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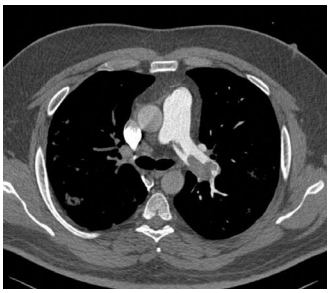

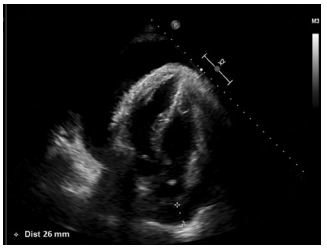

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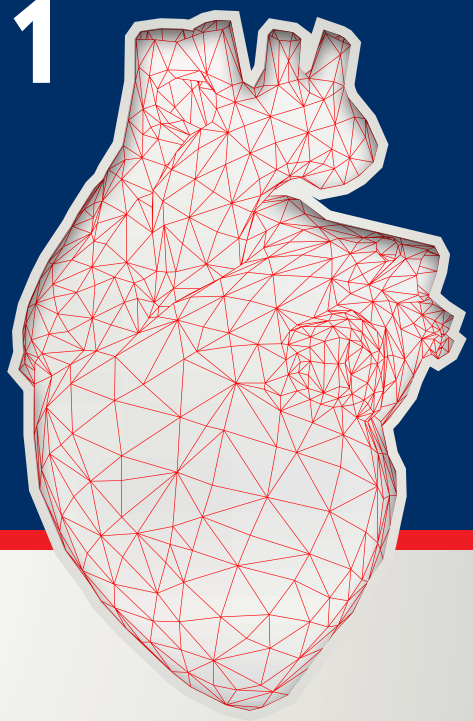

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Od Redaktora

Szanowni Państwo,
Drodzy Czytelnicy,

czerwcowy numer *Folia Cardiologica* do wielu z Państwa trafia podczas letniego urlopu, tym bardziej mi miło, że umieszczone w nim prace mogę Państwu rekomendować jako wartościowe i ciekawe.

„Clinical aspects of QTc interval analysis in adult patients with anorexia nervosa" to praca oryginalna dr. Karola Głowackiego i wsp. z I Katedry i Kliniki Kardiologii Górnośląskiego Centrum Medycznego Śląskiego Uniwersytetu Medycznego. Powikłania kardiologiczne pacjentów z jadłowstrętem psychicznym, chociaż znane, nie są zbyt często przedmiotem dysertacji naukowych, a zagadnienie to nie traci, a zyskuje na aktualności. Zwiększone ryzyko komorowych zaburzeń rytmu w tej grupie chorych wiąże się z wydłużeniem odstępu QT. Autorzy poddali analizie zapisy elektrokardiogramów 56 pacjentów z jadłowstrętem psychicznym, spośród których 3/4 nie stosowało leków wydłużających odstęp QT. Odstępy QT mierzono w 12-odprowadzeniowym zapisie elektrokardiograficznym i korygowano przy użyciu czterech wzorów: Bazetta, Fridericia, Framinghama i Hodgesa. Najmniej zależne od tętna okazały się odstępy QT ustalone przy użyciu formuł Framinghama i Fridericia.

Artykuł Klary Kowalczyk i wsp. z Międzyleskiego Szpitala Specjalistycznego Warszawskiego Uniwersytetu Medycznego pt. „The prevalence of cardiovascular risk factors related to lifestyle in medical students" jest poświęcony ocenie wybranych czynników ryzyka sercowo-naczyniowego zależnych od stylu życia oraz czynników kardioprotekcyjnych w grupie studentów Warszawskiego Uniwersytetu Medycznego. Osoby te, jak można byłoby się spodziewać, powinny wzorcowo wdrażać elementy zdrowego stylu życia w codziennym życiu, niestety — jak wykazała analiza — mimo wysokiej świadomości zagrożeń studenci kierunków medycznych nie są wolni od czynników ryzyka sercowo-naczyniowego. Odsetek osób używających nikotynę jest wysoki, sięgając prawie 36%, również inne elementy zachowań prozdrowotnych nie są w pełni realizowane. Okazuje się kolejny raz, że wiedza i praktyka nie zawsze idą w parze.

Niezwykle interesująca i nadal bardzo aktualna (niestety) jest praca poglądowa Jana Jurgiela i wsp. z Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu oraz Uniwersytetu Medycznego im. Marii Sklodowskiej-Curie i Warszawskiego Uniwersytetu Medycznego pt. „What have we learned about COVID-19 in 2020? Ten hypotheses explaining the differences in incidence and mortality from COVID-19 between countries". Od początku wybuchu pandemii COVID-19 obserwowano różnice w zapadalności i śmiertelności w różnych krajach i częściach świata. W artykule omówiono 10 hipotez będących tematem dyskusji naukowych i próbujących wyjaśnić tę obserwację.

Gorąco zachęcam Państwa również do lektury prac kazuistycznych oraz prac umieszczonych w stałych działach czasopisma.

Życząc udanego odpoczynku, pozostawiam Państwa z 3. numerem *Folia Cardiologica*.

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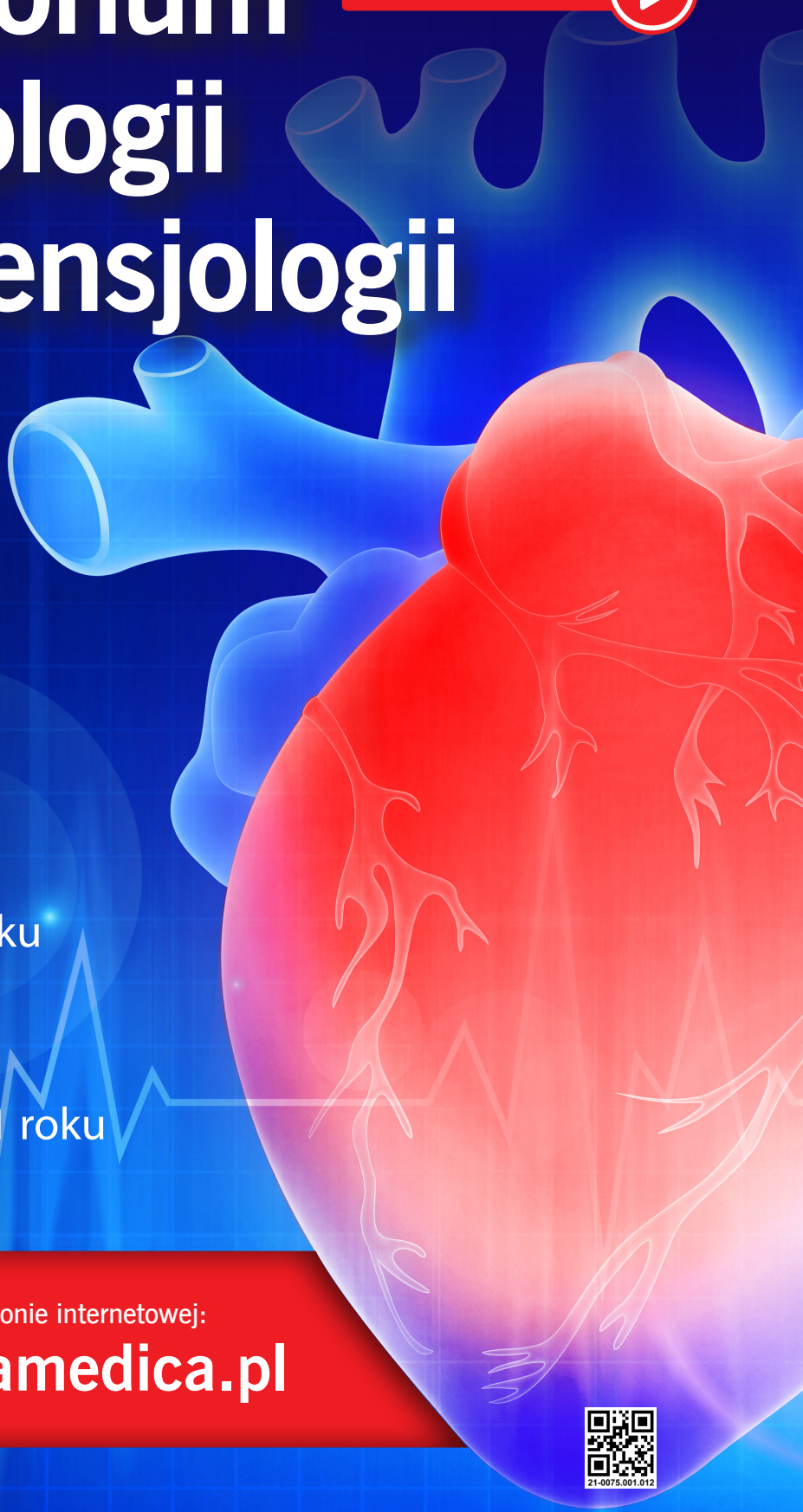

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Clinical aspects of QTc interval analysis in adult patients with anorexia nervosa

Analiza odstępu QT u pacjentów z jadłowstrętem psychicznym

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*Both authors equally participated in the study

Abstract

Introduction. Patients with anorexia nervosa (AN) are at increased risk of ventricular arrhythmias, which are considered to be associated with QT interval prolongation. The aims of this study was to analyze the QT interval in patients with AN considering the potential impact of pharmacotherapy and to verify various QT correction formulas.

Materials and methods. Fifty-six patients hospitalized with AN (average age: 22.8 ± 5.6 years; female/male: 54/2, mean body mass index = 13.6 ± 2.6 kg/m^2) were enrolled in analysis: group non-D (n = 44; 78.6%) included patients who did not use drugs that prolong the QT interval, group D (n = 12; 21.4%) included patients who were treated with such drugs. QT intervals were measured in a 12-lead electrocardiogram and corrected using the four formulas: Bazett, Fridericia, Framingham and Hodges.

Results. Mean heart rate (HR) was similar in both groups (61 ± 16.3 bpm in group D vs. 63.1 ± 18.7 bpm in non-D, p > 0.05). Pathological bradycardia (HR < 50 bpm) was present in 5 patients (41.7%) in group D and in 13 patients (29.5%) in group non-D. QTc interval corrected with Framingham formula was longer in group-D (459 ± 81 ms) vs. non-D group (413 ± 33 ms), p = 0.04. QT interval corrected with Bazett and Hodges formulas was significantly dependent on HR (R = –0.29, p = 0.03 and R = –0.42, p = 0.001, respectively). Influence of HR on results of Fridericia and Framingham formulas was not significant (R = –0.22, p = 0.1 and R = –0.11, p = 0.4).

Conclusions. Information about pharmacotherapy in AN patients is key for QTc assessment. Choice of correction formula has impact on the QTc. QTc obtained using Framingham and Fridericia formulas were the least dependent on heart rate.

Key words: anorexia nervosa, heart rate, QT correction formulas, QT interval, QTc prolongation

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Introduction

Anorexia nervosa (AN) is a severe, often deadly, eating disorder that leads to cachexia and many somatic complications [1]. Among mental disorders, AN has the highest mortality and, according to current data, about 10 percent of patients die from sudden cardiac death (SCD) [2].

Increased risk of SCD in AN is due to many negative factors occurring in the course of the disease that damage the cardiovascular system [1].

Sinus bradycardia is quite commonly observed in patients with AN [3], while the most common reasons of SCD are serious ventricular arrhythmias (such as ventricular tachycardia or ventricular fibrillation). Probability of ventricular arrhythmia increases with changes in repolarization of the ventricular muscle, what is reflected by the changes in the electrocardiogram (ECG). The most common changes associated with an increased risk of SCD in this group of patients are QT prolongation [4, 5] or QT shortening. Most reports on QT interval in AN are based on measurement of QT interval without correction or with correction using the Bazett formula, which is not recommended for patients with bradycardia [6], and these are often people with AN. An important factor causing the frequent occurrence of QT abnormalities in this group are the drugs used by these patients, which may affect the QT interval and have a proarrhythmic effect [7]. Most papers on this subject do not consider the impact of the drugs used by patients on the obtained results and in this group of patients this is particularly important. An example is that these patients often use e.g. antidepressants, many of which have a documented negative effect on the cardiovascular system, which is reflected by changes in the ECG.

The aims of this study was to analyze the QTc interval in patients with AN considering the potential impact of pharmacotherapy on the QTc interval and to verify various QT correction formulas.

Materials and method

This is a retrospective, single-center study. Data of 64 consecutive adult patients with anorexia nervosa hospitalized in the Department of Internal Medicine and Metabolic Diseases of the Medical University of Silesia between 2002 and 2017 were screened. The exclusion criteria were lack of ECG at admission, family history of long QT syndrome or sudden cardiac death, left or right bundle branch blocks, paced rhythms, repeated hospitalizations (only first hospitalization of each patient was taken into consideration). The final analysis included 56 patients who were divided into two groups: group non-D (n = 44; 78.6%) consisted of patients who did not use drugs that prolong the QT interval, group D (n = 12; 21.4%) included patients who had chronic pharmacotherapy with drugs that may prolong the QT interval. Demographic and clinical data at admission were analyzed.

Drug classification

To assess drug's potential to prolong QT interval and induce torsades de pointes (TdP), classification system from CredibleMeds was used [8]. Group D consisted of patients, who were taking drugs with:

- known risk of TdP — cisapride (n = 1);
- possible risk of TdP — mianserin (n = 2), mirtazapine (n = 1);
- conditional risk of TdP (under certain condition like electrolyte imbalance, drugs interaction) — fluoxetine (n = 1), sertraline (n = 2), olanzapine (n = 1), diuretics with omeprazole (n = 3), hydroxyzine (n = 1).

Electrocardiography

The standard 12-lead ECGs at rest were recorded (paper speed 25 mm/s, 10 mm/mV) at admission. Analyses of ECG recordings were performed by single, experienced cardiologist. We measured QT intervals looking for the longest and shortest ones to calculate QT dispersion (QTd). Results were corrected using the four commonly used formulas:

- Bazett: $QTc = QT / \sqrt{RR}$ [9]
- Fridericia: $QTc = QT / \sqrt[3]{RR}$ [10]
- Framingham: $QTc = QT + 0.154 \times (1 - RR)$ [11]
- Hodges: $QTc = QT + 1.75 \times (HR - 60)$ [12]

QT and QTc interval prolongation was defined as QT or QTc duration in women > 460 ms and in men > 450 ms [13].

Statistical analysis

All statistical analyses were performed using Statistica version 13 (TIBCO Software Inc., Palo Alto, California, United States). The continuous variables were expressed as the mean ± standard deviation or median and 1–3 quartile boundaries and the categorical variables as the number and percentage of subjects. The normality of distribution was verified with the Shapiro-Wilk test. Differences between any unpaired normally distributed samples were calculated using the Student's *t*-test, while the non-normal data were compared using the Mann-Whitney U test. The Wilcoxon signed-rank test was used for paired data (within group). Differences in categorical variables were assessed using the Fisher's exact test. The Spearman's rank correlation coefficient was used for testing the strength of the correlation between two variables. A p value of < 0.05 was considered to be significant.

Results

Demographic and clinical data

A total of 56 patients were incorporated into study. Detailed demographic and clinical characteristic of study population was presented in Table 1 as well as comparison of two

Table 1. Demographic and clinical characteristic of study population stratified by drugs that prolong QT*

Variable	Whole population (n = 56)	Group non-D (n = 44)	Group D (n = 12)	p value
Age (years)	21.5 (19–25)	20 (19–24.5)	23 (18.5–30)	NS
Male sex	2 (3.57%)	1 (2.23%)	1 (8.3%)	NS
Weight [kg]	35.6 (31.7–40.1)	35.7 (31.6–40.2)	35.8 (32–38.9)	NS
BMI [kg/m^2]	12.75 (11.5–15.6)	12.9 (11.5–15.7)	12.6 (11.7–14.9)	NS
HR [bpm]	57 (47–75)	58 (49–75)	68 (47–75)	NS
HR < 50 [bpm]	18 (32.1%)	13 (29.5%)	5 (41.7%)	NS
SBP < 90 [mm Hg]	24 (43.6%)	20 (45.5%)	4 (50%)	NS
WBC [×10^3/μL]	4.4 (3.6–5.7)	4.2 (3.5–5.4)	4.9 (3.7–7.3)	NS
Hemoglobin [g/dL]	12.3 (11.3–13.3)	12.3 (11.4–13.2)	12.2 (10.1–14.6)	NS
Sodium [mmol/L]	140 (138–142)	141 (139–144)	138.5 (134.8–140)	**0.02**
Potassium [mmol/L]	4 (3.7–4.3)	4 (3.7–4.6)	3.9 (3.5–4.0)	NS
Hypokalemia	11 (19.6%)	8 (18.2%)	3 (25%)	NS
Phosphate [mg/dL]	3.15 ± 1.04	3.24 ± 1.07	3.05 ± 1.12	NS
Total calcium [mg/dL]	9.24 ± 0.87	9.28 ± 0.86	8.95 ± 1.38	NS
Ionized calcium [mg/dL]	1.24 ± 0.04	1.24 ± 0.05	1.23 ± 0.03	NS
TSH [mIU/L]	1.95 (1.39–2.76)	1.86 (1.17–2.76)	1.99 (1.56–2.8)	NS
Total protein [g/dL]	6.48 ± 0.9	6.4 ± 0.86	6.74 ± 1.01	NS
Glucose [mg/dL]	75 (69–83)	75 (68–81)	80 (71.5–91.5)	**0.03**
Total cholesterol [mg/dL]	168 (131–194)	169 (131–192)	156 (109–261)	NS
HDL [mg/dL]	67.2 ± 21.1	66.4 ± 20.4	69.8 ± 24	NS
LDL [mg/dL]	85 (58–124)	84 (62–113)	102 (32–145)	NS
Triglyceride [mg/dL]	76.5 (55–125)	78 (58–138)	74 (54–82)	NS

Data are presented as mean ± standard deviation (SD), median (1 to 3 boundaries) or number (percentage). All measurements are taken at admission; n — number; NS — not significant; BMI — body mass index; HR— heart rate; SBP — systolic blood pressure; WBC — white blood count; TSH — thyroid-stimulating hormone; HDL — high-density lipoprotein; LDL — low-density lipoprotein

groups. The mean age was 22.8 ± 5.6 years. High female predominance was observed [female/male (F/M): 54/2]. Sodium level was lower and glucose level was higher in group D than in group non-D. No other differences were observed in laboratory findings.

ECG analysis

Sinus rhythm was present in all ECG. Mean heart rate (HR) was similar in both groups (61 ± 16.3 bpm in group D vs. 63.1 ± 18.7 bpm in non-D, p > 0.05). Pathological bradycardia (HR < 50 bpm) was observed in 5 patients (41.7%) in group D and in 13 patients (29.5%) in group non-D, p > 0.05. The mean QTd did not differ between group D and non-D (40 ms vs. 36.8 ms, respectively, p > 0.05).

QTc interval prolongation was found in 2 to 4 patients (16.7–33.3%) in D-group and in 3 to 5 patients (6.8–11.4%) in non-D group depending on correction formula. The percentage was significantly greater in group D than in group non-D when Fridericia formula was used. QTc interval tended to be longer in Group-D: 459 ± 81 ms vs. 413 ± 33 ms, p = 0.04, correction with Framingham formula, and borderline p values (0.05–0.07) was found for others (Table 2).

QTc interval prolongation over 500ms was present in 5 patients (all female) — 3 in group D and 2 in group non-D (25% vs. 4.5%, p = 0.06).

The variability of QTc values depending on used correction formula was assessed in whole population and within each group (Table 3). QTc interval obtained with Hodges formula was the longest. Significant differences were found between values of QTc interval obtained with Hodges, Framingham and Fridericia formulas in analysis for all patients and group non-D, but not in group D.

Relationship of the QTc internal with the selected clinical parameters

No significant correlations were found between QTc interval and potassium, sodium, calcium levels as well as weight and body mass index (BMI). QT interval corrected with Bazett and Hodges formulas was significantly dependent on heart rate: R = –0.29, p = 0.03 and R = –0.42, p = 0.001,

Table 2. QT interval in group non-D and group D corrected with four formulas

	Group non-D (n = 44)			Group D (n = 12)			p*	p**
	Mean ± SD [ms]	Range [ms]	> 460 ms# N [%]	Mean ± SD [ms]	Range [ms]	> 460 ms# N [%]		
Bazett correction	417 ± 35	350–500	5 (11.4%)	464 ± 92	383–698	2 (16.7%)	0.05	NS
Fridericia correction	416 ± 34	325–505	3 (6.8%)	465 ± 85	394–678	4 (33.3%)	0.06	0.03
Framingham correction	413 ± 33	335–505	3 (6.8%)	459 ± 81	391–665	3 (25%)	0.04	NS
Hodges correction	423 ± 36	339–532	4 (9.1%)	472 ± 82	393–660	4 (33.3%)	0.07	0.06

*Comparison between QTc intervals (ms) in both group; **comparison between number of prolonged QTc intervals in both group; #for men > 450 ms; n — number; NS — not significant; SD — standard deviation

Table 3. Comparison between QTc intervals depending on correction method

	p value for whole population (n = 56)	p value for group non-D (n = 44)	p value for group D (n = 12)
QTc Bazett vs. QTc Fridericia	NS	NS	NS
QTc Bazett vs. QTc Framingham	NS	NS	NS
QTc Bazett vs. QTc Hodges	NS	NS	NS
QTc Fridericia vs. QTc Framingham	**0.001**	**0.008**	0.07
QTc Fridericia vs. QTc Hodges	**< 0.001**	**< 0.001**	NS
QTc Framingham vs. QTc Hodges	**0.001**	**< 0.001**	NS

NS — not significant

respectively. Influence of heart rate on results of Fridericia and Framingham formulas was not significantly important (R = –0.22, p = 0.1 and R = –0.11, p = 0.4). *See* Table 4.

Discussion

The present study focused on analysis of QTc interval in patients suffered from AN depending on pharmacological treatment. We used and compared four QT correction formulas: Bazett, Fridericia, Framingham and Hodges to find the most appropriate one for patients with AN. The QTc interval tended to be longer in patients, who were administrated drugs with potential to prolong the myocardial repolarization (p value: 0.04–0.07, depending on used correction formula). The percentage of patients with prolong QTc (> 460 ms for women and > 450 ms for men) was depended on used formula and was greater in drug-group, when using Fridericia method.

There are several studies focused on the QT interval in patients with AN and the results are inconsistent. QTc interval prolongation was observed in considerable amount of small studies [4, 14–20]. Majority of those study used only Bazett formula, which is highly dependent on heart rate [21]. Another limitations were small samples and various upper limit of normal for QT interval. Most of novel studies are not in line with previous results and usually failed to prove higher prevalence of QTc interval prolongation in AN patients [22–27]. Bomba et al. [28] found reduced QTc interval in drug-free AN patients compared to controls. What is worth to mention, majority of those studies assessed patients on drug and those without treatment together, so influence of medication was not taken into account. Janzen at al. analyzed changes on the electrocardiogram in AN and considered impact of pharmacotherapy [29]. There were no differences in the QT interval and QTc with Hodges as well as T-wave abnormality between drug-free and drug-on patients. Drug-free patients were compared to controls and results were dependent on used formula — QTc interval in AN patients was shorter (Bazett, Fridericia), longer (Framingham) or similar (Hodges) than controls. Comparison between drug-on and drug-free patients was also conducted in study by Padfield et al. [26] — there was also no difference in QTc interval between these groups.

The choice of correction method is still not clear. Walter et al. suggested Hodges formula, because of lack of correlation with heart rate in their study [27]. It is not consistent with our results, Bazett and Hodges formulas correlated

Table 4. Correlation between QTc intervals and selected variables for whole population

	Variable	R Spearman	p value
QTc Bazett	**HR**	**0.29**	**0.03**
	Weight	0.17	NS
	BMI	0.15	NS
	Phosphate	–0.07	NS
	Sodium	–0.06	NS
	Potassium	0.2	NS
	Total calcium	–0.05	NS
	Ionized calcium	–0.14	NS
	TSH	–0.04	NS
QTc Fridericia	HR	–0.22	NS
	Weight	0.02	NS
	BMI	–0.06	NS
	Phosphate	–0.12	NS
	Sodium	–0.11	NS
	Potassium	0.17	NS
	Total calcium	–0.12	NS
	Ionized calcium	–0.33	NS
	TSH	0.1	NS
QTc Framingham	**HR**	**–0.11**	**NS**
	Weight	0.06	NS
	BMI	–0,01	NS
	Phosphate	–0.15	NS
	Sodium	–0.09	NS
	Potassium	0.15	NS
	Total calcium	–0.12	NS
	Ionized calcium	–0.3	NS
	TSH	0.1	NS
QTc Hodges	HR	–0.42	0.001
	Weight	–0.01	NS
	BMI	–0.11	NS
	Phosphate	–0.23	NS
	Sodium	–0.18	NS
	Potassium	0.16	NS
	Total calcium	–0.17	NS
	Ionized calcium	–0.29	NS
	TSH	0.12	NS

HR — heart rate; NS — not significant; BMI — body mass index; TSH — thyroid-stimulating hormone

significantly with heart rate in the present study. Hodges formula tended to overestimate QT duration. According to our results, Fridericia and Framingham were the least dependent on heat rate, so they may be useful with patients with bradycardia. On the other hand, duration of QT interval corrected with Hodges, Fridericia and Framingham differed significantly, but when compared to Bazett method, the results were similar. The larger research is needed to establish if QT interval duration corrected with specific method have prognostic value in long-term follow-up.

