibiotics in 13 patients (14.6%) in relation to the year before the pandemics when only two patients reported antibiotics as possible causes of increasing INR values above therapeutic values. Other causes of increased INR values INR >3.5 with patients on oral anticoagulant therapy are shown on figure 4. Research has shown that there is statistically significant difference in factors which influenced the increased INR value INR >3.5 during COVID pandemics (p=0.006).

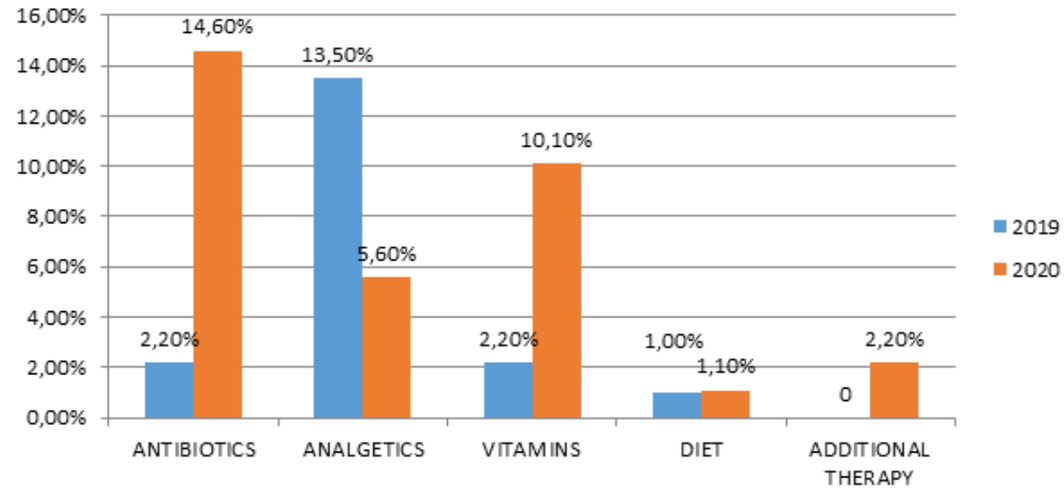

Figure 4. Causes of increased INR >3.5 2019 and 2020 year

Bleeding is a complication of INR value >3.5. In table 4 are patients who had symptoms of hemorrhagic syndrome (bruising, nose bleeding, hematuria).

Table 4. Manifestations of signs of hemorrhagic syndrome before and during the pandemics

Bleeding	2019		2020	
	Number	Percentage%	Number	Percentage%
Epistaxis	1	33.3	2	28.6
Hematoma	2	66.7	2	28.6
Hematuria	-	-	3	42.8
Total	3	100	7	100

As it was previously mentioned, during 2019 46 (51.7%) patients had normal INR values while 43 (48.3%) patients had oscillations in INR values outside the therapeutic range of warfarin. During 2020 only 28 (31.5%) patients had INR values inside therapeutic values while 61 (68.5%) patients had oscillations in INR values outside therapeutic values.

These points to the fact that COVID pandemics had significantly influences the maintaining INR values inside therapeutic values.

DISCUSSION

When the epidemics broke out, hospitals and infirmaries were originally used for treating COVID patients. In this way patients who came to regular controls for their INR values were denied from regular controls. Furthermore patients were worried because hospitals and infirmaries were an easy source of infection spreading. Taking all these factors into consideration, the number of examinations of patients on warfarin was reduced. In our study, all the examined patients came less often to controls or they made longer time breaks between regular controls during COVID pandemics. Warfarin has a narrow therapeutic range and wide variability in relation dosage-answer. In most situations target INR is 2.5 (target range 2.0 – 3.5). This range is appropriate for prophylaxis or treating vein thrombosis and reducing risk from system embolism in people with atrial fibrillation and valve heart disease [9]. During COVID, in the research in anticoagulant clinic (HAC) and Internet anticoagulant clinic (IAC) Nanjing Drum Tower Hospital it can be seen that 73.1% is in HAC group and 69.8% in IAC group had recommended INR values [10]. A research in Croatia showed that 93.1% examinees had targeted INR [11]. Almost identical share of examinees for targeted INR was in research by Li and all [12]. A total of 92.3% of their examinees also had targeted INR value 2 – 3 while in a study by Baker and all [13] 89.7% examinees had these INR values. This ratio of targeted INR values is to be expected because warfarin indications whose targeted INR value is 2-3, are more common in population. Warfarin therapy is in most cases lifetime. In our study, during 2019 51.7% patients had targeted INR values and during the pandemics only 31.5% patients had targeted INR values which is significantly less when compared to other researches. Warfarin is a medicine which most commonly interacts with other herbal preparations [14]. It is clinically confirmed that warfarin interacts with more than 50 plant species and Ramsay and associates study from 2005 shows that 58% patients takes some dietary supplements or herbal medicine along with warfarin and which can interact [15]. Our research has shown 10.1% patients in 2019 and 23.6% patients in 2020 added herbal preparations and vitamins to their diet. Many medicines and herbs act synergistic with warfarin and increase the INR values. Warfarin interactions with herbal preparations, dietary supplements and vitamins which affect the increase of INR (grapefruit juice, cranberry juice, ginger, gingko, glucosamine and chondroitin coenzyme Q10...)[16]. Medicines such as allopurinol, amiodarone, antibiotics especially macrolides, metronidazole, antifungal medicines, antidepressants anti-aggregation agents, anti-inflammatory agents, NSAID and others, also act synergistic with warfarin [17-19]. Warfarin also has pharmacodynamics reactions with NSAID medicines [20]. The research from Zadar from 2019 shows that 16% of patients had INR values >3.5 [21]. In USA before the COVID pandemics 82% of patients was exposed to changes of INR value>3.0 [22]. During COVID pandemics, a study in London showed that 73% examinees had high INR values. The most common reason for this was COVID infection (53% examinees), antibiotic therapy (57%), change of therapy (7%) and extended testing interval (3% examinees) [23]. Also, a study in Great Britain showed that the reasons for high INR values which were named by patients were 35% change of medicines, 25% change of lifestyle, 7% new infection, 7% change of dosage, 6% unknown cause and 20% taking the wrong dose of warfarin [24]. In our study in 2019 year 19.1% patients had INR >3.5, while 21.3% patients had oscillations 2>INR>3.5 during this period. In the period of pandemics in 2020, 33.7% patients had INR >3.5, and 31.5% had 2.0> INR >3.5 in 2019. And the most common cause of high INR values was the usage of analgesics (13.5%). In 2020 INR>3.5 was noticed in 14.6% patients because of the usage of antibiotics and in 10.1% of patients because of the usage of vitamins.