Another finding was that in our study there was no relationship between QTc interval and electrolytes or weight and BMI. Several studies reached similar conclusion [15, 26, 30]. In contrary, Swenne et al. showed significant relationship between QT value and BMI, weight and sodium concentration [18].

Study limitations

This is a retrospective, single center study. Main limitation is small number of patients, especially in group treated with drugs, which may prolong QT interval. We analyzed medication at the moment of the hospital admission, which reflected chronic treatment. There was variability of administrated drugs, which might affect myocardial repolarization, so group D was not homogenous. ECG was not reassessed after refeeding.

Conclusions

Information about pharmacotherapy in AN patient is key for QTc assessment. Choice of correction formula may have impact on results. Framingham and Fridericia formulas were the least dependent on heart rate in contrary to Bazett and Hodges formulas.

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Streszczenie

Wstęp. Pacjenci z jadłowstrętem psychicznym (AN) są narażeni na zwiększone ryzyko komorowych zaburzeń rytmu, które wiąże się z wydłużeniem odstępu QT. Celem pracy była analiza odstępu QT u pacjentów z AN z uwzględnieniem potencjalnego wpływu farmakoterapii oraz weryfikacja różnych formuł korekcji QT.

Materiał i metody. Do analizy włączono 56 pacjentów hospitalizowanych z powodu AN (średni wiek: 22,8 ± 5,6 roku; kobiety/mężczyźni: 54/2, średni wskaźnik masy ciała = 13,6 ± 2,6 kg/m^2): grupę nie-D (n = 44; 78,6%) stanowili chorzy niestosujący leków wydłużających odstęp QT, a grupę D (n = 12; 21,4%) chorzy leczeni takimi lekami. Odstępy QT mierzono w 12-odprowadzeniowym zapisie elektrokardiograficznym i korygowano przy użyciu czterech wzorów: Bazetta, Fridericia, Framinghama i Hodgesa.

Wyniki. Średnia częstość rytmuserca (HR) była podobna w obu grupach (61 ± 16,3 bpm w grupie D *vs.* 63,1 ± 18,7 bpm w grupie nie-D; p > 0,05). Bradykardia (HR < 50 bpm) była obecna u 5 chorych (41,7%) w grupie D i 13 chorych (29,5%) w grupie nie-D. Odstęp QTc skorygowany z użyciem wzoru Framinghama był dłuższy w grupie D (459 ± 81 ms) niż w grupie nie-D (413 ± 33 ms); p = 0,04. Odstęp QT skorygowany z użyciem wzorów Bazetta i Hodgesa był istotnie zależny od HR (odpowiednio R = –0,29, p = 0,03 i R = –0,42, p = 0,001). Wpływ HR na wyniki z wzorów Fridericia i Framinghama nie był istotny (R = –0,22, p = 0,1 i R = –0,11, p = 0,4).

Wnioski. Informacje na temat farmakoterapii u chorych na AN mają kluczowe znaczenie dla oceny QTc. Wybór wzoru korekcji wpływa na QTc. Odstępy QT uzyskane przy użyciu formuł Framinghama i Fridericia były najmniej zależne od tętna.

Słowa kluczowe: jadłowstręt psychiczny, częstość rytmu, wzory korekcji QT, odstęp QT, wydłużenie QT

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The prevalence of cardiovascular risk factors related to lifestyle in medical students

Występowanie czynników ryzyka sercowo-naczyniowego zależnych od stylu życia u studentów kierunków medycznych

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Abstract

Introduction. Knowledge about the importance of a healthy lifestyle in the prevention of cardiovascular diseases should be an integral part of the medical education of future physicians and other healthcare professionals. The aim of the study was to assess the presence of selected cardiovascular risk factors in comparison to cardioprotective factors in the group of students of the Medical University of Warsaw.

Material and methods. The study was conducted using a lifestyle questionnaire based on the questionnaire developed at the Loma Linda University with the participation of the American College of Lifestyle Medicine. It covered 280 students of medicine and physiotherapy.

Results. Although 81% of the respondents have a normal body mass index (with an average of 21.24 for women and 23.49 km/m^2 for men), 77% of the surveyed population does not eat the recommended 5 portions of vegetables and fruits a day. Forty-four percent of physiotherapy students and 32% of medical students do not attain the recommended minimum of 30 minutes a day of moderate or vigorous physical activity. Seventy-six out of 212, i.e. almost 36% of students, declare using nicotine in the last year.

Conclusions. Medical students are not free from lifestyle-related cardiovascular risk factors. The percentage of people using nicotine is high and further studies are needed to assess what factors contribute to the lack of adherence to healthy lifestyle recommendations among this group of respondents.

Key words: lifestyle medicine; cardiovascular risk, medical students

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Introduction

Cardiovascular diseases (CVD) are the leading cause of death in Europe according to EUROSTAT. Prevention of CVD should therefore be one of the fundamental topics included in the clinical studies at medical universities. Currently, it is believed that the main cardiovascular risk modifiers are factors constituting the pillars of lifestyle medicine — a balanced diet, regular physical activity, stress management, avoiding substance abuse, and sleep hygiene. Thus, they should be considered a core of modern prevention [1, 2].

Cardiovascular risk factors are classically divided into non-modifiable, which are age, gender, ethnicity or genetic predispositions, and modifiable, severity of which can be changed by appropriate lifestyle interventions and/or pharmacotherapy [3, 4]. This group includes, among others, hypertension, dyslipidemias, overweight or obesity. The NATPOL and WOBASZ studies show that the modifiable factors are the most common cardiovascular risk factors in the Polish population [3, 5].

On the other hand, cardioprotective lifestyle factors include, among others, a balanced Mediterranean diet abundant in vegetables and polyunsaturated fatty acids, regular, moderate-intensity physical activity, no use of tobacco products, and sufficient, uninterrupted sleep [4, 6].

Aim of the study

The aim of the study was to determine the presence of selected cardiovascular risk factors in comparison to cardioprotective factors in the group of students of the Medical University of Warsaw (MUW). Another aim was to assess whether the specific profile of professional interests translates into active prevention of CVD through diet, physical activity and smoking habits (Table 1).

Material and methods

The data was obtained from an anonymously completed survey based on a questionnaire developed by Loma Linda University in collaboration with the American College of Lifestyle Medicine. The study group consisted of 280 3rd and 4th year students who in 2019 and 2020 attended clinical classes at the 3rd Department of Internal Diseases and Cardiology at the Międzylesie Specialist Hospital in Warsaw. Due to irregularities in filling in the sheets (lacking information, omitting questions), 68 questionnaires were excluded from the analysis. Ultimately, the study analyses included results obtained from 212 students — 128 from the medical faculty (medical students further referred to as MS) and 84 from people studying physiotherapy (further referred to as PHS — physiotherapy students). Sixty-nine percent of the surveyed group were women, and 31% were men (Table 1). Statistical evaluation was performed using Statistica software.

Table 1. Distribution of the studied subpopulations — division by gender and faculty

	Medical students (MS)	Physiotherapy students (PHS)	Total
Women	81	65	146
Men	47	19	66
Total	128	84	212

Results

Weight and BMI

Eighty-one percent of students declared body weight and height corresponding to the body mass index (BMI) in the range of 19–25 kg/m^2, which is within the normal limits. The BMI of the remaining group (19.33%) was beyond normal. Both overweight (BMI 25–30 kg/m^2) and obesity (BMI > 30 kg/m^2) more often affected men. Only 4 respondents out of 212 reported results indicating obesity. The average BMI in women was 21.24 kg/m^2 and the average BMI of the surveyed men was 23.49 kg/m^2. The average MS BMI was comparable to the average BMI in the PHS group (21.78 and 22.19 kg/m^2, respectively).

Dietary habits

Seventy-seven percent of surveyed students admitted that they did not consume the recommended 5 portions of vegetables and fruit per day (1 portion is the amount that can fit in a hand, excluding fruit juices). Only 3% of students declared consuming more than 5 portions a day, and this group included only women. Twenty-eight percent of respondents reported that they eat less than 2 portions during an average day. This group included 36% of all men and 24% of all women. Forty-nine percent of students declared average consumption of 2–3 servings per day. MS slightly more often than PHS included in their daily diet 4 or more servings of vegetables and fruit (25% and 20%, respectively). However, these differences were not statistically significant ($p = 0.08$).

The consumption of sweetened beverages, fast-food or salty and sweet snacks at least several times within two weeks before completing the questionnaire was declared by 85% of the respondents — 92% of men and 82% of women, and a comparable percentage of MS and PHS (86% and 85%). Eight percent of all students reported that they ate these types of food almost every day. Thirty-one out of 212 students declared that they did not reach for the above-mentioned products. This group included 8% of all interviewed men and 18% of women.

Physical activity

Fifty-six percent of PHS and 68% of MS spent more than 30 minutes a day on moderate or vigorous physical activity. Moderately intense physical activity was defined as an activity sufficient to lightly sweat. Thirty-four percent of the MS population exercised 30–49 minutes a day. The same percentage of respondents chose training sessions lasting over 50 minutes. PHS most often undertook training lasting 10–29 minutes (38% of respondents). Over 47% of PHS exercised regularly for a minimum of 30 minutes (in this subpopulation almost 30% exercised for more than 50 minutes a day). In both groups, students least often decided to train for less than 10 minutes (10% of MS, 6% of PHS).

Fifty-seven percent of students declared engaging in physical activity at least 3–4 times a week, 41% of whom trained exactly 3–4 times a week. This group included 51% of all MS and over 67% of PHS as well as 41% of all women and 39% of men. The remaining 17% of respondents exercised at least 5 times a week, and 70% of this subpopulation were women. Twelve percent of respondents exercised less than once a week (a comparable percentage of women and men — approx. 12%). Students of both faculties most often chose their frequency of training to be 3–4 times a week.

Nicotine use

Thirty-six percent of the respondents declared using nicotine within the last year. This percentage was similar among students of both faculties. The use of nicotine was declared by 35% of women and 38% of men. The average number of cigarettes smoked daily was 2.7. Among MS, this value was slightly lower than in PHS (2.4 vs. 3.3 cigarettes a day). A difference between women who smoked an average of 2 cigarettes a day and men who smoked 4 cigarettes a day was noted. On a scale of 0 to 5, students rated their anxiety level regarding nicotine consumption as 1.

Motivation to change

When asked about the most important area of life requiring a change of habits, all subpopulations, regardless of their gender and faculty, most often chose physical activity. Twenty-six percent of respondents declared that they are most motivated to improve in this field, and 149 out of 212 (70%) considered physical activity as one of the three priorities necessary to improve their health and lifestyle. Changing dietary habits was one of the three priorities in 61% of students. Almost 19% of students reported the need to improve their diet and physical activity at the same time. Only 9% of students considered weight reduction to be their primary goal, but 34% put it in the top three priorities. The least frequently chosen area (1% of students) in terms of motivation to change habits was the use of addictive substances (nicotine, alcohol and drugs, collectively).

Discussion

The conducted analysis indicates a significant presence of lifestyle-related disease risk factors among MS and PHS. Despite their medical background, a large percentage of students smoking (36%), engaging in physical activity less than once a week (12%) and consuming insufficient amounts of vegetables and fruit every day (77%) can be observed. It should be borne in mind that the respondents may have coexisting non-modifiable risk factors for CVD, the detection of which exceeded the questionnaire used in the study. At this point, it is necessary to consider what factors contribute to the non-compliance with the recommendations in the student population, despite the declared motivation to change.

Nicotine use

The Kantar report (October 2019) on attitudes towards smoking constructed for the Chief Sanitary Inspectorate in Poland showed that 21% of respondents admit to habitual, everyday smoking. [7] In the WOBASZ I study (2003–2005), the percentage of respondents declaring nicotine usage was 31%, whereas in the WOBASZ II study (2013–2014) that percentage decreased to 25% [3]. The NATPOL 2011 study indicated the percentage of smokers was 29% in the 18–39 age group [5]. In a 2020 survey conducted by NIZP-PZH, in the 18–29 age group, everyday smoking was declared by 17.8% of men and 10.6 % of women, usage of e-cigarettes was declared by 13.3% of men and 11.9% of women [8]. Thus, the comparison shows that there is a greater problem of smoking among surveyed students than in the general population of Poland. In Warsaw, the percentage of smoking among medical university students was higher than in other cities. In a 2012 study conducted on medical students from Wrocław, the percentage of cigarette smokers was 21%, which is close to the population average [9]. Comparable results were obtained in studies on several groups of medical students from Łódź and Poznań [10, 11]. However, it should be noted that in the present study, it was impossible to separate the population of students smoking every day during the last year from those who smoked occasionally, relying on the questions regarding the use of tobacco products in the used questionnaire (Table 2). Therefore, this aspect requires clarification in subsequent studies.

Obesity and nutrition

The NATPOL study indicated BMI in the 18–39 years subgroup to be respectively: 25.8 kg/m^2 in men and 23.4 kg/m^2 in women. The results in the population of Poles aged 18–79 showed that the prevalence of obesity in men was 24% and 19.7% in women. The WOBASZ I and II studies in the 20–74 age group reported the obesity percentage to be 22% and 26%, respectively [3, 5]. The percentage of

Table 2. Assessment of selected health-related behaviors in the group of respondents

No.	Assessed habits	Multiple choice	N1	%N1	N2	%N2	N1+N2	%N1+N2
1.	During the last two weeks, how often did you eat fast food, sweet drinks (e.g. sweetened carbonated drinks, juice, sweetened isotonic drinks) or packaged snacks (e.g. chips, cookies, candies, crackers)?	Never	26	17,8	5	7,6	31	14,6
		Several times	92	63	42	63,6	134	63,2
		More than 7 times	17	11,7	13	19,7	30	14,2
		Almost everyday	11	7,5	6	9,1	17	8
2.	During an average day, how many portions of fruit and vegetables do you eat? (1 serving fits in the hand and does not include fruit juices)	< 2 portions	35	24	24	36,4	59	27,9
		2–3 portions	72	49,3	32	48,5	104	49
		4–5 portions	32	21,9	10	15,1	42	19,8
		> 5 portions	7	4,8	0	0	7	3,3
3.	During the past two weeks, how often have you engaged in moderate or vigorous physical activity (e.g. brisk walking or being active enough to lightly sweat)?	< 1 time a week	18	12,3	8	12,1	26	12,3
		1–2 times a week	43	29,5	22	33,3	65	30,7
		3–4 times a week	60	41,1	26	39,5	86	40,5
		≥ 5 times a week	25	17,1	10	15,1	35	16,5
4.	During an average training session, how many minutes do you spend on moderate or vigorous physical activity? (e.g. brisk walking or activity sufficient to make you lightly sweat)?	< 10 min	12	8,2	6	9,1	18	8,5
		10–29 min	45	30,8	15	22,7	60	28,3
		30–49 min	45	21,2	20	30,3	65	30,7
		≥ 50 min	44	30,1	25	37,9	69	32,5
5.	During the last year, have you consumed nicotine? (cigarettes, electronic cigarettes, innovative tobacco products, cigars)	Yes	51	35	25	37,9	76	35,8
		No	95	65	41	62,1	136	64,2

N1 — number of responding women; %N1 — percentage of all the responding women; N2 — number of responding men; %N2 — percentage of all the responding men; N1+N2 — number of all the respondents; %N1+N2 — percentage of all the respondents

obese people among the surveyed students was 2% and it concerned only men. It was therefore significantly less than in the general population. In the 2020 NIZP-PZH survey, the values were lower, indicating prevalence of obesity at 10% (12.3% of men and 7.8% of women) [8]. Regarding the 20–44 age group, obesity concerned 4.6% of women and 9.2% of men [8]. Studies conducted on student groups from large Polish cities confirm this tendency. A study of students from Poznań reported that men's average BMI was significantly higher than the average BMI of the surveyed women (23.41 vs. 20.52 kg/m^2) [12]. A similar correlation was observed in the Warsaw group. In a study conducted among pharmacy students of the Medical University of Wrocław, 28% of men and 7% of women were overweight, and obesity concerned 15% and 10% of respective genders [13]. Sixty-two percent of women and 75% of men in this group reported that they did not eat enough vegetables and fruit every day. These values were also similar to the results of the MUW student population.

Physical activity

In the WOBASZ I and II study, rare engagement in physical activity was declared by 52% and 55% of respondents, whereas frequent physical activity (more often than 3 times a week) was declared in the NATPOL study by 44% [3, 5]. According to "Health status of the Polish population and its determinants Report 2020" more than 67.2% of Polish people do not take up regular recreational physical activity. Moreover, during the coronavirus disease 2019 (COVID-19) pandemic (spring–autumn 2020), 34.3% of Poles reduced their physical activity and only 17.5% of the respondents increased their physical activity. In the age group of 20–44, reduced activity was declared by 38.6% men and 33% women, while an increase in physical activity — by 24.7% men and 26.6% women [8]. Considering these results, 57% of students who declared being active at least three times a week can be considered a progress. However, it should be noted that slightly more than 12% of the respondents were not physically active even once a week. In the study by Ślusarska et al. [9] that analyzed cardiovascular risk in medical students from Wrocław, 75% of respondents described their level of physical activity as medium, 22% as high, and only 6% as low. Compared to these values, the results from MUW were significantly worse; however, in the abovementioned study, the definitions (e.g. exercise duration and frequency) of each level of activity were not determined by the researchers, thus obtained data relied only on students' perception and therefore may be inconclusive. Nevertheless, such a large fraction of students of MUW who do not engage in the

recommended or even minimal physical activity should lead to intensifying the promotion of physical activity as a fundament of a healthy lifestyle.

Further actions

The results of this study indicate a necessity to include practical approach to the subject of lifestyle-related disease prevention in the compulsory curriculum at all faculties of medical universities. New light on the role of lifestyle medicine in medical education could be shed if one conducted a study comparing the awareness and prevalence of cardiovascular risk factors in students who completed a course of lifestyle medicine with a control group selected from other students of the same faculty who did not participate in such classes. An additional advantage of prioritizing prevention and putting emphasis on teaching lifestyle medicine is that the knowledge or skills acquired during these classes would contribute to increasing the students' motivation and sense of effectiveness when changing their own habits, which could then translate into personalizing the type of intervention to meet the needs of individual patients during clinical work in the future [14–16].

Study limitations

There are several limitations to this study. The group of respondents is relatively small and uneven considering the distribution of subpopulations. Moreover, a factor that should be taken into consideration when interpreting the results is the lack of objective methods to verify the accuracy of the information provided. Better quality of evidence would be ensured by complementing the questionnaire with precise anthropometric measurements of the respondents as well as basic laboratory tests. Another limit of the analysis is the lack of data on the actual awareness of the role of lifestyle in preventive cardiology in the group of students. Knowledge in this field should be verified by adding appropriate questions to the questionnaire.

Conclusions

The study indicates a significant prevalence of modifiable, lifestyle-related risk factors for CVD among students of MUW. Students only partially identify unfavorable habits and report their motivation to change them. The vastest group declared the need to improve on their physical activity or diet which corresponds well with the results obtained from respected sections of the questionnaire. Despite high prevalence of smoking, only a small percentage of students considered reducing nicotine usage to be their health priority. The knowledge of primary prevention and the role of lifestyle medicine in controlling the risk of lifestyle-related diseases requires verification and subsequent analysis. Identifying the causes that lead to suboptimal lifestyle decisions is necessary to design effective interventions and requires further research.

Conflict of interests

The authors declare no conflict of interest.

Streszczenie

Wstęp. Wiedza na temat zdrowego stylu życia w prewencji chorób układu sercowo-naczyniowego powinna być istotnym elementem zdobywania wykształcenia na kierunkach medycznych. Celem pracy było określenie występowania wybranych czynników ryzyka sercowo-naczyniowego zależnych od stylu życia oraz czynników kardioprotekcyjnych w grupie studentów Warszawskiego Uniwersytetu Medycznego.

Materiał i metody. Badanie przeprowadzono za pomocą ankiety, będącej polskim odpowiednikiem kwestionariusza opracowanego na uniwersytecie Loma Linda z udziałem *American College of Lifestyle Medicine*. Objęto nim 280 studentów kierunków lekarskiego i fizjoterapii.

Wyniki. W badanej populacji 77% osób nie spożywa 5 porcji warzyw i owoców dziennie. U 81% respondentów wskaźnik masy ciała jest prawidłowy (przy średniej wynoszącej 21,24 u kobiet i 23,49 km/m^2 u mężczyzn). Spośród przebadanych osoby aktywne fizycznie co najmniej 3 razy w tygodniu to 51% studentów kierunku lekarskiego i ponad 60% studentów fizjoterapii. Prawie 36% studentów, tj. 76 spośród 212, deklaruje używanie nikotyny w ostatnim roku.

Wnioski. Mimo wysokiej świadomości zagrożeń studenci kierunków medycznych nie są wolni od czynników ryzyka sercowo-naczyniowego. Odsetek osób używających nikotynę jest wysoki i konieczne są dalsze badania służące ocenie, jakie czynniki wpływają na brak przestrzegania zaleceń zdrowego stylu życia w tej grupie badanych.

Słowa kluczowe: medycyna stylu życia, ryzyko sercowo-naczyniowe, studenci medycyny

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What have we learned about COVID-19 in 2020? Ten hypotheses explaining the differences in incidence and mortality from COVID-19 between countries

Czego dowiedzieliśmy się o COVID-19 w 2020 roku? Dziesięć hipotez wyjaśniających różnice w zachorowalności i śmiertelności z powodu COVID-19 między krajami

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Abstract

Coronavirus disease 2019 pandemic is one of the most difficult challenges for modern medicine and health care. Since the beginning of its outbreak in different regions of the world, researchers have noticed differences in incidence and mortality rates. We herein present ten hypotheses that were a topic of scientific discussions and might explain this observation. Cultural, demographic, sociological characteristics of societies, differences in healthcare systems and vaccination schedules, genetic polymorphism, and other factors can serve as variables affecting the course of the pandemic in different regions of the world. Further study of those hypotheses might provide us with valuable insight and broaden knowledge in this unprecedented epidemiological situation.

Key words: COVID-19, epidemiology, One Health, pandemic

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Introduction

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) human-to-human transmission was confirmed on January 20th, 2020, and declared a pandemic by the World Health Organization on March 11th, 2020 [1, 2]. The year has passed since we are aware of the coronavirus disease 2019 (COVID-19) and the virus noted in almost every country of our globe [3].

From the very beginning of the COVID-19 pandemic, there have been significant differences in morbidity and mortality between countries. The natural development of pandemic, transmission from one area to the other, or the data analysis time could not merely explain this fact. All of it led to the formulation of several hypotheses — summed up and discussed more widely in our textbook — explaining why the epidemical situation differs between countries [4].

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At the beginning of the pandemic, Poland has noted a relatively low number of deaths with a high incidence rate. This observation was similar for most countries in Central and Eastern Europe, in contrast to Western Europe and America. Unfortunately for Poland, the tendency has changed due to poor control of the pandemic. It led to the healthcare system's paralysis and severe growth in mortality, with the highest number of almost one thousand deaths on 8th April (Figure 1).

Hereby we describe the most important contemporary hypotheses, explaining partially why the epidemic reports suggested that the course of COVID-19 was milder in some areas, and the percentage of deaths from COVID-19 was significantly lower.

Hypothesis 1

The hypothesis of the initial demographic and health status of the infected population

In this hypothesis, society's different demographic structure can cause the virus's heterogenic spread, the other morbidity and mortality rates. Countries with a higher proportion of young people have a milder incidence of infections, whilst countries with a high proportion of the elderly experience more deaths and hospitalization due to COVID-19 [5]. This theory perfectly explains the low incidence and mortality of COVID-19 in the continent with the youngest population in the world — Africa. Factors modifying these correlations may be individual societies' health status — the prevalence of additional risk factors such as smoking, obesity, diabetes, cancer, and respiratory system diseases [6]. Those factors can increase susceptibility to SARS-CoV-2 infection and mortality from COVID-19. Initially, this hypothesis explained the relatively low mortality from COVID-19 in China, compared with the other country that became the epicenter of the pandemic — Italy. However, this model cannot explain the significant difference in mortality from COVID-19 in societies with a similar demographic structure (e.g. Italy and Germany).

Hypothesis 2

The hypothesis of cultural and sociological differences

The hypothesis of cultural and sociological differences tried to fill this gap, explaining differences in the development of the epidemic in Asia and countries of Western Europe [7, 8]. In these countries, the pandemic spread more quickly and had higher mortality (Italy, Spain). There is a possible correlation between the easier spread of the virus and cultural behaviors, which differ between Mediterranean and Asian societies. In Southern Europe, people live very active social life: spending much time in restaurants and pubs, celebrating meals, enjoying feasts and parties, taking pleasure from the time shared (Italian *la dolce vita*, Spanish *fiesta*); when Asians are thought to be more focused on work and study and are significantly less social. There is a clear distinction between such simple day-to-day gestures as greeting — hugs and kisses of people regardless of gender in southern Europe versus keeping distance and nodding head in Asian countries. The rapid transmission of the infection could

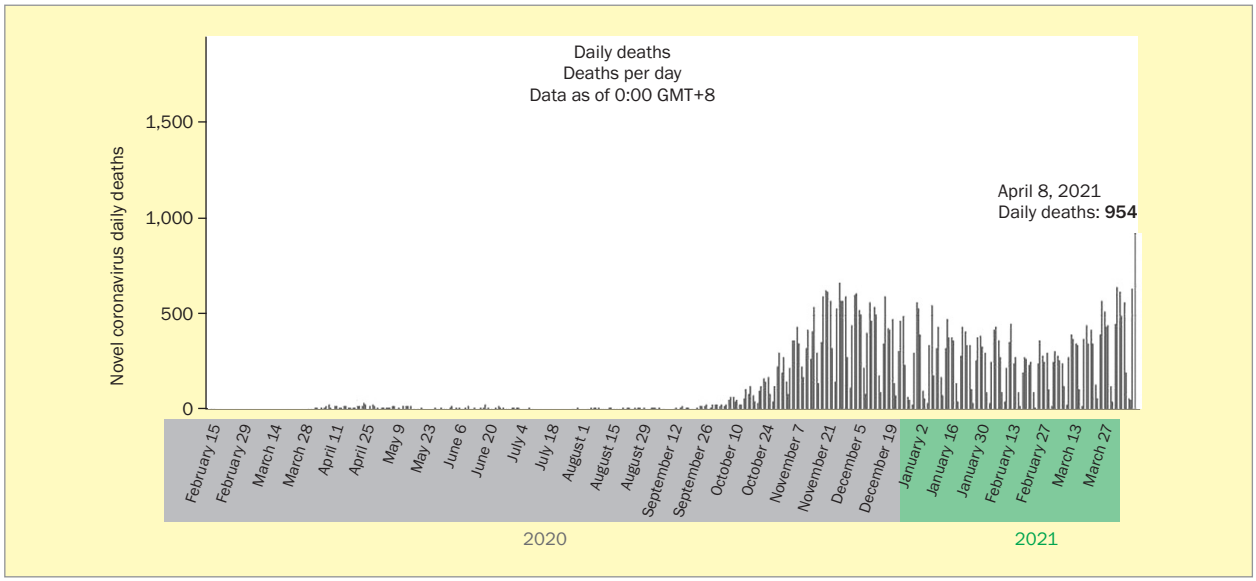

Figure 1. Daily deaths in Poland (na podstawie: https://www.worldometers.info/coronavirus/country/poland/)

significantly affect multi-generational families living in the same household.

Additionally, the traditional model of an Italian family with a late independent young generation being a vector of infection to the oldest members of the family living together could also play a role in transmitting disease [9]. However, this hypothesis still does not fully explain the high mortality rates from COVID-19 in the rich countries in Northern Europe — the Benelux countries: Belgium and Luxembourg. Nevertheless, cultural and sociological differences may have been related to seemingly trivial behavior in individual societies and be important in the initial stages of the virus's transmission.

Even difference in simple social habits concerning hygiene can play a role in the transmission of COVID-19. The results of a study carried out five years before the outbreak of the pandemic (WIN/Gallup International, 2015, assessed 30.12.2020 — https://www.statista.com/chart/4111/do-europeans-wash-their-hands-after-using-the-toilet/) determined the percentage of Europeans routinely washing their hands with water and soap after leaving the toilet. The percentage was the highest in some Islamic-mainly countries (Turkey, Bosnia and Herzegovina — 94 and 96% respectively), high in some countries (Germany — 78%, Sweden — 78%, Finland 76%, Great Britain — 75%), medium in other (Ukraine — 71%, Poland — 68%), and low in those highly impacted with COVID-19 five years later (France — 62%, Spain — 61%, Italy — 57%, Netherlands — 50%).

Hypothesis 3

The hypothesis of the efficiency of health care systems and the early implementation of preventive measures

The hypothesis of the efficiency of health care systems and the early implementation of preventive measures adds to the previous observations important factors modifying the spread of the virus. In an excellent organization, the health system's proper funding and efficiency could result in the low mortality rate from COVID-19 in countries such as Germany. Contrary, the absence or the late implementation of a 'lockdown' strategy in Sweden and the United Kingdom explains very high mortality rates from COVID-19 [10]. The general practice of wearing masks, social isolation and distancing in public are factors that could possible explain the relatively stable control of the pandemic in countries such as South Korea, Singapore, Taiwan, Japan and Hong Kong. Studies emphasized that those societies wore masks long before the epidemics outbreak and continued to do it during and afterwards [11]. People in those countries wore masks because of previous viral epidemics, but also due to air pollution. Thus, Asian countries quickly and effectively implemented preventive and protective methods. Other elements limiting transmissions have also been introduced more easily: for instance, frequent handwashing. Quickly introduced control of tourism and journeys could explain success achieved in Australia and New Zealand.

Assuming that the Chinese morbidity and mortality data are accurate, this country has managed the epidemic very well [12]. It was possible by using severe forms of 'lockdown': locking citizens in their homes and putting them under strict control, isolating certain cities and provinces, preventing the movement of people within these zones. These measures were a very troublesome strategy, but it is undoubtedly more effective than just reporting danger in individual districts without any control over the movement of people between them (a strategy implemented in Poland with so-called 'yellow' and 'red' districts). Sociologists also point out that effective methods of preventing pandemics in the population dimension are paradoxically easier to introduce in countries with authoritarian power than in liberal democracies.

Furthermore, the testing strategy and its testing capacity played a significant role in the pandemic's adequate control. In Poland, problems related to this matter might provide us with a possible explanation of the excess-all cause of mortality rate during the second and third wave [13]. The high rate of positive SARS-CoV-2 test — exceeding 20% with a peak of 50.3% — suggests that COVID-19 was underdiagnosed in the second and third wave period [14]. Consequently, patients died because of COVID-19 and its complications before diagnosis was made or were tested during screening in the emergency units of general hospitals, where they were admitted because of deterioration of COVID-19 and other somatic conditions. Diagnosis of COVID-19 in hospitalized patients impacted majorly on operations, as it led to the quarantine of medical personnel and closures of whole wards, limiting access to health services for the most severely ill people [13].

Furthermore, focusing on COVID-19 cases, many health professionals had to abandon their previous obligations with severe limitations of direct patient-doctor contact. Apart from the current issues related to the pandemic, there is a need to sustain the proper level of medical care in the whole system: efficient oncological diagnostics (7% decrease of fast-track oncological cards in Poland in 2020 vs. 2019) [15], cardiological services (15% decrease of myocardial infarction hospitalizations in Greater Poland region in 2020 vs. 2019) [16], brain stroke management (25% decrease in stroke patients treated with mechanical thrombectomy in Lesser Poland region in January–May 2020 vs. January–May 2019) [17], and managing an observed deterioration of the population's mental health are expected to be major significant challenges for the following months of the ongoing pandemic [18].

Hypothesis 4

The hypothesis of population density and accelerated transmission of infections

The hypothesis of population density and accelerated transmission of infections. Population density could be the main element explaining the differences in pandemic development in individual countries. It is a simple parameter that correlates with the risk of SARS-CoV-2 infection. The Scandinavian countries in Europe have become an excellent model to prove this hypothesis. In this hypothesis, we cannot compare the data from Sweden, where the authorities decided not to apply the 'lockdown' strategy but to opt for population immunization. Other countries — Norway, Denmark, Finland — have a similar socio-cultural picture with high economic growth, a similar healthcare organization, and a preventive and lockdown policy. These countries have almost identical populations (5.4–5.8 million citizens), but their population density varies Norway 15, Finland 15, Denmark 138 people/km^2. The reported mortality from COVID-19 is twice as high in Denmark as in Finland or Norway [19]. It is worth pointing out that also in Poland, the regions of the dense population — the Silesian agglomeration, Mazavia and Lesser Poland — had the highest morbidity rate of SARS-CoV-2.

The epidemiological literature also emphasizes the role of local communities that can increase virus transmission regardless of population density in large industrial factories, mines, military barracks, schools, educational institutions, dormitories, monasteries, temples. Similarly, the infection can be easily transmitted in crowded places: concerts, religious rites, weddings, funerals, large sports events. The conditions of contact can alter the effectiveness and the scale of transmission. Analyses suggest a higher chance of infection indoors than in open air, especially in the smaller spaces, when there is a closed air circuit, and there is no possibility of regular ventilation with opening windows [20, 21]. The hypothesis of the accumulation of transmission can also explain the accelerated and highly unfavorable initial course of the Italian Lombardy and Veneto epidemics. Some epidemiologists believe that it is no coincidence that the epidemic started there between February and March. This region is significantly industrialized and has high economic development due to numerous business contacts with Asian countries. January 2020 was when many people from China came to Italy after celebrating the Chinese New Year; similar migrations were also observed in Chinese provinces [22]. According to one of the hypotheses, some of these people could have been carriers of the coronavirus, thus forming a particular population of 'zero patients', which, by further transmitting the virus, caused an extreme progression in the number of infected people.

Hypothesis 5

The hypothesis of variable virulence of different strains of the virus

The hypothesis of variable virulence of different strains of the virus. At the beginning of the COVD-19 pandemic, studies analyzed the genetic variability of SARS-CoV-2. It was necessary because the newly discovered coronavirus showed a relatively high potential for genetic variability, which enabled it to break down the species barrier and switch from animals to humans. Many different mutations in SARS-CoV-2 have been described so far [23]. Currently, the most common subtype is D614G, which is commonly called G strain. It mutated into GR and GH clades at the end of February 2020. Studies show that the prevalence of G, GH and GR clades is continuously increasing worldwide. The 'old' S strain exists in some restricted areas in the US and Spain. The L and V strains are gradually disappearing.

Four other SARS-CoV-2 genetic clusters were identified as super-spreaders (SS) variants. They are also responsible for triggering the primary COVID-19 pandemic outbreaks in different countries. The SS1 cluster was widespread in Asia and the US, and it was probably responsible for the outbreaks in Washington and California and South Korea, and the SS4 cluster contributed to the pandemic in Europe. The British variant of SARS-CoV-2 has also been reported in December 2020 [24]. At present, there is no conclusive data that would enable to establish correlations between a specific genetic variant of SARS-CoV-2 and mortality. Significantly, none of the found mutations seems to affect the antigenic structure of the new coronavirus. This lack of antigenic mutation is an important facilitation in the design of vaccines directed against SARS-CoV-2, available since the end of December 2020.

Hypothesis 6

The hypothesis of genetic polymorphisms

The hypothesis of genetic polymorphisms always arises when a pandemic involves different countries, nations and societies. Since the beginning of the COVID-19 pandemic, attention has been drawn to the possible impact of genetic polymorphisms within the renin–angiotensin system, resulting in a different expression of ACE2 — a protein essential in entering host cells [25]. There were claims that people with specific ACE polymorphisms using ACE/sartan inhibitors may prevent severe alveolar damage. It has been emphasized that genetic polymorphism if affects mortality from COVID-19, should be linked to a gene located on chromosome X, thus would explain the higher mortality rate in men with one copy of this chromosome. Studies showed that the course of COVID-19 is particularly severe in individuals with mutations of the *TLR7* gene in chromosome X, which would affect the expression of genes for interferon.

There is also a hypothesis that the poor prognosis of COVID-19 is related to the gene's polymorphism for glucose 6-phosphate dehydrogenase (G6PD). Favism, associated with a deficiency of G6PD, is a disease that affects approximately 200 million people worldwide. Poland is one of the countries with a low prevalence of G6PD deficiency (0.1% of the population); higher percentages of people with this genetic defect are observed in Italy, Spain, the USA, India and southern China. That could explain higher morbidity and/or mortality in the course of COVID-19.

Other studies highlight the possible link between the prognosis of COVID-19 and gene polymorphism in:

- already mentioned genes encoding ACE2 — some genetic polymorphisms of ACE2 may favor the occurrence of neurological complications. Interestingly, the ACE2 polymorphisms rs35803318 and rs2285666 occur at a completely different frequency in the Italian population than in other parts of the world [26];
- genes encoding ACE1: where ACE1 II polymorphism is associated with higher mortality from COVID-19 and higher ACE1 I/D ratio would be associated with better prognosis [25, 27];
- genes encoding interferon-induced helicase 1 (IFIH1): which may involve the lower expression of INF-beta in some populations with a specific mutation of the single nucleotide IFIH1 (Afro-Americans in the USA) [28];
- a gene encoding the expression of a receptor — the TMPRSS2 serine protease — that is responsible for the attachment to the host cell: it was found that out of four alleles responsible for the expression of TMPRSS2 in the alveoli, those associated with increased expression of TMPRSS2 are more common in the European and American than in the Asian population [29];
- genes encoding dipeptidyl-peptidase-4 (DPP4) — CD26 protein, which may explain a worse prognosis in COVID-19 in people with diabetes [30];
- genes encoding glutathione s-transferase [31];
- genes encoding the major histocompatibility system HLA (human leukocyte antigens): type HLA- DQB1*06 increases the risk of SARS-CoV-2 infection, and types HLA-A*02, HLA-B*44 and HLA-C*05 have a potential protective role;
- genes encoding interferon-induced transmembrane protein 3 (IFITM3); its specific polymorphisms may be associated with a worse prognosis of COVID-19 [32];
- genes encoding the blood group system, with lower susceptibility to SARS-CoV-2 infection of people with blood group 'O' and higher susceptibility of people with blood group 'A' [33].

Hypothesis 7

The hypothesis of unspecific cellular immunity induced by tuberculosis vaccination. has gained many supporters and resonated with the public. Tuberculosis vaccination was introduced in 1921 (after the 'Spanish flu' epidemic) to prevent tuberculosis. The vaccine is produced from the BCG strain (Bacille Calmette-Guérin) — a mutant bovine bacillus deprived of virulence by multiple passages. The hypothesis of the protective effect of tuberculosis vaccination was proposed by observing large differences in SARS-CoV-2 infections and mortality from COVID-19. East Germany (former GDR — German Democratic Republic, a socialist state existing until 1989) mortality rates were lower compering to West Germany (former Federal Republic of Germany) [34]. The former GDR used the BCG vaccine until 1990; thus, all people over 30 years old are still immunized. In West Germany, due to the low risk of tuberculosis, citizens were not vaccinated with the BCG vaccine [34].

Similarly, studies showed significant differences in mortality rates between post-communist Eastern and Western Europe: Spain (BCG has not been vaccinated since 1981) and Portugal (BDG vaccinations until 2017 — 36 years longer) [35]. Other countries that do not carry out the mandatory BCG vaccination have experienced significant problems in controlling the epidemic: Great Britain, the USA, France, Belgium, the Netherlands, Denmark, Italy, Luxembourg, Spain, Australia, and Israel. Similarly, the high mortality rate from COVID-19 in Ecuador (no BCG vaccination) in comparison with Peru (BCG vaccination obligatory since 1945) and Colombia (BCG vaccination obligatory since 1960). Studies correlate the number of cases of COVID-19 with the lack of obligatory BCG vaccination [35]. Data indicate that the earlier in the life of an individual the BCG is given, the lower is the risk of death from COVID-19. It appears that there were fewer infections and fewer deaths during the first 30 days of the epidemic in countries where BCG vaccination was compulsory at least until 2000. In Poland, the Brazilian strain has been used since 1955 to 2005, on all children and infants with the birth-weight above 2000 grams (the first dose — given right after birth, and the second — at the age of seven). According to the information provided to us by the Polish national consultant in Pediatrics — prof. Teresa Jackowska — the BCG infant vaccination rate in Poland is over 90%. It could explain low mortality from COVID-19 in Poland. One dose of the BCG vaccine leads to anti-tuberculosis immunity for at least 15–20 years. The BCG vaccine does not stimulate the production of specific antibodies but activates T CD4 lymphocytes to produce cytokines. Increased INF-gamma production in vaccinated individuals has been found even after 10 to 30 years since the last vaccination. However, we still do not know if the BCG vaccine itself could be a protective factor against SARS-CoV-2 and whether it is worth giving an additional dose of BCG vaccine to people who have been vaccinated in the past or the first dose to people who never received BCG vaccine. The results of ongoing

randomized clinical trials, including the Australian BRACE (BCG vaccination to Reduce the impact of COVID-19 in Australian healthcare workers following Coronavirus Exposure) and the Dutch BCG-CORONA (Reducing Health Care Workers Absenteeism in COVID-19 Pandemic Through BCG Vaccine), will resolve this issue [36, 37]. Studies also suggested that BCG vaccination's protective effects against the COVID-19 may also apply to other early childhood vaccines, such as MMR vaccine [38, 39].

Hypothesis 8

The hypothesis of other factors inducing immune protection against SARS-CoV-2

Possibly, a vast number of other coronaviruses, symptomatically or asymptomatically infecting humans, may induce resistance to the coronavirus SARS-CoV-2 via the humoral and/or cellular pathway. Studies showed that the memory T cells, which have previously recognized the cold-causing coronaviruses, can also recognize the SARS-CoV-2 proteins (including the S protein responsible for its association with human cells). It may explain why some people have a milder course of the disease. Studies showed that 40% and 60% of people who have never contacted SARS-CoV-2 have memory T cells capable of responding against the virus. These cells recognize parts of the virus with which they have never been in contact before. Observations confirming this fact were conducted in the Netherlands, Germany, the UK, and Singapore. Flu and infections of the upper respiratory tract — more frequent in Central and Eastern Europe than in warm Mediterranean countries — could also, paradoxically, contribute to better protection in pandemic times. The mechanism explaining this phenomenon may be the occurrence of "cross-reactivity" — the presence of lymphocytes that can fight a dangerous virus due to the similarity of a previously recognized, less virulent one. This mechanism can be triggered by contact with 'animal' coronaviruses and to produce a protective immune system. According to anecdotal that veterinarians and pet owners — people who have frequent contact with animals — had a milder course of SARS-CoV2 infection [40]. However, these reports need to be verified.

Interestingly, Oxford University scientists promote the hypothesis that exposure to 'animal' coronaviruses can modify people's immune response against SARS-CoV-2. They prove that SARS-CoV-2 or a very similar coronavirus, long before the pandemic erupted in 2020, infected people in South-East Asian countries (Vietnam, Laos, Cambodia, Burma, Thailand). In these countries — contrary to South China — bats are the most common reservoir of many coronaviruses, including the species considered to be the one from which the SARS-CoV-2 infection started. These countries — including Indonesia — are characterized by the highest biodiversity of bats. According to this hypothesis, SARS-CoV-2 has repeatedly infected these countries' populations, making them immunologically protected. Then, the virus infected the pangolin and was dragged to Wuhan's province, where the population was 'immunologically unprepared'. This theory explains the very low incidence and mortality rate of COVID-19 in Vietnam, Laos, Cambodia, Burma or Thailand — countries very close to China with dense population and without strict lockdown restrictions. The cross-over SARS-CoV infections between humans and animals are not fully understood until now [41, 42].

Hypothesis 9

The hypothesis of additional lung damage and the impact of an industrially altered environment

The hypothesis of additional lung damage and the impact of an industrially altered environment was gaining supporters at the beginning of the US epidemic after observing the increased mortality rate from COVID-19 in regions with increased air pollution [21, 43–46]. It seems that an atmosphere with a high PM2.5 and PM10 content favors the transmission of the virus by transporting it on dust particles over long distances. PM2.5 and PM10 particles also induce inflammation in the lungs, which may increase the risk of infection and exacerbate the course of COVID-19 [47–51]. The rapid development of the pandemic in Italian Lombardy may also have depended on air pollution in Italian cities in the region [21]. If these concepts are valid and have clinical implications, they are bad news for Poland's epidemic — one of the most polluted countries in Europe. The coal-based economy leads to high annual concentrations of PM2.5 and PM10, especially in Silesia and Lesser Poland. Some experts emphasize that the 'lockdown' applied in Europe has resulted in significant air pollution reductions in March-April 2020, which would be crucial for reducing virus transmission [21]. Further observations of these dependencies and their impact on pandemic control are necessary.

Hypothesis 10

The climatic hypothesis

The climatic hypothesis suggests that the transmission of the virus and its infectivity depends significantly on the climatic conditions. At the very beginning of the pandemic, scientists suspected that the SARS-CoV-2 virus would disappear or significantly weaken with time — similarly to other coronaviruses causing flu and respiratory infections. It could probably happen in the summer period,

characterized by higher temperatures and more sunlight [52]. The higher temperature limits the transmission of the virus since it promotes aerosol droplets' drying on which the virus can spread or remain active on surfaces for longer [53]. Unfortunately, the effects of temperature and sunlight in high humidity conditions are unlikely to be significant. Studies show that UVC light can neutralize SARS-CoV-2, used to decontaminate surfaces, rooms and personal protective equipment [54]. The atmosphere of Earth stops the UVC radiation — it does not reach the ground surface and does not affect the virus. The significance of UVA and UVB radiation against the SARS-CoV-2 virus is not entirely clear. However, some data suggest that the pandemic development from February to May 2020 inversely correlates with the amount of UVA and UVB radiation, i.e. sunlight. It may suggest a lower number of SARS-CoV-2 infections in the northern hemisphere during the summer, with an increased incidence of COVID-19 in the southern hemisphere at the same time (Brazil, Australia). It is also consistent with the observations made in Bangladesh, India and Pakistan. Despite the hot climate, the epidemic is growing because monsoon clouds block solar radiation and high humidity. The correlation of the course of the epidemic and the climate requires further research. If such dependence exists, it is undoubtedly influenced by other modulating factors (mentioned above). These factors — easing of restrictions, holiday tourism, failure to follow recommendations, 'pandemic lassitude' — may have caused an increase in summer infections in a hot, sunny Europe in August 2020.

Conclusions

Many explanations exist that partially could answer why some world regions are differentially affected with the SARS-CoV-2 pandemic. In this paper, we have grouped those hypotheses into ten possible areas of impact. Nevertheless, we must emphasize that all the factors can interact, thus have a different impact on the course of the COVID-19 around the globe. It is worth remembering that the state of knowledge about SARS-CoV-2 and the COVID-19 pandemic remains highly speculative, controversial and difficult to verify, and the real explanation of the differences in morbidity and mortality from COVID-19 is probably the result of many factors. We cannot also reject the hypothesis of the difference morbidity and mortality, which says that different strategies of testing, the capacity of the health system, ability to track infections and eligibility criteria of COVID-19-related deaths vary from country to country, thus could create a false picture of the dynamics of the pandemic. The publicly available data from the European Centre for Disease Prevention and Control (ECDC) show a clear correlation between GDP per capita and the number of deaths per COVID-19 per million population in each country. It would indicate that wealthier countries are testing more, identifying more cases, and better qualifying COVID-19-related deaths. Nevertheless, this paper should stimulate others to do more research on the subject.

Conflict of interest

The authors declare that there is no conflict of interest.

Streszczenie

Pandemia choroby koronawirusowej 2019 jest jednym z najtrudniejszych wyzwań dla współczesnej medycyny i systemów ochrony zdrowia. Od początku jej wybuchu w różnych częściach świata zaobserwowano różnice w zapadalności i śmiertelności. W artykule omówiono 10 hipotez, które były tematem dyskusji naukowych i mogą wyjaśniać tę obserwację. Czynniki kulturowe, demograficzne oraz socjologiczne, różnice w systemach opieki zdrowotnej i harmonogramach szczepień, polimorfizm genetyczny mogą stanowić zmienne wpływające na przebieg pandemii w różnych regionach świata. Dalsze badanie tych hipotez może dostarczyć cennych informacji i poszerzyć dostępną wiedzę w tej bezprecedensowej sytuacji epidemiologicznej.

Słowa kluczowe: COVID-19, epidemiologia, *One Health*, pandemia

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Atrial fibrillation or patent foramen ovale: where is the cause of recurrent ischemic strokes?

Migotanie przedsionków czy przetrwały otwór owalny — gdzie leży przyczyna nawracających udarów niedokrwiennych mózgu?

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Abstract

Ischemic stroke is one of the major causes of death and disability in high-developed countries. Closure of patent foramen ovale (PFO) is recommended if other causes of ischemic stroke, such as atrial fibrillation (AF), are excluded, especially in young patients. We present a case report of a 75-years-old female patient with five ischemic strokes in her medical history and newly diagnosed PFO. Atrial fibrillation was detected 25 years after first ischemic event. Implementation of anticoagulation therapy has prevented new ischemic strokes in this patient. According to emerging meta-analyses such treatment is sufficient not only in AF, but also in PFO related ischemic strokes. The patient had other risk factors for paradoxical embolism such as varices, post-thrombotic syndrome of lower limbs and the Eustachian valve, so it is unclear whether AF has been the major cause of all ischemic strokes in present case. Significant bleeding from limb varices during anticoagulation treatment occurred and required urgent surgical intervention. Because of the high risk of recurrent hemorrhages (HAS-BLED Score — 4 points), the patient was considered for two percutaneous procedures: occlusion of the left atrial appendage and consecutively the second one — PFO closure as additional prevention of stroke.

This is an illustrative case that opens discussion on necessity and timing of cardiac interventions once possible cardiac sources of ischemic strokes are found and new facts arise.