A big number of groceries influences on reduction of INR value. Among those the biggest impact comes from groceries rich in vitamin K. Green vegetables (spinach, lettuce, arugula cabbage, kale, broccoli and others) are a source of the most represented form of vitamin K, phylloquinone. Other sources of phylloquinone are herbal oils, fruti, seeds and milk products [25]. Fast food also contains vitamin K because of the

oils used in preparing [20]. A study by Khan and associates (2004) has shown that for every increase of vitamin K in about 100 μg every four days, INR reduces by 0,2 [26]. Tann i Lee (2020) have recommended in an article that patients and health workers pay attention to warfarin interaction with chamomile tea, cannabis, green tea, spinach and sushi consumption [27]. Smoking also causes liver enzymes induction where there is increased clearance of warfarin and a need for bigger dosage [18]. Many medicines influence the reduction of INR values in patients on oral anticoagulant therapy with warfarin, such as hypnotics, antiepileptic drugs, vitamin K, oral contraception, blood or plasma transfusion, tegretol, phenobarbitone, primidol, antibacterial drugs such as rifampicin, anxiolytics, diuretics, ritonavir and other [1,28]. A study in Croatia from 2019 shows that INR<2 had 56% patients [21]. A research in CoagClinic from 2015 shows that more than 90 % of patients had at least one INR value bellow therapeutic range, and 23% of measured INR values were less than 2 [22]. A research from Salt Lake City, during COVID pandemics showed that there very little changes in the percentage of patients with low INR values. However, the average value of INR <1.5 during research in Utah was in 62.7% of patients, while in Washington it was recorded in 18.3% of patients [29]. Our research has shown that in 2019. INR<2.0 was recorded in 21.3% of patients. In the period of pandemics, 2020, 27% of patients had INR<2.0. The values of INR<2.0 in the period of pandemics were most commonly due to the fact that patients had not taken their therapy regularly (31.5% examinees), diet changes (23.6%). In 2019 the same causes were most common; 11.2% had not taken their therapy regularly, and 10.1% had not followed their diet recommendations.

Changes of INR values can lead to complications. In Turkey, out of 71 (20%) patients on oral anticoagulant therapy who had signs of bleeding, 60% did not require medical help, 6% of patients reduced their dosage on their own initiative, and 34% of patients came to their doctors [30]. In our study, during 2019, 3.4% patients said they had symptoms of hemorrhagic syndrome (nose bleeding, body bruising). 66.7% (2 out of 3 patients) did not require additional medical care, and only one patient (33,3%) was placed a nose tamponade, during examination a high blood pressure was noticed as well, 180/110 mmHg, which additionally increased the bleeding. However in 2020, in the pandemics period out of 89 examinees 7 (7.9%) had symptoms of hemorrhagic syndrome (epistaxis, body bruising, hematochezia, blood in eyes). 42.8% (3 out of 7) patients demanded additional medical help and they also checked in their attending doctor specialist, 2 (28.6%) patients from the total number of patients with symptoms of hemorrhagic syndrome who reduced their warfarin dosage on their own initiative did not demand medical assistance.

CONCLUSION

Our research has shown that all patients who use oral anticoagulant therapy came to control their INR values significantly less often during the pandemics.

The consequence of this is visibly smaller number of patients who had expected INR values 31.5% of patients, and in the period before the pandemics, 51.7% patient had expected INR values.

As a consequence of not regulating INR there is a statistically significant incidence of hemorrhages out of which 42.8% demands additional medical care. The reasons for increased INR values during the pandemics is the usage of antibiotics, 14.6% of patients and various supplements and vitamins as dietary supplements, 10.1% of patients in relation to the period before the epidemics when the most common reason for INR>3.5 was the usage of analgesics 13.5%.

In the examined groups, most common normal and best regulated INR values during 2019 were recorded in patients with MVR/AVR 22.5%, and during 2020 these were in patients PTE 13.5%. The least regulated values were recorded in patients with FA during 2019 12.4%, and during the pandemics only 5.6%.

RECOMENDATIONS

Considering the COVID pandemics and the way of spreading, patients will continue to avoid more frequent controls because of the risk of transmitting the virus. All patients and especially patients on permanent warfarin/acenocoumarol should be enabled an independent monitoring by a manual device.

Other patients, such as patients who use warfarin due to atrial fibrillation should be treated with new oral anticoagulant medicines because these can be controlled on distance, via phone or online based systems.

In practice, a positive reinforcement of protective net during warfarin treatment remains of great significance. Doctors have to keep tracking the patient and the medicine dosage to make sure that patients have the necessary knowledge about the medicine, to inform the doctor about every change of the medicine, lifestyle or health condition based on which a doctor will make an assessment about the need for more frequent INR controls.

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