Key words: anticoagulation therapy, atrial fibrillation, ischemic stroke, patent foramen ovale

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Introduction

Ischemic stroke is one of the major causes of death and disability in high-developed countries [1]. Atrial fibrillation (AF) is responsible for around one third of all ischemic strokes [2]. The role of patent foramen ovale (PFO) has been widely discussed especially in younger individuals and closure of PFO is recommended if other causes of ischemic stroke were excluded [3].

Case report

A 75-years-old female patient with five ischemic strokes in her medical history (1986–2012) and multiple other comorbidities (heart failure with reduced left ventricle ejection fraction, coronary artery disease treated with coronary-artery by-pass grafting in 2007, paroxysmal AF (PAF), systemic hypertension, diabetes mellitus type 2, lower limbs' varices disqualified to surgical treatment, post-thrombotic

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Table 1. Risk of Paradoxical Embolism (RoPE) Score results over the years

	1986	2003	2005	2009	2012
History of hypertension (No — 1 point; Yes — 0 points)	No	Yes	Yes	Yes	Yes
History of diabetes (No — 1 point; Yes — 0 points)	No	No	No	Yes	Yes
History of stroke/TIA (No — 1 point; Yes — 0 points)	No	Yes	Yes	Yes	Yes
Smoker (No — 1 point; Yes — 0 points)	No	No	No	No	No
Cortical infarct on imaging (Yes — 1 point; No — 0 points)	Yes	Yes	Yes	Yes	Yes
Age (18–29 yrs — 5 points; 30–39 yrs — 4 points; 40–49 yrs — 3 points; 50–59 yrs — 2 points; 60–69 yrs — 1 point; ≥ 70 yrs — 0 points)	43 yrs	60 yrs	62 yrs	66 yrs	69 yrs
	8 points	4 points	4 points	3 points	3 points
Chance of PFO-related stroke	84%	38%	38%	0%	0%

TIA — transient ischemic disease; PFO — patent foramen ovale

syndrome) was admitted because of non-ST elevation myocardial infarction in 2019. The coronary arteriography showed patent grafts and probably chronic occlusion of the left anterior descending artery (LAD) distal to anastomosis. An attempt to open chronically occluded LAD was unsuccessful and decision on conservative treatment was made by the Heart Team. The echocardiographic examination confirmed reduced left ventricular ejection fraction (LVEF 30%) and for the first time revealed spontaneous left-to-right shunt in interatrial septum (IAS) and presence of the Eustachian valve. Transesophageal echocardiography visualized patent PFO with right-to left shunt induced by Valsalva maneuver. This finding made paradoxical embolism another possible cause of recurrent ischemic strokes next to PAF. This arrhythmia was recorded for the first time in 2012 just after the last stroke (CHA_2DS_2-VASc score — 9 points). Anticoagulation therapy was started immediately after diagnosis. The patient had other risk factors for paradoxical embolism such as varices, post-thrombotic syndrome of lower limbs and the Eustachian valve [3]. Ultrasonography of the carotid arteries was normal.

We stratified the patient's risk using the Risk of Paradoxical Embolism (RoPE) score dedicated to differentiate stroke-related vs incidental PFO [4]. *See* Table 1.

At discharge, rivaroxaban (20 mg/d.) plus clopidogrel (75 mg/d.) were administered. One month after discharge a significant bleeding from limb varices occurred that required urgent surgical intervention. Because of the high risk of recurrent hemorrhages (HAS-BLED Score — 4 points), the patient was considered for two percutaneous procedures: occlusion of the left atrial appendage (LAA) and consecutively PFO closure as additional prevention of stroke [3, 5].

Discussion

Implementation of anticoagulation therapy in 2012 has prevented new ischemic strokes in our patient. According to emerging meta-analyses such treatment is sufficient not only in AF, but also in PFO related ischemic strokes [6–8]. Anticoagulation treatment is not inferior to PFO closure as comes to prevention of recurrence of ischemic strokes and both these options are superior to the antiplatelet therapy [6–8]. In European position paper on the management of patients with PFO expert recommend to carefully select patients for percutaneous closure of PFO in case of cryptogenic ischemic stroke [3]. It is advised especially in younger patients (18–65yrs) in the case of lack of other possible causes of ischemic stroke. Individual approach for patients over 65yrs is recommended. It is unclear whether AF has been the major cause of ischemic stroke in present case; especially, considering that it was detected 25 years after first ischemic event. The patient was evaluated using RoPE score, which did not give an exact conclusion on the role of PFO. Active bleeding during anticoagulation generated a new problem. LAA occlusion may be considered as an alternative to anticoagulation therapy in patients with contraindications to antithrombotic treatment [5]. Consensus Document for percutaneous occlusion of the LAA in patients with non-valvular AF also points to other indications for LAA closure than bleeding, such as elderliness or risk of frequent falls [9]. This is an additional argument in favor of LAA occlusion in our patient. The question about PFO closure is still open; however, it seems reasonable after LAA occlusion. This is an illustrative case that opens discussion on necessity and timing of cardiac interventions once possible cardiac sources of ischemic strokes are found and new facts arise. Probably no definite answers can be found yet if there is still time to wait with possible interventions in this kind of patient and continue pharmacological treatment. Should those procedures be performed simultaneously? If this is feasible, probably yes. This kind of attempt reduces complication rate linked to multiplying procedures and reduces necessity of repeating transesophageal echocardiography (TEE).

Conflict of interest

None declared.

Streszczenie

Udar niedokrwienny mózgu jest istotną przyczyną niepełnosprawności oraz zgonów w krajach wysokorozwiniętych. Zamknięcie drożnego otworu owalnego (PFO) jest zalecane, jeśli wykluczy się inne, częstsze przyczyny udaru niedokrwiennego, takie jak migotanie przedsionków (AF), co szczególnie dotyczy młodszych pacjentów. Zaprezentowano przypadek 75-letniej chorej z wywiadem pięciu udarów niedokrwiennych mózgu w okresie 26 lat oraz nowo wykrytym PFO. Migotanie przedsionków zdiagnozowano 25 lat po pierwszym udarze niedokrwiennym mózgu. Włączenie leczenia przeciwkrzepliwego zapobiegło wystąpieniu kolejnych udarów niedokrwiennych mózgu. Zgodnie z najnowszymi badaniami takie postępowanie jest skuteczne nie tylko w prewencji udarów związanych z AF, ale również z PFO. Chora była również obciążona wieloma innymi czynnikami ryzyka wystąpienia zatorów skrzyżowanych: żylakami kończyn dolnych, zespołem pozakrzepowym kończyn dolnych, zastawką Eustachiusza, dlatego też nie było jasne, czy to AF stanowiło główny czynnik wystąpienia wszystkich incydentów niedokrwiennych. Podczas leczenia przeciwkrzepliwego u pacjentki wystąpiło istotne krwawienie z żylaków kończyn dolnych, które wymagało pilnego leczenia chirurgicznego. Ze względu na wysokie ryzyko nawrotu krwawienia (HAS-BLED — 4 pkt.) u chorej rozważano wykonanie dwóch przezskórnych procedur: zamknięcia uszka lewego przedsionka oraz następnie zamknięcia PFO jako dodatkowej prewencji przed kolejnymi udarami niedokrwiennymi ośrodkowego układu nerwowego.

Współwystępowanie AF i PFO otworzyło dyskusję dotyczącą do głównej przyczyny nawracających udarów niedokrwiennych mózgu. Zamknięcie uszka lewego przedsionka i PFO są alternatywnymi metodami zapobiegającymi udarom niedokrwiennym mózgu w przypadku przeciwwskazań do antykoagulacji.

Słowa kluczowe: antykoagulacja, migotanie przedsionków, udar niedokrwienny mózgu, przetrwały otwór owalny

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Massive acute pulmonary embolism in 33-year-old male with low risk factors of venous thrombosis: management according to 2019 ESC guidelines

Masywna zatorowość płucna u 33-letniego mężczyzny z niskim ryzykiem żylnej choroby zakrzepowo-zatorowej — postępowanie według wytycznych ESC 2019

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Abstract

We present a case of a 33-year-old obese patient with pulmonary embolism (PE), admitted to the hospital with gradually worsening of dyspnea, general malaise, right lower limb redness and edema. During examination tachycardia (124/min) and hypoxemia (90% SpO_2) were recorded. Laboratory findings revealed elevated levels of D-dimer, cardiac troponin T and N-terminal pro-B-type natriuretic peptide. Electrocardiography showed clear signs of pulmonary embolism — SIQIIITIII and T-waves inversion in V1–V5. Diagnosis prediction was strengthened by transthoracic echocardiography, which uncovered signs of right ventricle overload and 60/60 sign. Despite little risk factors of venous thromboembolism (VTE), the patient was assessed to have a high clinical probability of PE according to revised Geneva clinical prediction rule. Predisposing condition to VTE could be past coronavirus disease 2019 infection. Patient was categorized into a group of intermediate-high risk of early mortality, received parenteral anticoagulation with unfractionated heparin and underwent computed tomography pulmonary angiography (CTPA) (class IB), which confirmed the diagnosis in this almost certain case. CTPA can cause many side-effects, including: contrast-induced nephropathy or anaphylaxis, which in such unequivocal situation may be questioned and other, safer methods of PE confirmation could prove their usefulness.

Key words: pulmonary embolism, computed tomography pulmonary angiography, ESC guidelines

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Introduction

Pulmonary embolism (PE) is a clinical outcome of venous thromboembolism (VTE), incidents of which are getting more common with age, especially among patients older than 70-years-old [1]. Higher prevalence of VTE in the elderly leads to misdiagnosis in younger patients, while 5–10% of in-hospital deaths are a direct result of PE [2]. Fast and efficient diagnostics and treatment are crucial to save and prolong patient' life. We present a case of a young man,

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a coronavirus disease 2019 (COVID-19) convalescent, with pulmonary embolism and little predisposing factors to VTE [3], whose was treated according to the 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of acute PE [4].

Case report

A 33-year-old obese [body mass index (BMI) 29 g/m^2] patient was admitted with dyspnea that had gradually worsened over the last 20 days, with exacerbation to resting dyspnea within last 24 hours. He observed right lower limb reddening and edema few days prior to admission. Measured vital signs were as follows: oxygen saturation of arterial blood (SaO_2) was 90%, up to 95% passive oxygen therapy, heart rate 124 beats/min (regular), blood pressure 126/76 mm Hg. Laboratory findings revealed elevated levels of D-dimer, cardiac troponin T (cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (Table 1). Electrocardiography registered sinus tachycardia 130/min, left axis deviation, SIQIIITIII sign and T-waves inversion in leads V1–V5 (Figure 1). Transthoracic echocardiography (TTE) showed signs of right ventricular overload — enlarged right ventricular diastolic diameter (RVDD 43 mm), decreased tricuspid annular plane systolic excursion (TAPSE 12–13 mm) and 60/60 sing. Patient scored 12 points in revised Geneva clinical prediction rule for PE and was in high clinical probability group. According to Pulmonary Embolism Severity Index/Simplified Pulmonary Embolism Severity Index (PESI/sPESI) patient had low mortality risk. The computed tomography pulmonary angiography (CTPA) confirmed PE and uncovered saddle pulmonary embolus (Figures 2, 3) and subpleural lesions characteristic for pneumonia attributed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Serological test confirmed the presence of IgM/IgG SARS-CoV-2 antibodies and further tests, including reverse transcriptase polymerase chain reaction (RT-PCR) test and Abott's antibody test, excluded active COVID-19 infection (Table 1). Due to stable clinical state without sings of hemodynamic shock, the patient was treated with initial parenteral anticoagulation therapy with unfractionated heparin followed by oral therapy with rivaroxaban.

Table 1. Laboratory findings

Variable	Date	
	November 21	November 22
D-dimer [mg/L] (< 0.50)	8.09	10.46
NT-proBNP [pg/mL] (< 125.0)	4581.0	–
cTnT [µg/L] (0.009–0.4 µg/L)	43	–
	33	
COVID-19 tests results	**November 21–24**	
RT-PCR SARS-CoV-2	Negative	
SARS-CoV-2 Abbott antigen test	Negative	
IgM SARS-CoV-2 antibodies	Positive COI: 22.1	
IgM SARS-CoV-2 antibodies [AU/mL]	Positive 103	

NT-proBNP — N-terminal pro-B-type natriuretic peptide; cTnT — cardiac troponin T; COVID-19 — coronavirus disease 2019; RT-PCR — reverse transcriptase polymerase chain reaction; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2

Discussion

The 2019 ESC Guidelines for diagnosis and management of acute PE have introduced a new standard across the

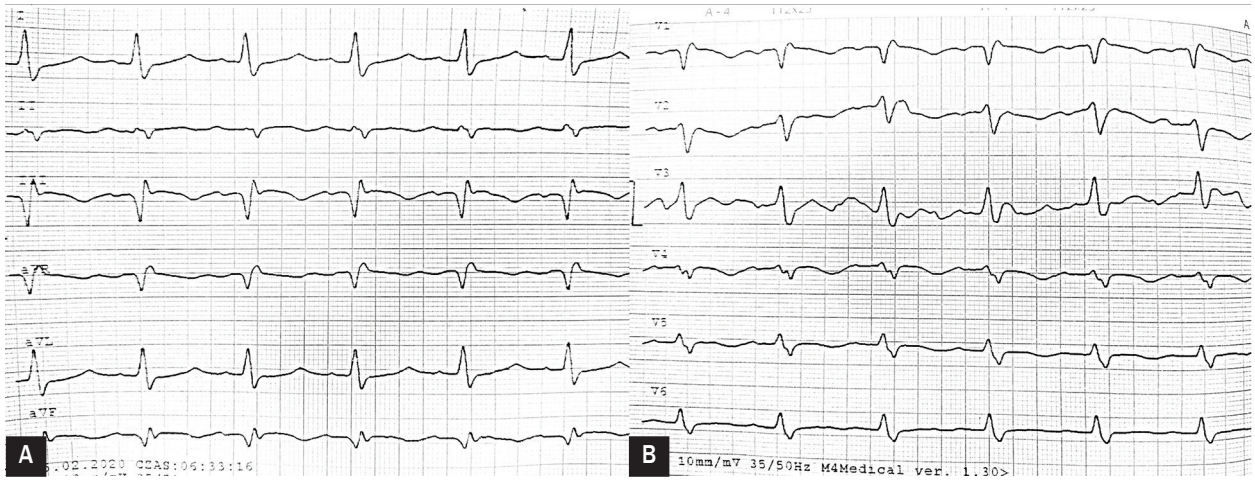

Figure 1. Electrocardiogram (50 mm/s; 1 mV = 10 mm) — sinus tachycardia, left axis deviation, SIQIIITIII sign, T-waves inversion in precordial leads V1–V5

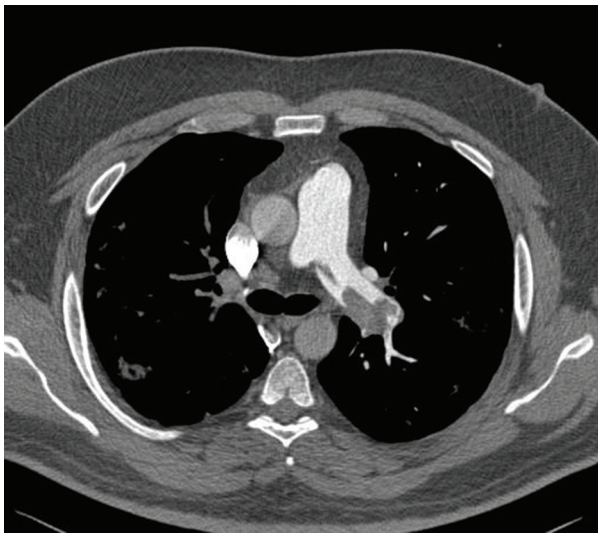

Figure 2. Embolus extending from pulmonary trunk bifurcation to left main pulmonary artery (CTPA)

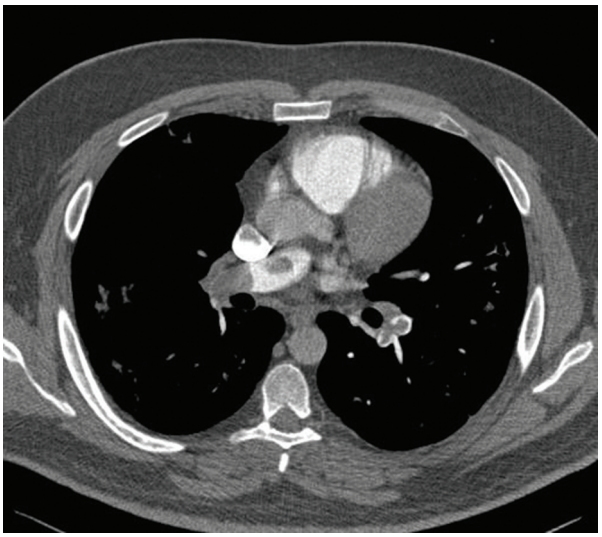

Figure 3. Arterial embolus in right main pulmonary artery (CTPA)

whole Europe. Diagnosis and treatment are strongly tied with PE's clinical probability, indicators of risk and early mortality risk.

The patient developed VTE despite only low predisposing factors for this condition — obesity. Other possible causes of VTE (coagulopathies, autoimmune diseases) cannot be excluded. However, recent COVID-19 infection was confirmed and new studies acknowledged the positive correlation between this disease and VTE incidents [5]. Importance of being placed in intermediate-high risk group of early mortality and earlier mentioned electrocardiographic (ECG) findings relating to disadvantageous short-term outcomes in PE [6] cannot be undermined. According to the guidelines, the patient should undergo the CTPA for diagnosis confirmation (IB recommendation class). In patients with high pre-test PE probability, CTPA positive predictive value was 92–96% [7]. Taking the above into consideration, PE in this patient was almost certain and chances that CTPA's outcome would influence treatment process are slim, as the treatment should be implemented during diagnostic procedures in patients with high clinical probability (class IC). However, according to guidelines, CTPA in this case and among the patients with positive D-dimer is a "must-have" step. There is still the safest way to confirm the diagnosis in PE suspected patient by using compression ultrasonography (CUS) — class IA, but it was unavailable at the time. Worth mentioning is that computed tomography with contrast exposes the patient to dangerous radiation and other side-effects such as anaphylactic shock or contrast-induced nephropathy[8], which could be easily avoided.

Conclusion

In the new guidelines, CTPA takes a lead in a race for being a golden standard for confirmation or exclusion of pulmonary embolism. In our case, PE is almost certain based on clinical signs, symptoms, results of ECG, transthoracic echocardiography (TTE) and laboratory tests indicating initial assumption. Still, CTPA had to be performed to confirm clinically nearly certain diagnosis and exposed the patient to potential risk of complications, including contrast-induced nephropathy. Therefore, we should seek another, safer PE confirmation method, especially in such unequivocal situation.

Conflict of interest

Authors declare no conflict of interest.

Streszczenie

Zaprezentowano opis przypadku 33-letniego otyłego mężczyzny z zatorowością płucną (PE), przyjętego z powodu stopniowo narastającej duszności, osłabienia oraz zaczerwienienia i obrzęku prawej kończyny dolnej. U pacjenta stwierdzono tachykardię (124/min) i hipoksemię (90% SpO_2). W badaniach uwagę zwracały podwyższone stężenia D-dimerów, troponiny T i N-końcowego fragmentu propeptydu natriuretycznego typu B. Badanie elektrokardiograficzne wykazało zmiany typowe dla PE — konfigurację SIQIIITIII oraz ujemne załamki T w odprowadzeniach V1–V5. Kliniczne podejrzenie PE dodatkowo potwierdzono w echokardiografii przezklatkowej, w której uwidoczniono cechy przeciążenia prawej komory i objaw 60/60. Mimo słabych czynników ryzyka choroby zakrzepowo-zatorowej (VTE), pacjenta cechowało wysokie prawdopodobieństwo kliniczne PE według skali genewskiej. Warunkiem predysponującym do VTE mogła być przebyta choroba koronawirusowa 2019. Pacjent w obrazie pośrednio wysokiego ryzyka wczesnego zgonu w przebiegu PE otrzymał parenteralnie heparynę niefrakcjonowaną i przebył badanie angiografii płucnej metodą tomografii komputerowej (CTPA) (klasa zaleceń IB), które potwierdziło wcześniejsze przypuszczenia w tym pewnym klinicznie przypadku, narażając chorego na działania niepożądane, głównie związane z podaniem środka kontrastowego, między innymi nefropatię pokontrastową czy anafilaksję. W opisywanym przypadku CTPA jest metodą z wyboru, która niesie za sobą ryzyko powikłań. Należy poszukiwać nowych metod diagnostycznych lub algorytmów postępowania pozwalających na pewne postawienie dignozy w przypadkach niebudzących wątpliwości klinicznych.

Słowa kluczowe: zatorowość płucna, angiografia płucna metodą tomografii komputerowej, wytyczne ESC

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Arrhythmia from hell. Idiopathic left fascicular ventricular tachycardia in a young woman

Arytmia z piekła rodem. Idiopatyczny pęczkowy częstoskurcz komorowy u młodej kobiety

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Abstract

Idiopathic left fascicular ventricular tachycardia (ILFVT) is characterized by right bundle branch block morphology and left axis deviation. We report a case of ILFVT in a young 27-year-old female patient presenting with a narrow complex tachycardia resistant to vagal manoeuvers, adenosine, lidocaine, and electrical cardioversion.

Key words: idiopathic left fascicular ventricular tachycardia, verapamil, ventricular tachycardia

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Introduction

Idiopathic left fascicular ventricular tachycardia (ILFVT) is characterized by right bundle branch block (RBBB) morphology and left axis deviation.

Verapamil-sensitive ILFVT is a Purkinje-related arrhythmia mainly occurring in patients with structurally normal hearts [1, 2]. The underlying mechanism is assumed to be reentry in most cases [1, 3]. The most common type, called "Belhassen VT" [4, 5], exits near the left posterior fascicle and exhibits a morphology of RBBB and left axis deviation.

The underlying mechanism is believed to be a reentry tachycardia involving the Purkinje fibers of the fascicles — typically the left posterior fascicle of the left bundle branch and features of an automatic tachycardia. In 1981, Belhassen et al. [4] demonstrated that intravenous (i.v.) administration of verapamil significantly decreased the recurrence rate of IFLVT in afflicted patients. Vagal manoeuvers, adenosine, and lidocaine are ineffective in suppressing fascicular tachycardia [6]. We report a case of ILFVT in a young 27-year-old female patient presenting with a narrow complex tachycardia.

Case report

A 27-year-old female patient presented to the emergency department with sudden onset of palpitations of 2 hours duration. She has no history of chest pain, shortness of breath, or syncopal attack. There was no significant past medical, family, and she was not on any regular medication. She denied any use of alcohol or illicit drug.

Physical examination revealed blood pressure (BP) of 110/70 mm Hg and a heart rate of 218 beats/min. The cardiac examination did not reveal anything abnormal. Electrocardiogram (ECG) revealed a narrow complex tachycardia (QRS 110 ms), iRBBB, and left axis deviation (Figure 1A). Laboratory tests revealed normal hemoglobin, liver function tests, renal function tests, serum electrolytes,

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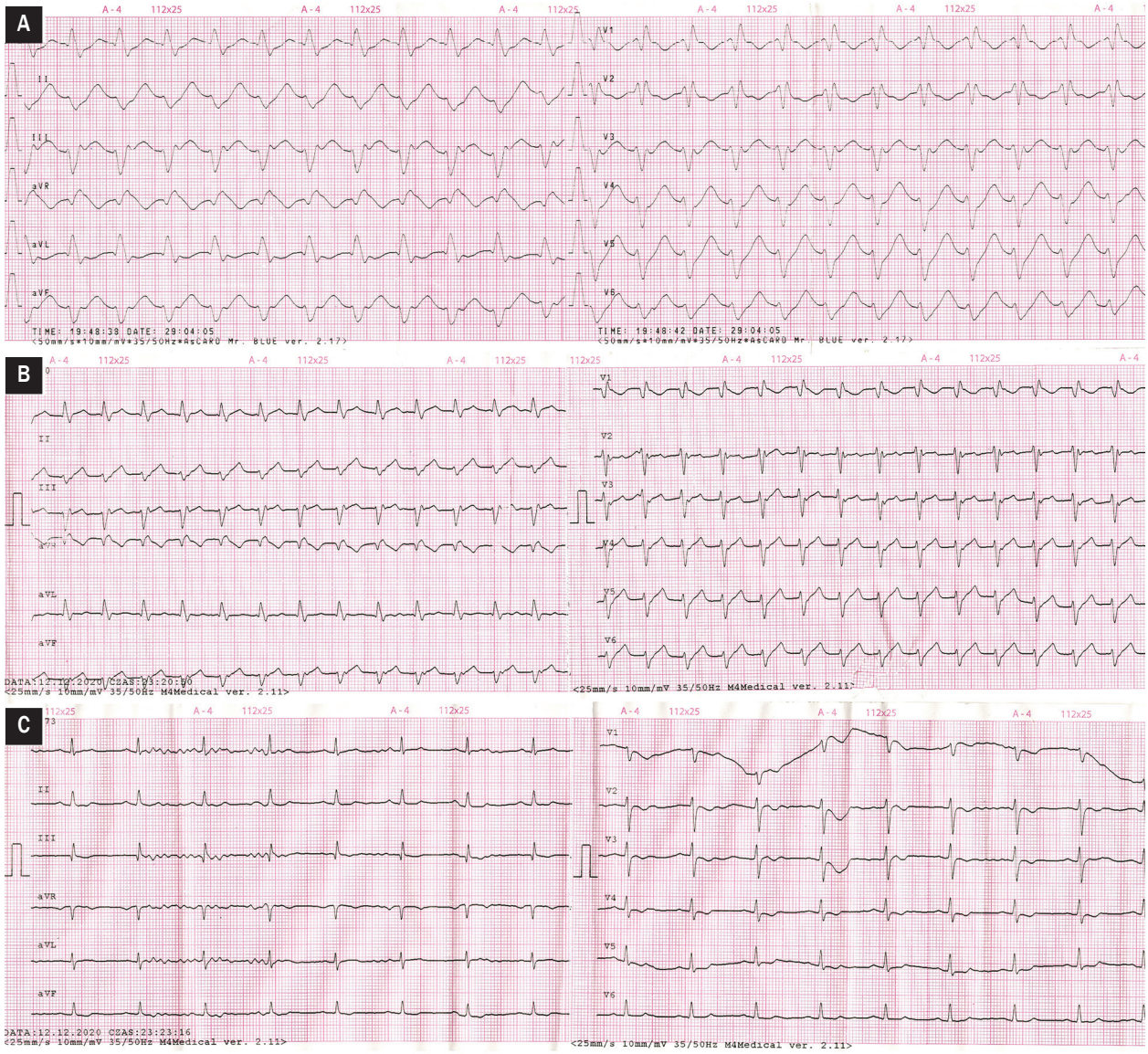

Figure 1A. Fascicular ventricular tachycardia on admission; **B.** Fascicular ventricular tachycardia following electrical cardioversion; **C.** Sinus rhythm after arrhythmia termination

and thyroid-stimulating hormone. Transthoracic echocardiography showed no structural abnormalities, normal valve function, and left ventricle ejection fraction of 55%. Initial treatment with vagal manoeuvers and i.v. adenosine up to 18 mg failed to terminate the arrhythmia. After a subsequent time, the patient developed hypotension, dizziness, and nausea.

Electrical cardioversion with increased biphasic energy levels 75–120–200 J was attempted but failed to terminate the arrhythmia. Intravenous boluses of 150 mg of amiodarone and 2 g of magnesium sulfate were administered before the next cardioversion attempt with monophasic energy 360 J but also failed (Figure 1B). An additional i.v. dose of 100 mg of lidocaine was administered, and arrhythmia self-terminated after a few minutes. After 20 minutes, arrhythmia recurred with a heart rate of 130/min. Moreover, the patient remained clinically stable. Intravenous extra doses of 100 mg of lidocaine and 150 mg of amiodarone were administered once again but without success. A diagnosis of fascicular tachycardia was suspected based on ECG findings of narrow complex tachycardia, iRBBB, and left axis deviation, failure in initial and subsequent treatment. An additional oral dose of 160 mg of verapamil was given, which resulted in permanent arrhythmia termination (Figure 1C). The patient was started on verapamil 120 mg daily and discharged from the cardiac department after 48 hours with no arrhythmia recurrence during follow-up.

Discussion and conclusion

If adenosine is not effective in reverting presumed SVT, this diagnosis of IFLVT should be considered.

Malignant arrhythmias usually occur in the presence of significant structural heart disease and carry a significant risk of sudden cardiac death.

ILFVT most frequently presents as paroxysmal episodes of palpitations and dizziness. Although most episodes occur at rest, exercise, emotional stress, and catecholamine infusion can trigger them. Studies showed that IFLVT behaves electrophysiologically as a reentrant tachycardia [7].

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Conflict of interest

The authors declare that there is no conflict of interest.

Streszczenie

Idiopatyczny lewokomorowy częstoskurcz komorowy pęczkowy (ILFVT) charakteryzuje obecność zespołów QRS o morfologii bloku prawej odnogi pęczka Hisa oraz lewogramu. W artykule przytoczono opis przypadku 27-letniej kobiety z ILFVT, która zgłosiła się z częstoskurczem z wąskimi zespołami QRS opornym na zabiegi zwiększające napięcie nerwu błędnego, adenozynę, lidokainę czy kardiowersję elektryczną.

Słowa kluczowe: idiopatyczny lewokomorowy częstoskurcz komorowy pęczkowy, werapamil, częstoskurcz komorowy

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Life-threatening pericarditis and pleuritis caused by influenza B and successfully treated during COVID-19 pandemic

Zagrażające życiu zapalenie osierdzia i opłucnej spowodowane przez grypę B i skutecznie wyleczone podczas pandemii COVID-19

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Abstract

In 2020, World Health Organization declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [coronavirus disease 2019 (COVID-19)] a pandemic. Nowadays, Influenza A (InfA) and COVID-19 seem to be a major threat. We report the rare case of life-threatening exudative pericarditis (without myocardial involvement) and pleuritis in an adult patient without inherited diseases, caused by Influenza B (not by COVID-19/InfA) and successfully treated (including: oseltamivir, pericardiocentesis 700 mL, pleurocentesis 1100 mL) in the COVID-19 pandemic. Although Influenza B is a rare cause of pericarditis, we should consider it as a possible reason of a potentially lethal disease.

Key words: influenza B, pericarditis, pleuritis, COVID-19 pandemic, SARS-CoV-2

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Introduction

Influenza causes 300,000 deaths per year in the world [1]. Although the respiratory system is commonly affected, cardiac involvement also occurs (direct virus impact on heart or preexisting cardiovascular disease exacerbation) [2]. In 2020, World Health Organization (WHO) declared SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection (COVID-19, coronavirus disease 2019) a pandemic. Influenza A (InfA) and COVID-19 seem to be a major threat. Influenza B (InfB) is considered less severe than InfA, typically causing mild upper respiratory symptoms [3].

Authors report the rare case of life-threatening pericarditis (without myocardial involvement) and pleuritis, caused by InfB and successfully treated during a COVID-19 pandemic.

Case report

A 74-year-old patient with I/II/III degree atrioventricular block, after pacemaker implantation (19.02.2020) and right ventricular (RV) electrode replacement (dysfunction, 21.02.2020), was admitted to hospital (19.03.2020) because of confirmed (Doppler-ultrasound) left brachial, axillary vein thrombosis and fever (up to 38°C) for 7 days.

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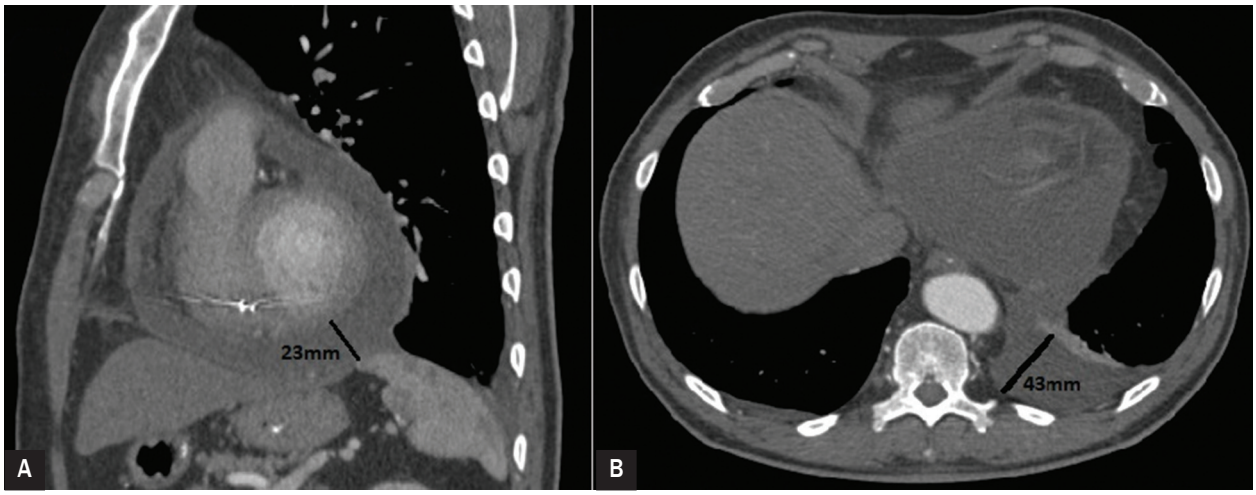

Figure 1A. Chest computed tomography (CT): fluid in pericardium 23 mm; **B.** Chest CT: fluid in left pleura 43 mm

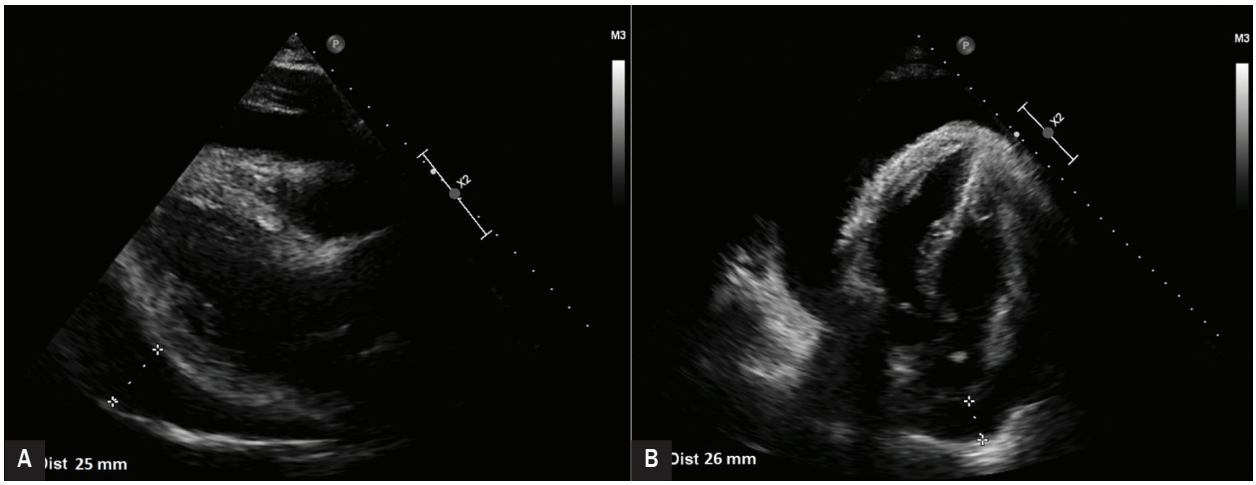

Figure 2. Transthoracic echocardiography prior to pericardiocentesis: pericardial effusion at right ventricle 15 mm, posterior wall of left ventricle (LV) 25 mm, lateral wall of LV 27 mm, right atrium 26 mm: **A.** Long axis view; **B.** Four chamber apical view

Initially, the patient's state was good, without dyspnea, stenocardia, cough; 36.8°C, the pacemaker pocket healed properly. Upper left extremity was swollen, warm.

COVID-19 was excluded. "Cassette" screening test and reverse transcriptase polymerase chain reaction (RT-PCR) (nasopharyngeal swab, days: 1, 14) were negative.

Methicillin resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae* carbapenemase (KPC) (swabs), tuberculosis (QuantiFERON) were excluded. Inflammatory markers elevated: C-reactive protein (CRP) 205 mg/L, D-dimers 0.69 mg/L FEU, white blood cells WBC 12,000/μL, with negative procalcitonin.

Cardiac device-related infectious endocarditis (CDRIE) was suspected. Transthoracic echocardiography (TTE) revealed pericardial effusion at RV 5 mm, no systolic RV and left ventricular (LV) dysfunction. Transesophageal echocardiography (TOE) showed no vegetations. Pharmacotherapy was provided: ointment (heparin, phenyl butasone), rivaroxaban 2 × 15 mg, ketoprofen, and empirical treatment with vancomycin. Inflammatory markers decreased, but hectic fever (to 38.5°C) of unclear etiology persisted.

Urine cultures and tumor markers [CA125, CA19.9, carcinoembryonic antigen (CEA), CA15.3, prostatic specific antigen (PSA)] were negative. Abdominal computed tomography (CT) revealed fluid in pelvis 17 mm; chest CT fluid in pericardium 23 mm, in left pleura 43 mm (Figure 1). TTE showed fluid at RV 5 mm, LV posterior wall (LVPW) 11 mm, right atrium (RA) 11 mm, without wall perforation.

Proteinogram confirmed acute inflammation. Hypothyroidism was excluded.

Blood cultures were negative. TOE was repeated (days 1, 7): no vegetations, pericardial effusion 22 mm, without tamponade, 5 mm fibrin layer. There was no data for CDRIE. Initial diagnosis was reactive/inflammatory pericardial and pleural effusion. Colchicine, ibuprofen, levofloxacin were administered.

Control Doppler-ultrasound (after week) showed residual 1.5–2.0 mm thick wall thrombus in left axillary veins. Rivaroxaban dose was reduced (20 mg/day).

After 10 days of treatment: clinical worsening, still fever, increasing CRP (238 [mg/l]), WBC (14,500/μL), D-dimers (7.89 mg/l FEU)) were observed. Paroxysmal atrial fibrillation/atrial tachycardia appeared (after fluid evacuation: spontaneous sinus rhythm recurrence). TTE showed pericardial effusion at RV 15 mm, LVPW 25 mm, RA 26 mm (Figure 2).

Nasopharyngeal swab samples were negative for InfA, positive for InfB. Oseltamivir 2 × 75 mg and furosemide were provided (control swab after 5 days: negative).

Due to pericardial and pleural (82 mm) effusion, pericardiocentesis (700 mL, serosanguinous fluid) and pleurocentesis (1100 mL, serous fluid) were performed (02.04.2020), with clinical improvement. Pericardial fluid examination revealed exudate, negative cultures (aerobic, anaerobic, fungal, TBC). Pleural fluid analysis showed exudate, negative cultures (aerobic, anaerobic, TBC).

Anti-cardiolipin antibodies (ACA: IgM, IgG), anti-nuclear nRNP, anti-neutrophil (cANCA, pANCA), antinuclear and cytoplasmic ANA (HEP-2), *Legionella, Bartonella, Tularemia* antibodies were negative. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* IgM antibodies were negative, IgG were positive (previous infections). Prednisone (30–100–0 mg) was provided.

Finally, clinical improvement, no fever recurrence and CRP reduction (15) were achieved. Control TTEs revealed stable pericardial effusion at LVPW 18 mm, RA 13 mm. The patient was discharged with diagnosis of exudative pericarditis and pleuritis in the course of InfB.

Follow-up: continuous decrease in pericardial effusion.

Discussion

Cardiac involvement is more common and better described with InfA than InfB [3].

Few cases of myopericarditis were described in the course of: COVID-19 (pericardiocentesis 540 mL) [4], and InfB (fatal tamponade, pericardiocentesis 240 mL) [3].

Only few cases of pericarditis (without myocardial involvement) were reported, but in "high risk" patients with co-morbidities, during: InfA (first case: hypertension, nicotinism; pericardiocentesis 250 mL, ibuprofen, colchicum, oseltamivir [2]; second case: alcohol, cocaine; pericardiocentesis, antibiotic, oseltamivir, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicum [5]) and InfB (21 trisomy, ASD; ibuprofen, colchicum, oseltamivir, steroids, furosemide) [1].

We report a rare case of life-threatening exudative pericarditis (without myocardial involvement) and pleuritis in an adult patient without inherited diseases caused by InfB (not by COVID-19/InfA) and successfully treated in a COVID-19 pandemic. However, InfB is a rare cause of pericarditis we should consider it as a possible reason of a potentially lethal disease.

Funding

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Conflict of interest

The authors declare no conflict of interest.

Streszczenie

W 2020 roku Światowa Organizacja Zdrowia ogłosiła panedmię spowodowaną SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*) (choroba koronawirusowa 2-19 [COVID-19]). Infekcje grypą A (InfA) i COVID-19 są obecnie traktowane jako większe zagrożenie niż infekcja grypą B. Zaprezentowano rzadki przypadek zagrażających życiu wysiękowego zapalenia osierdzia (bez zajęcia miokardium) i opłucnej u dorosłego pacjenta (bez chorób dziedzicznych), wywołanych przez grypę B (nie przez COVID-19/InfA) oraz skutecznie wyleczonych (w tym: oseltamiwir, perikardiocenteza 700 ml, pleurocenteza 1100 ml) w czasie pandemii COVID-19. Mimo że grypa B jest rzadką przyczyną zapalenia osierdzia, to należy ją traktować jako możliwą przyczynę potencjalnie śmiertelnej choroby.

Słowa kluczowe: grypa B, zapalenie osierdzia, zapalenie opłucnej, pandemia COVID-19, SARS-CoV-2

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Clinician's guide for dapagliflozin use in heart failure with reduced ejection fraction

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Abstract

Dapagliflozin belongs to a new class of drugs used for the treatment of heart failure — sodium-glucose cotransporter type 2 inhibitors (SGLT2i). Based on the DAPA-HF study results, dapagliflozin has become the first SGLT2i approved for the treatment of symptomatic chronic heart failure with reduced ejection fraction. The present review summarizes the most important clinical issues related to the treatment with this drug.

Key words: heart failure with reduced ejection fraction, SGLT2 inhibitors, dapagliflozin

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Introduction

Heart failure (HF) is present in about 1.2 million patients in Poland [1]. The population of patients with HF continues to grow and poses an increasing financial burden, mostly related to hospitalizations due to HF exacerbation. Of note, effective treatment for HF and preventing its progression are possible with innovative drugs that, shortly after their introduction, have been shown to bring significant clinical benefits including a reduction in the risk of cardiovascular mortality and admissions due to HF. One of these therapies is dapagliflozin.

The mechanism of action of sodium-glucose cotransporter type 2 inhibitors (SGLT2i)

Inhibitors of the sodium-glucose cotransporter type 2, which is present in the proximal renal tubule, results in urinary glucose excretion by reducing glucose reabsorption and lowering the renal glucose threshold [2]. It is the basic mechanism of action of these drugs in the treatment of diabetes. **Glucosuria results in osmotic diuresis and is associated with a negative energy balance, which leads to weight reduction and improves insulin sensitivity** [3]. This effect is insulin-independent and is not associated with a risk of hypoglycaemia.

Other beneficial mechanism of action of SGLT2i which are particularly important in HF include **a reduction of sodium reabsorption in the renal tubule [4]. The resultant increased natriuresis and osmotic diuresis, plasma volume reduction and blood pressure lowering lead to a reduction in left ventricular preload and afterload.** At the same time, an increased sodium load reaching the macula densa decreases activation of the sympathetic system and the renin–angiotensin–aldosterone (RAA) system. In addition, **increased production and use of ketone bodies** in the myocardium **improve myocardial metabolism and inhibit myocardial remodelling [4]**. Another beneficial effect of SGLT2i is a **nephroprotective effect** resulting from afferent arteriolar constriction, leading to a reduction of glomerular hyperfiltration and urinary albumin excretion [5].

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Table 1. Inclusion and exclusion criteria in the DAPA-HF study (source [6])

Major inclusion criteria
Men and women ≥ 18 years of age, with diabetes type 2 or without diabetes
Documented diagnosis of symptomatic HFrEF for ≥ 2 months (NYHA class II–IV)
LVEF ≤ 40% within the last 12 months
Increased NT-proBNP level (≥ 600 pg/mL, or ≥ 400 pg/mL if hospitalization for HF within 12 months, or ≥ 900 pg/mL if atrial fibrillation/flutter was diagnosed, regardless of the history of hospitalization for HF)
Optimal standard drug treatment for HF and device therapy (cardioverter-defibrillator and/or cardiac resynchronization therapy)
Optimal and stable (for ≥ 4 months) standard drug treatment for HFrEF according to the local guidelines (unless contraindicated or not tolerated), including ACEI/ARB or ARNI, beta-blocker, and MRA if indicated
eGFR ≥ 30 mL/min/1.73 m^2
Major exclusion criteria
Treatment with SGLT2i within 8 weeks prior to study inclusion or SGLT2i intolerance
Diabetes type 1
Symptomatic hypotension or systolic blood pressure < 95 mm Hg
Current acute exacerbated HF or hospitalization due to exacerbated HF within the last 4 weeks
Myocardial revascularization (PCI or CABG), valve repair/replacement, implantation of a cardiac pacemaker (CRT) within the last 12 weeks or such procedure planned in the post-randomization period
HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic cardiomyopathy, or uncorrected primary valve disease
eGFR < 30 mL/min/1.73 m^2 or rapidly worsening renal function

HFrEF — heart failure with reduced ejection fraction; NYHA — New York Heart Association; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; HF — heart failure; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; ARNI — angiotensin receptor blocker and neprilysin inhibitor; MRA — mineralocorticoid receptor antagonist; eGFR — estimated glomerular filtration rate; SGLT2i — sodium-glucose cotransporter type 2 inhibitor; PCI — percutaneous coronary intervention; CABG —, coronary artery bypass grafting; CRT — cardiac resynchronization therapy

DAPA-HF study results

The clinical efficacy of dapagliflozin in the treatment of symptomatic chronic heart failure with reduced ejection fraction (HFrEF) has been documented in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study, a prospective multicentre randomized placebo-controlled phase III trial to evaluate the efficacy and safety of dapagliflozin compared to placebo [6]. Dapagliflozin was added to standard guideline-recommended HFrEF therapy, i.e., an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or an angiotensin receptor blocker and neprilysin inhibitor (ARNI), beta-blocker, and/or mineralocorticoid receptor antagonist (MRA) in stable doses for at least 4 weeks. The study included 4,744 symptomatic New York Heart Association (NYHA) class II–IV patients with chronic HF and left ventricular ejection fraction ≤ 40%. Both patients with diabetes type 2 and non-diabetic ones were recruited to the study and randomized in the 1:1 ratio to dapagliflozin 10 mg once daily or placebo. The DAPA-HF study was the first dapagliflozin trial that included non-diabetic patients and those with renal dysfunction, i.e., with the estimated glomerular filtration rate (eGFR) of 30–60 mL/min/1.73 m^2.

The inclusion and exclusion criteria are shown in Table 1.

Of note, the patients included in the DAPA-HF study received optimal HF treatment, as 94% were treated with ACEI/ARB/ARNI (including 11% treated with ARNI), 96% with a beta-blocker, and 71% with a MRA. Compared to earlier studies in HFrEF, more patients in the DAPA-HF study were treated with an implanted cardiac device, including an implantable cardioverter-defibrillator (ICD) in 26%, and cardiac resynchronization therapy (CRT) in 8%.

Compared to placebo, **dapagliflozin treatment was associated with a 26% lower risk of the primary endpoint of cardiovascular death, hospitalization for HF, or an urgent HF-related visit without hospitalization (p < 0.0001)** during the median follow-up of 18.2 months (**Table 2**). **The reduction in the primary endpoint rate was documented as early as at 28 days of treatment** [hazard ratio (HR) 0.51, 95% confidence interval (CI): 0.28–0.94, p = 0.03]. A risk reduction was also seen for all the components of the primary endpoint (Table 2). The study also showed a reduction in the risk of secondary endpoints (Table 2) including [6]:

- cardiovascular death or hospitalization for HF;
- total number of hospitalizations (initial and recurrent) for HF and cardiovascular deaths;
- all-cause mortality;

Table 2. Primary and secondary endpoints in the DAPA-HF study (source [6])

Outcome	Dapagliflozin n = 2,373	Placebo n = 2,371	Relative risk 95% CI	p
Primary endpoint	386 (16.3)	502 (21.2)	0.74 (0.65–0.85)	< 0.001
Hospitalization or urgent visit for HF	237 (10.0)	326 (13.7)	0.70 (0.59–0.83)	–
Cardiovascular death	227 (9.6)	273 (11.5)	0.82 (0.69–0.98)	–
Hospitalization for HF	231 (9.7)	318 (13.4)	0.70 (0.59–0.83)	–
Urgent visit for HF	10 (0.4)	23 (1.0)	0.43 (0.20–0.09)	–
Secondary endpoints				
Cardiovascular death or hospitalization for HF	382 (16.1)	495 (20.9)	0.75 (0.65–0.85)	< 0.001
All hospitalizations for HF and cardiovascular deaths	567	742	0.75 (0.65–0.88)	< 0.001
All-cause death	276 (11.6)	329 (13.9)	0.83 (0.71–0.97)	0.022**
Change in KCCQ* at 8 months	6.1 ± 18.6	3.3 ± 19.2	1.18 (1.11–1.26)	< 0.001
Renal function worsening	28 (1.2)	39 (1.6)	0.71 (0.44–1.16)	–

*Kansas City Cardiomyopathy Questionnaire (KCCQ) score 0 to 100, with high scores indicating lower severity of heart failure (HF) symptoms; **[7]; CI — confidence interval

— improvement in the quality of life as measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 8 months compared to baseline;
— worsening of renal function, defined as persistent eGFR reduction by ≥ 50%, occurrence of end-stage renal failure (defined as permanent eGFR reduction to < 15 mL/min/1.73 m^2), chronic dialysis therapy, or kidney transplantation), or death due to renal causes.

Improved clinical outcomes in the DAPA-HF study were seen in both patients with diabetes type 2 and non-diabetic patients. Dapagliflozin is the only SGLTi that reduced cardiovascular and all-cause mortality in patients with HFrRF (by 18% and 17%, respectively). Detailed results of the DAPA-HF study are shown in Table 2.

The benefits of dapagliflozin in regard to the primary endpoint rate were similar regardless of the left ventricular ejection fraction, aetiology of HF, concomitant guideline-recommended HF treatment in terms of drug classes used and medication doses, use of device therapy (ICD/CRT) and duration of the disease. The patients with long-standing HF (duration > 5 years) were also shown to benefit from dapagliflozin therapy [8]. The beneficial effects of the drug were seen in all NYHA classes and were greater in milder disease, i.e., in patients in NYHA class II. Thus, dapagliflozin therapy should be initiated early and not postponed until more severe HF symptoms develop.

The benefits of dapagliflozin were similar in all baseline systolic blood pressure categories (p for interaction 0.78) but patients with higher systolic blood pressure, i.e., ≥ 130 mm Hg, benefited more (HR 0.67, 95% CI: 0.60–0.97) compared to patients in the lowest systolic blood pressure category, i.e., with systolic blood pressure < 110 mm Hg (HR 0.76, 95% CI: 0.51–0.87) [9].

In the DAPA-HF study, absolute risk reduction for the primary endpoint was greatest in the group with a history of a hospitalization for HF within 12 months before inclusion into the study [absolute risk reduction (ARR) 9.9%], compared to patients hospitalized for HF more than 12 months before inclusion into the study (ARR 4.1%) and patients without a history of hospitalization for HF (ARR 2.1%, p for interaction 0.052). These findings mean that **the treatment with dapagliflozin should be initiated early after a hospitalization for HF** [10].

Based on the DAPA-HF study results, dapagliflozin was approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in 2020 for the management of symptomatic chronic HFrEF. **Dapagliflozin, marketed as Forxiga™, is the first SGLT2i approved for the management of HFrEF.**

The aim of this publication is to provide clinicians with practical guidance regarding the use of dapagliflozin in HFrEF.

In whom should dapaglifozin be initiated for the management of heart failure?

According to the summary of product characteristics (SmPC), dapagliflozin is indicated for the treatment of symptomatic chronic HFrEF in adult patients [11]. Based on data from the large U.S. Get With The Guidelines-Heart Failure (GWTG-HF) registry, 81% patients with HFrEF would quality for dapagliflozin treatment according to its labelling [12].

The optimal candidate for dapagliflozin treatment is characterized by [6]:

- **HFrEF with left ventricular ejection fraction of ≤ 40%;**
- **NYHA class II–IV symptoms of HF,** although the experience with dapagliflozin in NYHA class IV patients is limited due to a relatively low number of such patients included in the DAPA-HF study;
- **systolic blood pressure of ≥ 95 mm Hg;**
- **ongoing standard treatment for HFrRF, i.e., with a beta-blocker, a renin-angiotensin system inhibitor (ACEI/ARB or ARNI), and a MRA if indicated;**
- **eGFR of ≥ 30 mL/min/1.73 m^2.**

In patients with HFrEF, dapagliflozin dose does not have to be modified if renal dysfunction is present [9]. However, the experience with the use of dapagliflozin in the treatment of HF in patients with severe renal dysfunction (eGFR < 30 mL/min/1.73 m^2) is limited.

There is also no need for drug dose adjustment in patients with mild to moderate hepatic dysfunction [11].

How to initiate dapagliflozin treatment?

Experts recommend that dapagliflozin treatment should be initiated early, optimally before the hospital discharge or during a follow-up visit directly after hospital discharge following hospitalization for exacerbated HFrEF [13]. Dapagliflozin may be added to any chronic HFrEF therapy [6], including drug therapy and device therapy, and regardless of the drug doses used. According to the SmPC, the recommended dapagliflozin dose in HFrEF is 10 mg once daily. The drug may be administered at any time of the day, regardless of meals (either with a meal or between meals).

The drug may be given regardless of the diabetes status and diabetes treatment. However, sulphonylurea and/or insulin dose reduction by about 30% should be considered in patients receiving concomitant treatment with these drugs due to a risk of hypoglycaemia [9]. Of note, SGLT2i may be insufficiently effective for blood glucose lowering with eGFR below 45 mL/min/1.73 m^2 and other antidiabetic medications should be considered in such patients to control their blood glucose levels [11].

Safety of dapagliflozin treatment

Dapagliflozin has been used for the treatment of diabetes type 2 for 8 years, and more than 2.5 million patients received this drug in 2019 [14]. Several years of experience, including clinical trials and real-world evidence (RWE), indicate that **dapagliflozin is a safe drug. Adverse events (AE), serious AE, and AE leading to discontinuation of dapagliflozin treatment are rare, occurring with the rates similar to the rates in the placebo group [6].** The safety data including AE rates are shown in Table 3.

The most common AE categories in the DAPA-HF study were hypovolaemia and renal events (including serious AE: 38 in the dapagliflozin group vs. 65 in the placebo group, p = 0.009) [6], while genital and urinary infections were a marginal problem.

According to the SmPC, there is no need to discontinue dapagliflozin treatment in case of a mild to moderate fungal urogenital infection. Local antifungal therapy or administering a single dose of oral antifungal drug is recommended.

The DAPA-HF study subgroup analyses indicate that dapagliflozin was safe and well tolerated regardless of gender, concomitant diabetes, renal function, and age category [6]. In patients 75 years of age and over, serious renal AE were less frequent in the dapagliflozin group compared to the placebo group (P for interaction 0.031) [15]. Also in patients with eGFR below 60 mL/min/1.73 m^2 treated with dapagliflozin, the risk of serious AE was significantly lower compared to the placebo group (p = 0.03) [16].

In the DAPA-HF study, only rare serious hypoglycaemia and diabetic ketoacidosis events were noted, **exclusively in patients with diabetes type 2** (with the rates of 0.4% and 0.3%, respectively) [6].

Of note in the context of standard HFrRF treatment, dapagliflozin may reduce the risk of moderate to severe hypokalaemia in patients treated with MRA [17].

Practical guidance

Due to possible hypovolaemia and hypotension during dapagliflozin treatment, the patients should be advised that a modification of diuretic, other antihypertensive drug, and HF drug therapy doses may be required, and adequate fluid intake should be maintained. The risk of symptomatic hypovolaemia and hypotension is increased in those with a history of hypotension, and in the elderly patients [11].

During dapagliflozin treatment, glucosuria is detected on urinalysis, which is consistent with the drug's mechanism of action. Urinary glucose excretion may be associated with an increased risk of external urogenital organ infection, and less frequently urinary tract infection.

Table 3. Adverse events in the DAPA-HF study [6]

Adverse event, n [%]	Dapagliflozin n = 2,368	Placebo n = 2,368	p
Hypovolaemia	178 (7.5)	162 (6.8)	0.40
Renal function-related adverse event	153 (6.5)	170 (7.2)	0.36
Fracture	49 (2.1)	50 (2.1)	1.00
Amputation	13 (0.5)	12 (1.3)	1.00
Severe hypoglycaemia	4 (0.2)	4 (0.2)	n/a
Diabetic ketoacidosis	3 (0.1)	0	n/a
Fournier gangrene	0	1 (< 0.1)	n/a
Severe urinary system infection	14 (0.6)	17 (0.7)	
Severe genital organ infection	0	1 (0.0)	
Adverse event leading to drug discontinuation	111 (4.7)	116 (4.9)	0.79

n/a — not applicable

Discontinuation of dapagliflozin treatment should be considered in case of pyelonephritis or urosepsis. During dapagliflozin treatment, patients should be advised to pay attention to maintaining adequate urogenital hygiene, including daily underwear changes, wearing non-tight cotton undergarments, and avoiding irritants and scented detergents.

The following changes were noted during dapagliflozin treatment in the DAPA-HF study [6]:

- systolic blood pressure lowering (on average by 1.92 mm Hg);
- N-terminal pro-B-type natriuretic peptide (NT-proBNP) level lowering (on average by 196 pg/mL);
- weight reduction (on average by 0.88 kg);
- haemoglobin A_{1c} level reduction in diabetic patients (on average by 0.21%);
- increase in haematocrit (on average by 2.31%);
- increase in serum creatinine level (on average by 0.07 mg/dL).

A transient eGFR reduction may be initially expected during dapagliflozin treatment, particularly in the first 2 weeks. This phenomenon is related to afferent arteriolar constriction due to the tubuloglomerular feedback triggered by an increased sodium influx to the macula densa. During further follow-up in the DAPA-HF study, the rate of eGFR changes in the dapagliflozin group was lower compared to the placebo group, reflecting a nephroprotective effect. Over the entire duration of follow-up, the mean eGFR reduction by about 4 mL/min/1.73 m^2 was documented, while eGFR at 12 months was similar in both study groups [6].

Renal function should be evaluated prior to the initiation of dapagliflozin treatment and monitored thereafter, with serum creatinine level measurement and eGFR calculation at least annually. If eGFR is reduced below 30 mL/min/1.73 m^2 during dapagliflozin treatment, it is recommended to evaluate volume status, blood pressure, and other reversible factors that might contribute to renal function worsening (e.g., other medications, imaging with the use of a contrast agent), correct any contributing factors, and perform follow-up eGFR determination with an individual decision whether to continue dapagliflozin treatment in given clinical settings.

Diabetic ketoacidosis

Diabetic ketoacidosis during treatment with SGLT2i does not occur in non-diabetic patients with HFrEF, and is a rare occurrence in patients with diabetes type 2 (in the DAPA-HF study, only 3 such cases were identified among patients with diabetes type 2 treated with dapagliflozin) [6], although it may occur with only mildly elevated blood glucose values. It is more frequent during insulin therapy, with poor blood glucose control, and during the first two months of therapy. Diabetic ketoacidosis may be a life-threatening condition. Patients should be educated regarding the symptoms of diabetic ketoacidosis and the need to contact a physician and discontinue SGLT2i therapy should these symptoms occur. Reinitiation of SGLT2i therapy is possible following stabilization of the clinical condition and reduction of ketonemia (ketone bodies should be measured in blood), when some other obvious cause for diabetic ketoacidosis has been identified and corrected.

Symptoms of diabetic ketoacidosis include nausea, vomiting, anorexia, abdominal pain, excessive thirst, rapid and deep breathing with sweet and fruity breath odour, confusion, and atypical fatigue or somnolescence.

The patients should be **evaluated for the risk of diabetic ketoacidosis** which is increased in the following situations:

- conditions leading to reduced oral food intake or severe dehydration;
- sudden fall in insulin level;

— increased insulin requirement due to acute illness, surgery, or alcohol abuse;
— low beta cell functional reserve, e.g., in patients with diabetes type 2 and low peptide C level or latent autoimmune diabetes in adults and in patients with a history of pancreatitis.

Precautions

Dapagliflozin should be used with caution in the following situations:
— severe renal dysfunction;
— history of diabetic ketoacidosis;
— in case of recurrent genitourinary infections;
— the treatment should be interrupted in patients with diabetes type 2 hospitalized due to a major acute illness and before surgical procedures (with drug withdrawal for 3 days before the procedure).

Alcohol abuse and use of ketogenic diets are contraindicated during dapagliflozin treatment.

Contraindications to dapagliflozin

According to the SmPC [11], use of Forxiga™ is contraindicated in patients with hypersensitivity to the active substance or any other component of this product. Tablets contain lactose. The drug should not be used in patients with rarely occurring hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption syndrome. Dapagliflozin is also contraindicated in the second and third trimester of pregnancy.

Summary

Sodium-glucose cotransporter type 2 inhibitors have become a breakthrough in the management of patients with HFrEF. Dapagliflozin is the first SGLT2i approved for the treatment of chronic HFrEF. It is a well-tolerated, safe, and easy-to-use drug. Benefits of dapagliflozin treatment have been documented regardless of standard HFrEF therapies, drug doses, and device therapy, indicating a complementary effect of dapagliflozin over other HFrEF therapies. Dapagliflozin modifies the clinical course of HFrEF, reduces the rate of hospitalizations for HF, cardiovascular deaths, and all-cause deaths, and improves the quality of life of patients with HFrEF regardless of concomitant presence of diabetes type 2.

Conflict of interests

Lectures for AstraZeneca.

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Dapagliflozyna w niewydolności serca z obniżoną frakcją wyrzutową lewej komory — przewodnik klinicysty

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Streszczenie

Dapagliflozyna jest przedstawicielem nowej grupy leków w terapii niewydolności serca — inhibitorów kotransportera sodowo-glukozowego typu 2 (SGLT2i). Na podstawie wyników badania DAPA-HF dapagliflozyna uzyskała rejestrację do stosowania w objawowej przewlekłej niewydolności serca z obniżoną frakcją wyrzutową lewej komory jako pierwszy SGLT2i. W pracy przedstawiono najważniejsze aspekty kliniczne dotyczące terapii tym lekiem.

Słowa kluczowe: niewydolność serca z obniżoną frakcją wyrzutową, inhibitory SGLT2, dapagliflozyna

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Wprowadzenie

W Polsce na niewydolność serca (HF, *heart failure*) choruje około 1,2 miliona pacjentów [1]. Populacja chorych z HF systematycznie się powiększa i pochłania coraz większe nakłady finansowe, głównie związane z hospitalizacjami z powodu zaostrzenia HF. Należy pamiętać, że skuteczne leczenie HF oraz zapobieganie postępowi tej choroby jest możliwe. Pozostają do dyspozycji innowacyjne leki, w odniesieniu do których udokumentowano w krótkim czasie od rozpoczęcia ich stosowania istotne korzyści kliniczne, między innymi pod postacią redukcji ryzyka wystąpienia zgonu z przyczyn sercowo-naczyniowych lub hospitalizacji z powodu HF. Dapagliflozyna należy do tych terapii.

Mechanizm działania inhibitorów SGLT2

Inhibitory kotransportera sodowo-glukozowego typu 2 (SGLT2i, *sodium-glucose co-transporter type 2 inhibitors*), który znajduje się w bliższych kanalikach nerkowych, powodują wydalanie glukozy z moczem na drodze zmniejszenia reabsorpcji glukozy i obniżenia progu nerkowego dla glukozy [2]. Jest to podstawowy mechanizm działania w leczeniu cukrzycy. **Glikozuria powoduje diurezę osmotyczną oraz jest związana z wystąpieniem ujemnego bilansu energetycznego, co wywołuje utratę masy ciała i poprawia wrażliwość tkanek na insulinę** [3]. Efekt ten jest niezależny od insuliny oraz uzyskiwany bez ryzyka hipoglikemii.

Spośród innych korzystnych mechanizmów działania SGLT2i, szczególnie istotnych w HF, należy wymienić **zmniejszenie wchłaniania zwrotnego sodu w cewce nerkowej [4]. Nasilona natriureza i diureza osmotyczna, zmniejszenie objętości osocza i ciśnienia tętniczego prowadzi do obniżenia obciążenia wstępnego i następczego lewej komory**. Natomiast zwiększone dostarczanie jonów sodu do plamki gęstej zmniejsza aktywację współczulną i układu renina–angiotensyna–aldosteron (RAA). Dodatkowo w miokardium **zwiększa się produkcja ciał ketonowych i ich wykorzystania, co powoduje poprawę metabolizmu mięśnia sercowego i hamowanie jego remodelingu [4].** Kolejnym korzystnym efektem SGLT2i jest **działanie nefroprotekcyjne** wynikające z obkurczenia nerkowej tętniczki doprowadzającej, co zmniejsza hiperfiltrację wewnątrz kłębuszka nerkowego i wydalanie albumin z moczem [5].

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Wyniki badania DAPA-HF

Skuteczność kliniczną leku dapagliflozyna w leczeniu objawowej przewlekłej niewydolności serca z obniżoną frakcją wyrzutową lewej komory (HFrEF, *heart failure reduced ejection fraction*) udokumentowano w badaniu DAPA-HF (*Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure*) — wieloośrodkowym, prospektywnym, randomizowanym badaniu klinicznym III fazy, kontrolowanym placebo, służącym ocenie skuteczności i bezpieczeństwa dapagliflozyny w porównaniu z placebo [6]. Dapagliflozynę dodawano do standardowej terapii HFrEF zgodnej z aktualnymi wytycznymi, tj. inhibitora konwertazy angiotensyny (ACEI, *angiotensin-converting enzyme inhibitor*)/antagonisty receptora AT_1 dla angiotensyny II (ARB *angiotensin* AT_1 *receptor blocker*) lub antagonisty receptora angiotensyny i inhibitora neprylizyny (ARNI, *angiotensin receptor neprilysin inhibitor*) oraz beta-adrenolityku i/lub antagonisty receptora mineralokortykoidowego (MRA, *mineralocorticoid receptor antagonist*), w stabilnych dawkach, od co najmniej 4 tygodni. Badanie przeprowadzono z udziałem 4744 wykazujących objawy pacjentów w II–IV klasie niewydolności według *New York Heart Association* (NYHA), z przewlekłą HF z obniżoną frakcją wyrzutową nieprzekraczającą 40%. Do badania rekrutowano zarówno chorych na cukrzycę typu 2, jak i bez cukrzycy, których poddawano randomizacji w stosunku 1:1 do grupy otrzymującej dapagliflozynę w dawce 10 mg raz/dobę lub placebo. Badanie DAPA-HF było pierwszym z zastosowaniem dapagliflozyny, w którym możliwe było włączenie chorych bez cukrzycy oraz z upośledzoną funkcją nerek, tj. z szacowanym współczynnikiem przesączania kłębuszkowego (eGFR, *estimated glomerular filtration rate*) między 30 a 60 ml/min/1,73 m^2.

Kryteria włączenia do badania i wyłączenia przedstawiono w tabeli 1.

Warto podkreślić, że populacja pacjentów w badaniu DAPA-HF była leczona optymalnie, tj. 94% otrzymywało ACEI/ARB/ARNI (w tym ARNI — 11%), 96% beta-adrenolityk oraz 71% MRA. W porównaniu z wcześniejszymi badaniami przeprowadzonymi w HFrEF większa część chorych badania DAPA-HF miała urządzenia wszczepialne — wszczepialny kardiowerter-defibrylator (ICD, *implantable cardioverter-defibrillator*) 26% i do terapii resynchronizującej (CRT, *cardiac resynchronization therapy*) 8%.

W okresie obserwacji (mediana 18,2 miesiąca), w porównaniu z placebo, **dapagliflozyna obniżyła o 26% ryzyko wystąpienia pierwszorzędowego punktu końcowego, na który składały się zgon z przyczyn sercowo-naczyniowych,**

Tabela 1. Kryteria włączenia i wyłączenia w badaniu DAPA-HF (źródło [6])

Główne kryteria włączenia
Mężczyźni i kobiety w wieku ≥ 18 lat chorzy na cukrzycę typu 2 lub bez cukrzycy
Udokumentowane rozpoznanie objawowej HFrEF w okresie ≥ 2 miesięcy (II–IV klasa czynnościowa wg NYHA)
LVEF ≤ 40% w ciągu ostatnich 12 miesięcy
Zwiększone stężenie NT-proBNP (≥ 600 pg/ml lub ≥ 400 pg/ml, jeżeli hospitalizacja z powodu HF wystąpiła w ciągu 12 miesięcy, lub ≥ 900 pg/ml, jeżeli rozpoznano migotanie/trzepotanie przedsionków bez względu na wywiad hospitalizacji z powodu HF)
Optymalne standardowe leczenie farmakologiczne HF i elektroterapia (kardiowerter-defibrylator i/lub układ resynchronizujący)
Optymalne i stabilne (trwające ≥ 4 tygodnie) podstawowe leczenie standardowe z powodu HFrEF zgodnie z lokalnymi wytycznymi (chyba że takie leczenie jest przeciwwskazane lub nietolerowane), obejmujące ACEI/ARB lub ARNI, beta-adrenolityk i w stosownych przypadkach MRA
eGFR ≥ 30 ml/min/1,73 m^2
Główne kryteria wyłączenia
Terapia SGLT2i w okresie 8 tygodni przed włączeniem do badania lub nietolerancja SGLT2i
Cukrzyca typu 1
Objawowe niedociśnienie lub ciśnienie skurczowe < 95 mm Hg
Występująca obecnie ostra niewyrównana HF lub hospitalizacja z powodu niewyrównanej HF w okresie ostatnich 4 tygodni
Rewaskularyzacja mięśnia sercowego (PCI lub CABG), naprawa/wymiana zastawki, wszczepienie stymulatora serca (CRT) w ciągu ostatnich 12 tygodni lub taki zabieg planowany na okres po randomizacji
Niewydolność serca z powodu kardiomiopatii zaciskającej, czynnego zapalenia mięśnia sercowego, zaciskającego zapalenia osierdzia, kardiomiopatii przerostowej lub niewyrównanej pierwotnej choroby zastawek
eGFR < 30 ml/min/1,73 m^2 lub szybko pogarszająca się czynność nerek

HFrEF (*heart failure reduced ejection fraction*) — niewydolność serca z obniżoną frakcją wyrzutową lewej komory; NYHA — *New York Heart Association*; LVEF (*left ventricular ejection fraction*) — frakcja wyrzutowa lewej komory; NT-proBNP (*N-terminal pro-B-type natriuretic peptide*) — N-końcowy fragment propeptydu natriuretycznego typu B; HF (*heart failure*) — niewydolność serca; ACEI (*angiotensin-converting enzyme inhibitor*) — inhibitor konwertazy angiotensyny; ARB (*angiotensin* AT_1 *receptor blocker*) — antagonista receptora AT_1 dla angiotensyny II; ARNI (*angiotensin receptor neprilysin inhibitor*) — antagonista receptora angiotensyny i inhibitora neprylizyny; MRA (*mineralocorticoid receptor antagonist*) — antagonista receptora mineralokortykoidowego; eGFR (*estimated glomerular filtration rate*) — współczynnik przesączania kłębuszkowego; SGLT2i (*sodium-glucose co-transporter type 2 inhibitors*) — inhibitory kotransportera sodowo-glukozowego typu 2; PCI (*percutaneous coronary intervention*) — przezskórna interwencja wieńcowa; CABG (*coronary artery bypass grafting*) — pomostowanie aortalno-wieńcowe; CRT (*cardiac resynchronization therapy*) — terapia resynchronizująca

Tabela 2. Pierwszorzędowe i drugorzędowe punkty końcowe w badaniu DAPA-HF (źródło [6])

Wynik	Dapagliflozyna n = 2373	Placebo n = 2371	Współczynnik ryzyka 95% CI	Wartość p
Pierwszorzędowy złożony punkt końcowy	386 (16,3)	502 (21,2)	0,74 (0,65–0,85)	< 0,001
Hospitalizacja lub pilna wizyta z powodu HF	237 (10,0)	326 (13,7)	0,70 (0,59–0,83)	–
Zgon z przyczyn sercowo-naczyniowych	227 (9,6)	273 (11.5)	0,82 (0,69–0,98)	–
Hospitalizacja z powodu HF	231 (9,7)	318 (13,4)	0,70 (0,59–0,83)	–
Pilna wizyta z powodu HF	10 (0,4)	23 (1,0)	0,43 (0,20–0,09)	–
Drugorzędowe punkty końcowe				
Zgon sercowo-naczyniowy lub hospitalizacja z powodu HF	382 (16,1)	495 (20,9)	0,75 (0,65–0,85)	< 0.001
Wszystkie hospitalizacje z powodu HF i zgony sercowo-naczyniowe	567	742	0,75 (0,65–0,88)	< 0.001
Zgon z dowolnej przyczyny	276 (11,6)	329 (13,9)	0,83 (0,71–0,97)	0,022**
Zmiana w KCCQ* w 8. miesiącu badania	6,1 ± 18,6	3,3 ± 19,2	1,18 (1,11–1,26)	< 0.001
Pogorszenie funkcji nerek	28 (1,2)	39 (1,6)	0,71 (0,44–1,16)	–

**Kansas City Cardiomyopathy Questionnaire* (KCCQ) obejmuje zakres od 0 do 100 punktów; wysokie wyniki świadczą o mniejszym nasileniu objawów niewydolności serca (HF, *heart failure*); **[7]; CI (*confidence interval*) — przedział ufności

hospitalizacja z powodu HF lub pilna wizyta związana z HF niezakończona hospitalizacją (p < 0,0001) (tab. 2). Korzystny efekt pod postacią redukcji ryzyka wystąpienia pierwszorzędowego punktu końcowego udokumentowano już od 28. dnia terapii tym lekiem (współczynnik ryzyka [HR, *hazard ratio*] 0,51, 95-proc. przedział ufności [CI, *confidence interval*] 0,28–0,94; p = 0,03). Redukcję ryzyka udokumentowano w odniesieniu do składowych pierwszorzędowego punktu końcowego liczonych osobno (tab. 2). W badaniu udokumentowano również korzyści w zakresie redukcji ryzyka wystąpienia drugorzędowych punktów końcowych (tab. 2), do których należały [6]:

- zgon z przyczyn sercowo-naczyniowych lub hospitalizacja z powodu HF;
- całkowita liczba hospitalizacji (pierwszych i kolejnych) z powodu HF i zgony z przyczyn sercowo-naczyniowych;
- zgon z jakiejkolwiek przyczyny;
- poprawa jakości życia oceniana za pomocą kwestionariusza *Kansas City Cardiomyopathy Questionnaire* (KCCQ) po 8. miesiącu obserwacji w porównaniu z jakością życia na początku badania;
- wystąpienie pogorszenia funkcji nerek, tj. utrzymujący się spadek wartości eGFR o 50% albo więcej lub schyłkowa niewydolność nerek (zdefiniowana jako trwałe obniżenie eGFR < 15 ml/min/1,73 m^2, przewlekła dializa lub przeszczepienie nerki) lub zgon z przyczyn nerkowych.

Korzyści kliniczne w badaniu DAPA-HF odnosili zarówno pacjenci ze współistniejącą cukrzycą typu 2, jak i bez cukrzycy. Dapagliflozyna jest jedynym SGLT2i, który redukuje ryzyko wystąpienia zgonu z przyczyn sercowo-naczyniowych oraz z jakiejkolwiek przyczyny wśród chorych z HFrEF (odpowiednio o 18% i 17%). Szczegółowe wyniki badania DAPA-HF przedstawiono w tabeli 2.

Korzyści w zakresie pierwszorzędowego punktu końcowego ze stosowania dapagliflozyny były podobne niezależnie od wielkości frakcji wyrzutowej lewej komory, etiologii HF, sposobu leczenia w zakresie grup leków i dawek standardowej terapii oraz niezależnie od zastosowanej elektroterapii (ICD/CRT) i czasu trwania choroby. Udokumentowano, że chorzy z długotrwającą, bo od ponad 5 lat, HF również odnosili korzyści z terapii dapagliflozyną [8]. Pozytywne efekty terapii tym lekiem dotyczyły osób ze wszystkich klas według NYHA, przy czym były większe w niższej klasie czynnościowej, tj. II klasie według NYHA. Dlatego z włączeniem dapagliflozyny nie należy czekać do wystąpienia bardziej nasilonych objawów HF, lecz rozpoczynać to leczenie wcześnie.

Korzyści ze stosowania dapagliflozyny były podobne we wszystkich analizowanych kategoriach wyjściowego

skurczowego ciśnienia tętniczego (p dla interakcji 0,78), aczkolwiek bardziej korzystali pacjenci z wyższym ciśnieniem tj. wyższym lub równym 130 mm Hg (HR 0,67; 95% CI: 0,60–0,97) w porównaniu do najniższego, tj, wynoszącego poniżej 110 mm Hg (HR 0,76; 95% CI: 0,51–0,87) [9].

Z analiz badania DAPA-HF wiadomo, że redukcja ryzyka bezwzględnego dla pierwszorzędowego punktu końcowego była najwyższa w grupie po przebytej hospitalizacji z powodu HF w okresie 12 miesięcy przed włączeniem do badania (absolutna redukcja ryzyka [ARR, *absolute risk reduction*] 9,9%) w porównaniu z pacjentami hospitalizowanymi dawniej, tj. ponad 12 miesięcy (ARR 4,1%) lub chorymi bez wywiadu hospitalizacji (ARR 2,1%) — p dla interakcji 0,052. Oznacza to, że **terapię dapagliflozyną powinno się inicjować wcześnie po hospitalizacji z powodu HF** [10].

Na podstawie wyników badania DAPA-HF Europejska Agencja Leków (EMA, *European Medicines Agency*) i amerykańska Agencja ds. Żywności i Leków (FDA, *Food and Drug Agency*) zatwierdziły w 2020 roku dapagliflozynę do stosowania w leczeniu pacjentów z objawową przewlekłą HFrEF. **Produkt leczniczy Forxiga™ jest pierwszym preparatem z grupy SGLT2i zarejestrowanym do stosowania w leczeniu HFrEF.**

Celem publikacji jest przedstawienie lekarzom praktykom wskazówek do stosowania dapagliflozyny w HFrEF.

U kogo włączać dapagliflozynę w niewydolności serca?

Zgodnie z charakterystyką produktu leczniczego (ChPL) dapagliflozyna jest wskazana do stosowania u osób dorosłych w leczeniu objawowej przewlekłej HFrEF [11]. Według danych dużego amerykańskiego rejestru GWTG-HF 81% pacjentów z HFrEF można uznać za kwalifikujących się do leczenia dapagliflozyną zgodnie ze wskazaniami rejestracyjnymi [12].

Optymalny kandydat do terapii dapagliflozyną charakteryzuje się [6]:

- **HFrEF z frakcją wyrzutową nie większą niż 40%;**
- **objawami HF od II do IV klasy czynnościowej według NYHA**, aczkolwiek doświadczenia ze stosowaniem dapagliflozyny u pacjentów w IV klasie według NYHA jest ograniczone ze względu na relatywnie małą liczbę takich pacjentów włączonych do badania DAPA-HF;
- **skurczowym ciśnieniem tętniczym wyższym lub równym 95 mm Hg;**
- **tym, że jest poddany standardowej terapii HFrEF, tj. beta-adrenolityk, inhibitor układu renina–angiotensyna (ACEI/ARB lub ARNI) oraz MRA, jeśli zalecane;**
- **klirensem kreatyniny wyższym lub równym 30 ml/min/1,73 m^2.**

U pacjentów z HFrEF nie ma konieczności zmiany dawki dapagliflozyny w związku z zaburzeniami czynności nerek [9]. Natomiast doświadczenia z zastosowania dapagliflozyny w leczeniu HF u pacjentów z ciężkimi zaburzeniami czynności nerek (GFR < 30 ml/min) są ograniczone.

Nie ma również konieczności dostosowania dawki leku u pacjentów z łagodnymi lub umiarkowanymi zaburzeniami czynności wątroby [11].

Jak zainicjować leczenie dapagliflozyną?

Według opinii ekspertów leczenie dapagliflozyną u chorego z HFrEF należy rozpoczynać wcześnie, najlepiej jeszcze przed wypisaniem ze szpitala lub podczas kontrolnej wizyty ambulatoryjnej bezpośrednio po wypisaniu chorego ze szpitala z powodu zaostrzenia HFrEF [13]. Dapagliflozynę można dodawać do każdej terapii przewlekłej HFrEF [6] — zarówno farmakoterapii, jak i elektroterapii oraz niezależnie od wielkości dawek przyjmowanych leków. Zgodnie z ChPL w HFrEF zalecaną dawką dapagliflozyny jest 10 mg podawane raz/dobę. Lek chory może przyjmować o każdej porze dnia, niezależnie od spożywanych posiłków (łącznie z posiłkiem lub pomiędzy nimi).

Lek można dodawać niezależnie od statusu cukrzycy oraz jej leczenia, przy czym w przypadku równoczesnej terapii pochodnymi sulfonylomocznika i/lub insuliną należy rozważyć zmniejszenie o około 30% dawek tych leków ze względu na ryzyko wystąpienia hipoglikemii [9]. Należy pamiętać, że przy eGFR poniżej 45 ml/min/1,73 m^2 skuteczność SGLT2i w obniżaniu glikemii może być niewystarczająca i w związku z tym należy rozważyć dodatkowe leczenie przeciwcukrzycowe w celu poprawy kontroli glikemii [11].

Bezpieczeństwo stosowania dapagliflozyny

Dapagliflozyna jest stosowana w praktyce klinicznej w leczeniu cukrzycy typu 2 od 8 lat, na świecie w 2019 roku leczono nią ponad 2,5 mln pacjentów [14]. Z przeprowadzonych badań klinicznych oraz obserwacji RWE (*real-world evidence*) i kilkuletnich doświadczeń wynika, że **dapagliflozyna jest lekiem bezpiecznym. Zdarzenia niepożądane (AE, *adverse events*), poważne AE oraz te, które prowadziły do przerwania leczenia dapagliflozyną, występują rzadko i z podobną częstością jak w grupie przyjmującej placebo [6].** Dane dotyczące bezpieczeństwa terapii z AE przedstawiono w tabeli 3.

Do najczęściej rejestrowanych AE w badaniu DAPA-HF były niedobór płynów i zdarzenia związane z nerkami (w tym poważne: 38 w grupie leczonej dapagliflozyną *vs.* 65 w grupie przyjmującej placebo; p = 0,009) [6]), natomiast zakażenia zewnętrznych narządów płciowych oraz infekcje układu moczowego stanowiły marginalny problem.

Zgodnie z ChPL w przypadku wystąpienia infekcji grzybiczych zewnętrznych narządów moczowo-płciowych

Tabela 3. Zdarzenia niepożądane dotyczące dapagliflozyny na podstawie wyników badania DAPA-HF (źródło [6])

Zdarzenie niepożądane, n (%)	Dapagliflozyna n = 2368	Placebo n = 2368	Wartość p
Niedobór płynów	178 (7,5)	162 (6,8)	0,40
Zdarzenia niepożądane związane z czynnością nerek	153 (6,5)	170 (7,2)	0,36
Złamania	49 (2,1)	50 (2,1)	1,00
Amputacje	13 (0,5)	12 (1,3)	1,00
Ciężka hipoglikemia	4 (0,2)	4 (0,2)	nd
Cukrzycowa kwasica ketonowa	3 (0,1)	0	nd
Zgorzel Fourniera	0	1 (< 0,1)	nd
Poważne zakażenia układu moczowego	14 (0,6)	17 (0,7)	
Poważne zakażenia narządów płciowych	0	1 (0,0)	
Zdarzenia niepożądane prowadzące do przerwania leczenia	111 (4,7)	116 (4,9)	0,79

nd — nie dotyczy

o łagodnym lub umiarkowanym stopniu nasilenia nie ma konieczności przerwania leczenia dapagliflozyną. Zaleca się leczenie miejscowe preparatem przeciwgrzybiczym lub przyjęcie pojedynczej dawki leku przeciwgrzybiczego.

Z przeprowadzonych subanaliz badania DAPA-HF wynika, że dapagliflozyna była bezpieczna i dobrze tolerowana niezależnie od płci, współistnienia cukrzycy, funkcji nerek oraz kategorii wiekowej [6]. U pacjentów 75-letnich i starszych lat poważne AE nerkowe występowały w grupie leczonej dapagliflozyną rzadziej niż w grupie przyjmującej placebo (p dla interakcji 0,031) [15]. W populacji pacjentów z eGFR poniżej 60 ml/min/1,73 m^2 leczonych dapagliflozyną ryzyko wystąpienia poważnych AE było istotnie niższe niż w grupie otrzymującej placebo (p = 0,03) [16].

Epizody poważnej hipoglikemii oraz cukrzycowej kwasicy ketonowej w badaniu DAPA-HF były pojedyncze i występowały **wyłącznie u chorych na cukrzycę typu 2** (odpowiednio 0,4% i 0,3%) [6].

Ważną informacją w kontekście standardowej terapii HFrEF jest to, że dapagliflozyna może obniżać ryzyko umiarkowanej/ciężkiej hiperkaliemii u pacjentów leczonych MRA [17].

Wskazówki praktyczne

W związku z możliwością wystąpienia objawów niedoboru płynów i hipotensji podczas stosowania dapagliflozyny należy poinformować pacjenta o ewentualnej potrzebie modyfikacji dawek stosowanych dotychczas leków diuretycznych, leków w terapii nadciśnienia tętniczego oraz stosowanych w leczeniu HF, jak również przypomnieć o odpowiednim nawodnieniu. Ryzyko wystąpienia objawów niedoboru płynów i hipotensji jest zwiększone w populacji osób z hipotensją w wywiadzie oraz u pacjentów w podeszłym wieku [11].

Podczas terapii dapagliflozyną wynik badania ogólnego moczu wykazuje obecność glukozy, co wynika z mechanizmu działania leku. Wydalanie glukozy z moczem może się wiązać ze zwiększonym ryzykiem zakażeń zewnętrznych narządów moczowo-płciowych, rzadziej układu moczowego. Należy rozważyć przerwanie stosowania dapagliflozyny w trakcie leczenia odmiedniczkowego zapalenia nerek lub ogólnego zakażenia wywodzącego się z dróg moczowych. W trakcie terapii dapagliflozyną należy zwrócić uwagę pacjenta na higienę okolic intymnych z uwzględnieniem codziennej zmiany bielizny, noszenia luźnej bawełnianej bielizny, unikania środków mogących powodować podrażnienia oraz zapachowych detergentów.

Podczas leczenia dapagliflozyną w badaniu DAPA-HF obserwowano poniższe zmiany [6]:

- obniżenie skurczowego ciśnienia tętniczego (śr. o 1,92 mm Hg);
- obniżenie stężenia N-końcowego fragmentu propeptydu natriuretycznego typu B (NT-proBNP, *N-terminal pro-B-type natriuretic peptide*) (śr. o 196 pg/ml);
- zmniejszenie masy ciała (śr. o 0,88 kg);
- obniżenie wartości hemoglobiny glikowanej u pacjentów z cukrzycą (śr. o 0,21%);
- wzrost hematokrytu (śr. o 2,31%);
- wzrost stężenia kreatyniny (śr. o 0,07 mg/dl).

Lekarz może się spodziewać przejściowego obniżenia eGFR podczas leczenia początkowego dapagliflozyną, głównie w pierwszych 2 tygodniach. Zjawisko to jest

związane z obkurczeniem tętniczki doprowadzającej, co wynika z odruchu cewkowo-kłębuszkowego, który jest uruchamiany przez zwiększony napływ sodu do plamki gęstej. W dalszej obserwacji badania DAPA-HF tempo zmian eGFR w grupie leczonej dapagliflozyną było wolniejsze niż w grupie przyjmującej placebo, co jest wyrazem efektu nefroprotekcyjnego. W całej obserwacji badania w grupie leczonej dapagliflozyną udokumentowano zmniejszenie średniej wartości eGFR o około 4 ml/min/1,73 m^2, natomiast po 12 miesiącach wartość eGFR była podobna w obu grupach terapeutycznych [6].

Funkcję nerek należy ocenić przed rozpoczęciem leczenia dapagliflozyną oraz monitorować, wykonując oznaczenie stężenia kreatyniny w surowicy krwi i wartości eGFR przynajmniej raz w roku. Jeśli w trakcie terapii dapagliflozyną dojdzie do obniżenia eGFR poniżej 30 ml/min/1,73 m^2, to zaleca się ocenę stanu nawodnienia, ciśnienia tętniczego oraz innych odwracalnych czynników warunkujących pogorszenie czynności nerek (np. inne leki, badania obrazowe z użyciem środka kontrastowego), ich korektę oraz wykonanie kontrolnego oznaczenia eGFR z indywidualną decyzją, czy kontynuować terapię dapagliflozyną dostosowaną do sytuacji klinicznej.

Cukrzycowa kwasica ketonowa

Cukrzycowa kwasica ketonowa w trakcie terapii SGLT2i nie występuje u pacjentów z HFrEF bez cukrzycy. Natomiast u pacjentów z cukrzycą typu 2 występuje rzadko (w badaniu DAPA-HF w grupie chorych na cukrzycę typu 2 leczonych dapagliflozyna zidentyfikowano 3 takie przypadki) [6] i może mieć miejsce w przypadku nieznacznie podwyższonej glikemii. Częściej zdarza się przy terapii insuliną, przy niezadawalającej kontroli glikemii i w pierwszych 2 miesiącach terapii. Cukrzycowa kwasica ketonowa może mieć przebieg zagrażający życiu. Należy informować pacjentów o objawach kwasicy ketonowej i konieczności zgłoszenia się do lekarza, jeśli wystąpią, oraz o konieczności przerwania terapii SGLT2i. Wznowienie leczenia SGLT2i jest możliwe po uzyskaniu stabilizacji stanu klinicznego oraz obniżeniu stężenia ciał ketonowych (oznaczać we krwi), gdy zidentyfikowano i usunięto inną wyraźną przyczynę cukrzycowej kwasicy ketonowej.

Do objawów cukrzycowej kwasicy ketonowej należą: nudności, wymioty, jadłowstręt, ból brzucha, nadmierne pragnienie, szybkie i głębokie oddechy połączone ze „słodkim", owocowym zapachem oddechu, splątanie, nietypowe zmęczenie lub uczucie senności.

Zaleca się **ocenę ryzyka cukrzycowej kwasicy ketonowej**, które jest podwyższone w następujących sytuacjach:

- stany prowadzące do ograniczenia spożywania pokarmów lub ciężkiego odwodnienia;
- nagły spadek stężenia insuliny;
- podwyższone zapotrzebowanie na insulinę z powodu ostrego stanu chorobowego, zabiegów chirurgicznych, nadużywania alkoholu;
- niska rezerwa czynnościowa komórek beta, na przykład u pacjentów z cukrzycą typu 2 i z niskim stężeniem peptydu C lub utajoną chorobą autoimmunologiczną dorosłych oraz u chorych po zapaleniu trzustki.

Środki ostrożności

Dapagliflozynę należy stosować z ostrożnością w następujących sytuacjach:

- w ciężkich zaburzeniach funkcji nerek;
- w przypadku wywiadu cukrzycowej kwasicy ketonowej;
- w przypadku powtarzających się infekcji układu moczowo-płciowego;
- leczenie należy czasowo przerwać u pacjentów z cukrzycą typu 2 hospitalizowanych z powodu ciężkich ostrych chorób oraz przed zabiegami chirurgicznymi (3-dniowa przerwa przed zabiegiem).

W trakcie terapii dapagliflozyną przeciwwskazane jest nadużywanie alkoholu oraz stosowanie diet ketogenicznych.

Przeciwwskazania do stosowania dapagliflozyny

Zgodnie z ChPL [11] stosowanie preparatu Forxiga™ jest przeciwwskazane u pacjentów z nadwrażliwością na substancją czynną lub którąkolwiek substancję pomocniczą. Tabletki zawierają laktozę. Lek nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, całkowitym niedoborem laktazy lub zespołem złego wchłaniania glukozy–galaktozy. Przeciwwskazaniem do stosowania dapagliflozyny są również II i III trymestr ciąży.

Podsumowanie

Inhibitory SGLT2 są przełomem w leczeniu chorych z HFrEF. Dapagliflozyna jest pierwszym SGLT2i zarejestrowanym w leczeniu przewlekłej HFrEF. To lek dobrze tolerowany, bezpieczny i łatwy w stosowaniu. Korzystny efekt leczenia dapagliflozyną udokumentowano niezależnie od podstawowej terapii HFrEF oraz dawek przyjmowanych leków i elektroterapii. Wskazuje to na komplementarne działanie dapagliflozyny w stosunku do innych terapii HFrEF. Dapagliflozyna jest lekiem modyfikującym przebieg HFrEF, redukuje częstość hospitalizacji z powodu HF, zgonów sercowo-naczyniowych i zgonów z jakiejkolwiek przyczyny oraz poprawia jakość życia u chorych z HFrEF niezależnie od współwystępowania cukrzycy typu 2.

Konflikt interesów

Wykłady dla AstraZeneca.

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Hybrid intravascular management of pediatric complex tubular aortic coarctation in the shadow of SARS-CoV-2 pandemic

Hybrydowa przezskórna terapia złożonej koarktacji aorty w cieniu pandemii SARS-CoV-2

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Abstract

Introduction. Coarctation of the aorta (CoA) is a congenital heart defect defined as a narrowing in the region of aortic isthmus, clinically presenting with peripheral perfusion disturbances in physical examination. Newborns are majority of the affected and surgery is the management of choice in these patients. However, some may not present with CoA symptoms until later childhood, with mostly percutaneous interventions as a favorable method of treatment. Aneurysms, heart failure and stroke are the main complications of untreated CoA, which explains low survival rate of undiagnosed patients.

Case report. A 5-year-old female patient in good general condition presented with a heart murmur during a prophylactic pediatric control. The patient was referred to pediatric cardiologist, but unfortunately due to ongoing coronary disease 2019 pandemic only telemedical consultation was available, precluding physical examination. Finally, the patient was referred to hybrid pediatric cardiac surgery department as an urgent consultation of the dubious anamnesis.

The echocardiographic study revealed continuous, non-pulsatile flow in the abdominal aorta with a narrowed descending aorta behind the left atrium, and the CoA was a suspected diagnosis. The angio-computed tomography (CT) confirmed tubular (55 mm long) narrowed section of thoracic aorta (up to 2.5 mm diameter) with concomitant collateral circulation.

Due to the anatomy of the aortic lesion the patient was referred for transcatheter stent graft (Bentley BeGraft© 9 mm/ /57 mm) implantation with ECC-backup. An initial dilatation to 9 mm except the region around 6mm long narrowed to 5.2 mm was performed. After 2 months, the stent graft was dilated again, and echocardiography confirmed uniformed aortic lumen (9 mm).

The postprocedural course was uncomplicated; the patient was discharged home and referred for further follow-up.

Conclusions. The CoA rarely occupies a non-typical region and therfore may be diagnostically challenging without a profound phisical examination, particularly in later childhood and pandemic settings, and may result in serious complications, if untreated.

Key words: coarctation of aorta, congenital heart defects, interventional cardiology, pediatric cardiac surgery, hybrid treatment

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Introduction

Coarctation of the aorta (CoA) is a congenital heart defect defined as a narrowing in the region of aortic isthmus. Although the condition usually manifests itself as a discrete constriction of the aortic isthmus, it may also present as a tubular hypoplasia and different morphological variations between these two [1].

As the fetal echocardiographic diagnosis remains difficult, the postnatal transthoracic echocardiography along with physical examination are the most common diagnostic tools for CoA. Moreover, the magnetic resonance imaging is preferred as the advanced imaging method [2], if available. The physical examination findings usually include delayed or reduced femoral pulse, a supine arm-leg blood pressure gradient (> 20 mm Hg), or a murmur due to rapid blood flow across the CoA [2].

Newborns and infants are the majority of the presenting children, and the urgent surgical correction is the management of choice in these patients. However, some rare cases may present with mild CoA symptoms until later childhood or adolescence, with mostly percutaneous interventions as a favorable method of treatment [3]. Heart failure, aortic aneurysms and stroke are the main complications of untreated CoA, which explains the low survival rate of undiagnosed patients [1–3].

Case report

A 5-year-old female patient in a good general condition presented with a heart murmur during a routine prophylactic pediatric control. As the first case of coronavirus disease 2019 (COVID-19) was confirmed on 4th of March 2020 in Poland, the National Health Found Institution recommended the limitation of elective admissions and surgical procedures from the 23rd of March 2020 until further notice. [4] Therefore, the patient was referred to pediatric cardiologist. Unfortunately, due to ongoing COVID-19 pandemic, only the telemedical consultation was available which precluded physical examination. Finally, after several remote consultations, the patient was referred to hybrid pediatric cardiac surgery department as an urgent admission of the dubious anamnesis.

The echocardiographic study revealed continuous, non-pulsatile flow in the abdominal aorta with a narrowed descending aorta behind the left atrium, and the CoA was a suspected diagnosis (Figure 1). The angio-computed tomography (CT) confirmed tubular (55 mm long) narrowed section of thoracic aorta (to 2,5 mm diameter) with concomitant collateral circulation (Figure 2).

Due to the anatomy of the aortic lesion the patient was referred for hybrid transcatheter stent graft implantation (Bentley BeGraft © 9 mm/57 mm) in hybrid operating theatre with extracorporeal circulation — backup. The first procedure finished with an initial dilatation to 9 mm except the region of the thoracic aorta around 6 mm long narrowed to 5.2 mm (Figure 3). After 2 months, the stent graft was dilated again, and the echocardiography confirmed uniformed aortic lumen (9 mm) (Figure 4).

The postprocedural course was uncomplicated and the patient was discharged home and referred for further clinical follow-up. The 2-month follow up confirmed good result of the procedures without any residual restenosis.

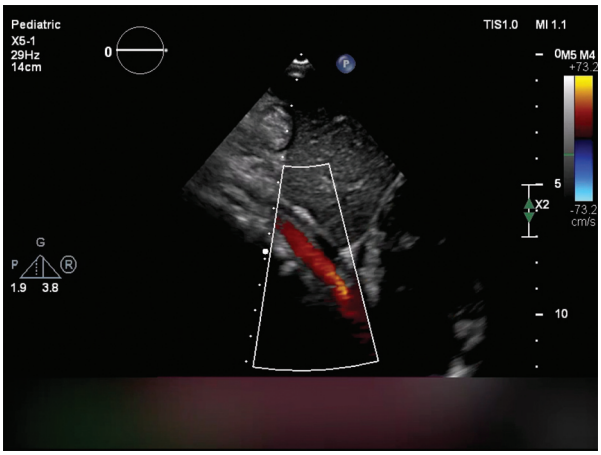

Figure 1. Echocardiographic study — continuous, non-pulsatile flow in the abdominal aorta

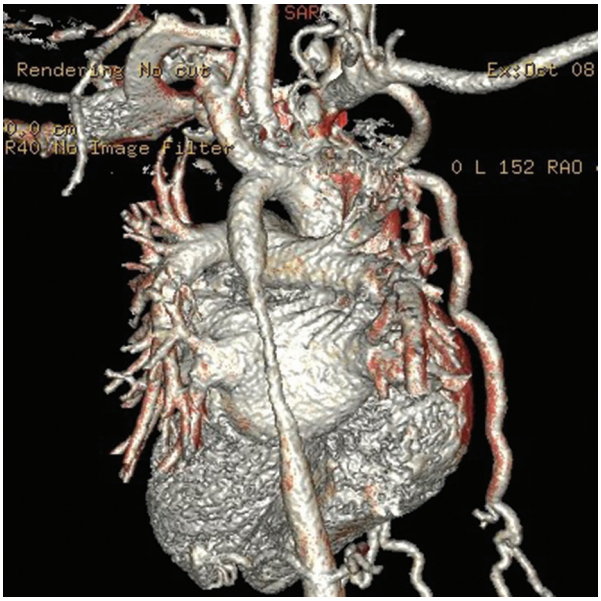

Figure 2. Computed tomography (CT) three-dimensional (3D) reconstruction — narrowing tubular (55 mm long) narrowed section of thoracic aorta (to 2.5 mm diameter) with concomitant collateral circulation

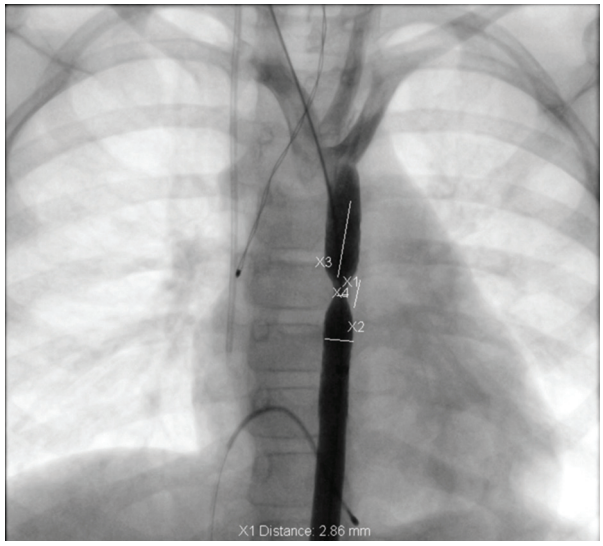

Figure 3. Angiography — the result after the first stent graft implantation. X1 distance: 2.86 mm, X2 distance: 6.94 mm, X3 distance: 18.56 mm, X4 distance: 6.86 mm

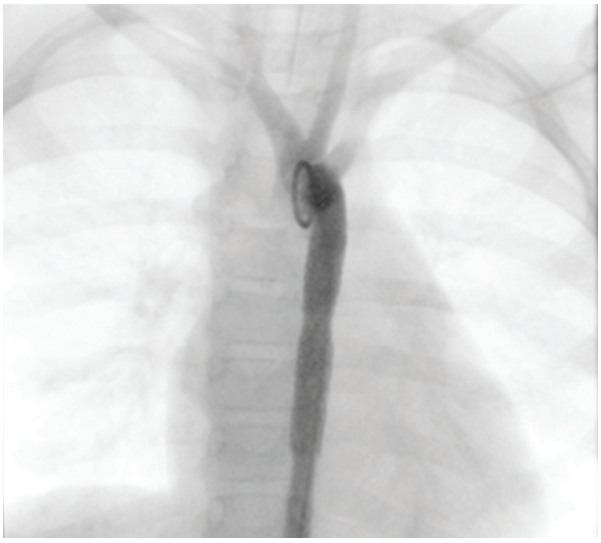

Figure 4. Angiography — the result after the final stent dilatation showing no residual stenosis

Conclusions

The CoA rarely occupies a non-typical region and therefore may be diagnostically challenging. A profound physical examination, particularly in a later childhood and COVID-19 pandemic settings, relevantly supplies the anamnesis in the patients who require dedicated strategy of treatment and may develop serious complications, if untreated.

Conflict of interest

None declared.

Streszczenie

Wstęp. Koarktacja aorty (CoA) to wrodzona wada serca definiowana jako zwężenie w okolicy cieśni aorty, klinicznie charakteryzująca się zaburzeniami perfuzji obwodowej w badaniu przedmiotowym. Większość pacjentów, u których rozpoznaje się CoA, stanowią noworodki, a korekcja chirurgiczna jest w tej grupie leczeniem z wyboru. Przezskórne interwencje kardiologiczne stanowią terapię rzadkich przypadków, w których objawy występują dopiero w kolejnych latach życia dziecka. Tętniak aorty, niewydolność serca oraz udar to główne powikłania nieleczonego CoA, co wyjaśnia niski wskaźnik przeżywalności niezdiagnozowanych pacjentów.

Opis przypadku. Podczas profilaktycznej kontroli pediatrycznej 5-letniej pacjentki w dobrym stanie ogólnym wykazano szmer nad sercem. Chorą skierowano do kardiologa dziecięcego, ale niestety ze względu na trwającą pandemię choroby koronawirusowej 2019 dostępna była tylko konsultacja telemedyczna, wykluczająca dokładne badanie przedmiotowe. Ostatecznie chorą skierowano na oddział kardiochirurgii dziecięcej w celu pilnej konsultacji.

Badanie echokardiograficzne wykazało ciągły, niepulsacyjny przepływ w aorcie brzusznej oraz zwężenie światła aorty zstępującej za lewym przedsionkiem. Angiografia tomografii komputerowej potwierdziła zwężenie światła aorty piersiowej (o długości 55 mm do średnicy 2,5 mm) z towarzyszącym krążeniem obocznym.

Ze względu na anatomię zmiany aorty pacjentkę zakwalifikowano do przezskórnej implantacji stent-graftu (Bentley BeGraft© 9 mm/57 mm) w hybrydowej sali operacyjnej z zapleczem krążenia pozaustrojowego. Wykonano wstępną dylatację aorty do 9 mm, z wyjątkiem obszaru o długości około 6 mm zwężonego do 5,2 mm. Po 2 miesiącach stent-graft ponownie poszerzono, a badanie echokardiograficzne potwierdziło dobry wynik zabiegu (średnica aorty piersiowej na całym odcinku 9 mm).

Przebieg pooperacyjny bez powikłań, pacjentkę wypisano do domu i skierowano na kontrolę ambulatoryjną.

Wnioski. Rzadko CoA obejmuje nietypowy obszar, wywołując trudne diagnostycznie objawy w warunkach pandemii i ograniczenia dostępności lekarzy specjalistów, szczególnie u starszych pacjentów pediatrycznych obciążonych ryzykiem wystąpienia poważnych powikłań bez wdrożenia odpowiedniego leczenia.

Słowa kluczowe: koarktacja aorty, wrodzone wady serca, kardiologia interwencyjna, kardiochirurgia dziecięca, leczenie hybrydowe

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Progress in the treatment of cardiovascular diseases News from the American Heart Association Scientific Sessions 2020

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Introduction

The sanitary and epidemiological risk related to the severe acute respiratory syndrome-related coronavirus 2 (SARS-COV-2) pandemic has forced the organisers of major scientific congresses to conduct these events as interactive online meetings. American Heart Association (AHA) Scientific Sessions were not an exception. By choosing the "Virtual Experience" format, the organisers provided online access to live presentations and the possibility to view the congress materials at a later date. This paper presents short descriptions of the most interesting issues that were discussed during the sessions presenting the most interesting clinical trials.

RIVER: Rivaroxaban vs. Warfarin in Atrial Fibrillation in Patients with Bioprosthetic Mitral Valves

Novel oral anticoagulants [non-vitamin K oral anticoagulatns (NOAC)] currently constitute the first-choice treatment in the prevention of venous thromboembolic events in patients with non-valvular atrial fibrillation (AF). While the use of vitamin K antagonists (VKA) is a recognised therapy in patients who underwent mechanical mitral valve replacement with concurrent AF, in the case of patients with a sinus rhythm, the continuation of anticoagulant treatment with the use of VKA for 3–6 months is preferred, even though the 2021 guidelines of the AHA allow the use of antithrombotic therapy exclusively.

The possibility to use rivaroxaban in patients with AF who had a bioprosthetic mitral valve implanted was investigated in the RIVER (Rivaroxaban vs. Warfarin in AFib Patients With Bioprosthetic Mitral Valves) trial. It involved 1005 patients with AF (paroxysmal, persistent or chronic) or atrial flutter (AFL). The intervention was applied in those of the aforementioned patients who had a bioprosthetic mitral valve implanted at least two days before and were natural candidates for anticoagulant therapy. Patients were randomly assigned for treatment with rivaroxaban at a daily dose of 20 mg or with warfarin at a dose calculated according to the international normalized ratio (INR). The primary endpoint was a composite event comprising death and serious cardiovascular event or serious haemorrhage within 12 months.

Rivaroxaban therapy met the expectations — the occurrence of the primary endpoint was recorded after a mean of 347.5 days in the rivaroxaban group and after 340.1 days in the warfarin group ($p < 0.001$ for equivalence — a trend of the superiority of rivaroxaban could be observed in patients who received randomly selected treatment). Death from cardiovascular causes occurred in 3.4% of patients treated with rivaroxaban and in 5.1% of patients in the warfarin group [without a significant difference; hazard ratio (HR) 0.65; 95% confidence interval (CI): 0.35–1.20]. Rivaroxaban significantly better prevented stroke which was diagnosed in the course of observation in 0.6% of patients in this group, while in the warfarin group it occurred in 2.4% participants (HR 0.25; 95% CI: 0.07–0.88). Serious haemorrhage was observed in 1.4% versus 2.6% of patients respectively (without a significant difference, HR 0.54; 95% CI: 0.21–1.35).

The results of the study confirm at least full equivalence of the simpler NOAC therapy to the older standard. The

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evident benefits of the use of NOAC, such as no need for INR dosing and a lower risk of dangerous haemorrhages, encourage continued research into the issue addressed in the RIVER trial [1].

GALACTIC-HF: Registrational Study with Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure with Reduced Ejection Fraction

Contemporary therapy for chronic heart failure does not generally use inotropic medications (digoxin may be an exception). In particular, medications that improve systolic force by affecting the metabolism of calcium ions were associated with worse survival in clinical trials. Nevertheless, the search for new avenues for the pharmacotherapy of heart failure continues. Direct support for the molecular mechanism of cardiac muscle cell contraction through the activation of myosin is the postulated action demonstrated by omekamtiv mekarbil. It accelerates the formation of strong binding of myosin heads to actin filaments which results in an increased number of these bonds and, consequently, leads to increased force of fibre contraction. The clinical objective of this medication is to improve myocardial contractility in patients with reduced ejection fraction without increasing myocardial oxygen demand.

The GALACTIC-HF trial assessed the risk of the first heart failure-related incident and cardiovascular death in patients receiving omekamtiv mekarbil or placebo combined with the standard therapy. Patients with symptomatic heart failure and reduced left ventricular ejection fraction (≤ 35%) were included in the study. A total of 8,256 patients received the intervention. The mean age was 64.5 years, with balanced sex ratios. More than 3/4 of the group was Caucasian. Nearly 90% of patients were chronically on renin–angiotensin–aldosterone system (RAAS) inhibitors and beta-blockers. The observation lasted less than 2 years.

The primary endpoint, consisting of the first heart failure incident (need for an urgent outpatient appointment or hospital admission due to the intensity of heart failure symptoms) or cardiovascular death occurred in 37% of patients receiving the investigated medication, while in the placebo group — it occurred significantly more often, in 39.1% of patients (HR 0.92; 95% CI: 0.86–0.99, p = 0,03). Cardiovascular death occurred in 19.6% and 19.4% patients respectively (HR 1.01; 95% CI: 0.92–1.11). In the group receiving omekamtiv mekarbil, there was a 10% decrease in the median of N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, but the subjective improvement of the quality of life reported by patients in the Kansas City Cardiomyopathy Questionnaire did not significantly differ between the groups.

Significant, albeit moderate, reduction in the incidence of the first heart failure-related incident in the group receiving the investigated medication allows us to consider the possibility of its use in the therapy of heart failure in patients with reduced ejection fraction. However, in the context of the new wave of medications with proven efficacy in the treatment of heart failure (phlorizin, riociguat), the appropriate positioning of omekamtiv mekarbil in treatment schemes requires extended research [2].

AFFIRM-AHF: Ferric Carboxymaltose for Iron Deficiency at Discharge after Acute Heart Failure: a Multicentre, Double-Blind, Randomised, Controlled Trial

The starting point for the AFFIRM-AHF trial was a clinical observation confirmed by multicentre studies [3] on the worse course of chronic heart failure in patients with iron deficiency. Intravenous supplementation of iron and carboxymaltose had a beneficial effect on the quality of life of those patients, as well as on the prognosis [4, 5]. Ferric carboxymaltose is the pharmacological form that allows the controlled administration of iron to target tissues. In a relatively short time, about 80% of the dose is deposited in the bone marrow and the remaining 20% in the liver and spleen.

A group of 1,108 patients with iron deficiency (defined as ferritin level < 100 µg/L, or 100–299 µg/L with iron transferrin saturation < 20%) and left ventricular ejection fraction < 50% admitted to hospital due to acute heart failure was assessed during a 52-week observation. The mean ejection fraction in the analysed group was 33%. The participants were randomly assigned to groups receiving intravenous ferric carboxymaltose complex (FCM) or placebo. Doses were determined based on body weight and haemoglobin (Hb) levels. The medication was administered before hospital discharge and after 6 weeks following the discharge. If iron deficiency persisted and Hb levels ranged from 8 to 15 g/dL, patients received subsequent doses after 12 and 24 weeks. Primary treatment was consistent with contemporary standards — nearly 90% of patients received RAAS inhibitors, beta-blockers and diuretics.

The primary endpoint was a composite event of the total number of hospital readmissions for heart failure or cardiovascular deaths — during the observation period; in the FCM group, the primary endpoint was observed in 293 cases (57.2/100 patients/year). In the placebo group, it occurred insignificantly less often (p = 0.059) — in 372 patients. The study can therefore be considered to have missed its aim; more optimistic themes were observed in the analysis of the composite secondary endpoint — the total number of hospital admissions for cardiovascular reasons and cardiovascular deaths: it was found in 20% less (370) cases in the FCM group and 451 patients in the placebo group [relative risk (RR) 0.80; 95% CI: 0.64–1.00, p = 0.05]. Supplementation with the investigated medication also allowed to

reduce the rate of hospital admissions for cardiovascular causes compared to the placebo group (RR = 0.74; 95% CI: 0.58–0.94, p = 0.013) but the treatment was not proven to affect the reduction of mortality rate (p = 0.81) [6].

EARLY-AF: Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation

Percutaneous ablation is a procedure with an undisputed and well-established position in treating arrhythmia. In the case of the first episode of AF, it is usually recommended that before ablation, treatment with at least one anti-arrhythmic medication should be attempted. Until present, no convincing data was available to confirm that this approach is more effective in maintaining sinus rhythm than ablation as the first-choice therapy.

The EARLY-AF trial involved a group of 303 patients with symptomatic, previously untreated paroxysmal AF. The patients were randomly assigned for treatment with balloon cryoablation (154 patients with a mean age of 57.7 years — 72.2% of whom were men) or for anti-arrhythmic pharmacological treatment (149 patients with a mean age of 59.5 years — 68.5% of whom were men). In an observation period of 12 months, all the patients were monitored with an implantable loop recorder.

The primary endpoint was defined as a recurrence of AF or AFL or atrial tachycardia in the period from day 91 until the end of the observation in the case of the ablation-treated group, or from the commencement of treatment until the end of observation. The event occurred in 42.9% of ablation-treated patients and 67.8% of patients receiving pharmacological treatment (p < 0.001). Symptomatic atrial tachyarrhythmia recurred in 11% and 26.2% of patients, respectively (HR 0.39; 95% CI: 0.22–0.68). Importantly, serious adverse events – including complications of the ablation procedure — occurred in 3.2% of patients treated procedurally, that is no more frequently than in patients treated conservatively (4%).

The study involved a relatively small group of patients and the effect of the intervention on overall cardiovascular risk was not determined. However, the results of the study provide a basis for considering ablation as a first-line treatment in patients with symptomatic AF. Novum EARLY-AF consists in the inclusion of patients with a new diagnosis rather than those after failed pharmacological treatment, as in most previous studies; the importance of evidence is also enhanced by the use of an electrocardiogram event recorder for detecting relapses [7].

SAMSON: Self-Assessment Method for Statin Side-effects Or Nocebo

The beneficial effect of statins in the prevention of cardiovascular diseases is undeniable. Although anti-scientific community groups frequently attempted to undermine that status, accurate scientific data unequivocally support the need for the use of statins in both primary and secondary prevention of numerous cardiovascular diseases. Muscular side effects are among the most common reasons for discontinuation of statin therapy among patients. However, many studies did not show any objective increase in the incidence of those symptoms during statin therapy compared to placebo therapy. Due to the non-specificity of the musculoskeletal symptoms and the intensification of the harmful activities of anti-statin lobbyists in the media, these drugs appear to particularly put patients at risk of a nocebo effect. This effect involves reporting the adverse effects of the drug regardless of its actual potential to cause such effects. The reason for the occurrence of such adverse effects is the patient's negative attitude towards therapy. That is why the nocebo effect can be called the inverse of the placebo effect.

The potential of statins to cause symptomatic side effects was the issue addressed in the precisely designed SAMSON study. The study involved 60 patients who discontinued statins within 2 weeks of starting treatment. Each patient received a total of 12 phials, 4 packagings (each for one month of therapy) containing 20 mg of atorvastatin, placebo, and 4 empty phials for the non-therapy time. The subject of randomisation was the order according to which the patient took an active drug or placebo. Patients used an electronic patient diary to report the onset of symptoms. They also had the option to discontinue the medication in the event they experienced particularly severe symptoms.

The primary endpoint was the intensification of nocebo-dependent side effects — the ratio of the severity of symptoms reported while taking placebo minus the severity of symptoms reported during the periods without intervention to the severity of symptoms reported by patients while taking statins, adjusted in the same manner.

During the follow-up, 11 patients stopped taking statins (4 by their own decision; in 3 cases it was the researchers' decision). The mean symptom severity (on a scale of 0–100) during non-treatment periods was 8 (95% CI: 4.7–11.3). While taking a placebo, patients rated the symptom severity at 15.4 points on average (a highly significant increase compared to non-treatment periods). During the actual statin treatment, the mean symptom severity was 16.3. Therefore, when comparing symptom severity during the statin treatment and placebo periods, the differences proved to be statistically insignificant (p = 0.39). The nocebo ratio was 2.2 (95% CI: 62.3–66.7); those calculations were distorted by individual cases of patients who reported high severity of side effects during periods without therapy, which was reflected in the undervaluation of values used for calculating the ratio. Individualised calculations ultimately determined the value of nocebo, which is 0.9.

The conclusions of the data analysis clearly state that the effect of statins on the severity of symptoms perceived as side effects is not significantly greater than the placebo effect. These results are of great importance as an argument against false but popular views concerning frequent statin intolerance [8].

OMENI: Omega-3 Fatty Acid Supplements in Elderly Patients after Myocardial Infarction

The n-3 polyunsaturated fatty acids (PUFAs) are considered to be an essential component of a balanced diet. However, there are many doubts concerning the advisability of their supplementation as a method of reducing cardiovascular risk. The authors of the OMENI study focused on a specific group of elderly patients after myocardial infarction (MI) to determine the effect of n-3 PUFA supplementation on the risk of cardiovascular events at a 2-year follow-up.

The effect of the intervention was evaluated in 1,027 patients, aged 70–82, who 2–8 weeks earlier had a clinical incident meeting criteria for MI. Patient cooperation was monitored by determining plasma fatty acid levels. The primary endpoints included nonfatal MI, unplanned revascularisation, stroke, death from any cause, and hospitalisation due to heart failure. A new diagnosis of AF was the secondary endpoint.

The incidence of the primary endpoint was not significantly different between the group receiving n-3 PUFAs — 108 (21.4%) and placebo-taking patients — 102 (20%) ($p = 0.06$). A similar relationship was observed for the secondary endpoint — 28 and 15 patients, respectively ($p = 0.06$). The study results clearly showed that supplementation with n-3 PUFAs had no clinical benefit, neither in the secondary prevention of MI nor in terms of reducing the broader concept of cardiovascular risk in elderly patients after MI. Those data are consistent with numerous already-completed prospective studies of this issue [9].

HARP-MINOCA: Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of MINOCA in Women

Contemporary definitions of MI, for any subsequent modification, are based on the determination of cardiac troponin levels. Supporting and interchangeable criteria are other clinical determinants included in the definition. Despite a consistent definition, the aetiology of MI can vary and its accurate identification enables the choice of the most beneficial treatment for the patient. By far the most common cause of MI is coronary occlusion caused by a rupture of the atherosclerotic plaque. Therefore, coronary angiography and coronary angioplasty are the treatment of choice for most MI patients. According to the statistics of medical registers, coronary angiography fails to reveal significant coronary stenosis in 6–15% of patients, the vast majority of whom are women, despite meeting criteria for MI and the absence of a non-coronary cause for this diagnosis.

The authors of the HARP-MINOCA study further diagnosed 170 women with detected MI with non-obstructive coronary arteries (MINOCA, myocardial infarction with non-obstructive coronary arteries). In addition to coronary angiography, a coronary optical coherence tomography (OCT) imaging technique and cardiac magnetic resonance (CMR) were performed. A total of 145 and 116 cases were obtained respectively, which, for reasons of technical nature, could be fully analysed using a specific method. The OCT examination resulted in the detection of 67 (46.2%) cases of lesions that may affect the onset of MI (ruptures of the atherosclerotic plaque, atherosclerotic intraplaque haemorrhage). CMR confirmed an ischemic background of MI in 62 female patients (53.4%) while the non-ischemic background of MI (myocarditis, takotsubo syndrome) was found in 24 female patients (20.7%).

The use of two methods to identify the causes of MINOCA increased the effectiveness of each method in making a definitive diagnosis — 84.5% of diagnoses. An ischemic cause was confirmed in 63.8% of cases while a non-ischemic cause in 20.7% of cases. Assuming that the majority of patients would have received therapy typical of the ischemic form of MI in the case of the absence of a verified diagnosis, it can be concluded that the used diagnostic intervention enabled, in more than 20% of cases, an adequate treatment of which the patients might otherwise have been deprived of [10]. The results of this study confirm the growing interest in MINOCA and highlight the potential therapeutic implications of a precise diagnostic procedure regarding this uncommon disease entity.

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Postępy farmakoterapii chorób układu sercowo-naczyniowego Doniesienia z *American Heart Association Scientific Sessions* 2020

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Należy cytować wersję pierwotną

Wstęp

Ryzyko sanitarno-epidemiologiczne związane z pandemią spowodowaną SARS-COV-2 (*severe acute respiratory syndrome-related coronavirus 2*) wymusiło na organizatorach największych kongresów naukowych przeprowadzenie tych wydarzeń w formie interaktywnych spotkań internetowych. Nie ominęło to Sesji Naukowych *American Heart Association* (AHA) w roku 2020. Organizatorzy, wybierając format „virtual experience", zapewnili dostęp *on-line* do prezentacji na żywo oraz możliwość zapoznania się z materiałami kongresowymi w późniejszym terminie. W tym opracowaniu zaprezentowano krótkie opracowania najciekawszych tematów, jakie pojawiły się na sesjach dotyczących najważniejszych badań klinicznych.

RIVER: *Rivaroxaban vs. Warfarin in Atrial Fibrillation in Patients with Bioprosthetic Mitral Valves*

Terapia nowymi lekami przeciwzakrzepowymi (doustymi antykoagulantami niebędącymi antagonistami witaminy K [NOAC, *non-vitamin K oral anticoagulatns*]) stanowi obecnie pierwszy wybór w zapobieganiu incydentom zakrzepowo-zatorowym u pacjentów z niezastawkowym migotaniem przedsionków (AF, *atrial fibrillation*). U chorych po zabiegu implantacji mechanicznej protezy zastawki mitralnej z towarzyszącym migotaniem przedsionków uznaną terapią jest stosowanie antagonistów witaminy K (VKA, *vitamin K antagonists*) natomiast u pacjentów z rytmem zatokowym preferuje się utrzymanie po operacji 3–6 miesięcy leczenia przeciwzakrzepowego za pomocą VKA, chociaż w amerykańskich wytycznych AHA z 2021 roku dopuszcza się stosowanie wyłącznie terapii przeciwpłytkowej.

Możliwość zastosowania riwaroksabanu u chorych z AF poddawanych wszczepieniu bioprotezy zastawki mitralnej oceniano w badaniu RIVER (*Rivaroxaban vs. Warfarin in AFib Patients with Bioprosthetic Mitral Valves*). Wzięło w nim udział 1005 pacjentów z AF (napadowym, przetrwałym lub utrwalonym) albo trzepotaniem przedsionków (AFL, *atrial flutter*). Interwencji podlegali wyżej wspomniani chorzy, którzy byli przynajmniej 2 doby po implantacji bioprotezy mitralnej i stanowili naturalnych kandydatów do leczenia przeciwkrzepliwego. Pacjentów przydzielano losowo do leczenia riwaroksabanem w dawce 20 mg/dobę lub warfaryną w dawce ustalonej według wartości międzynarodowego współczynnika znormalizowanego (INR, *international normalized ratio*). Głównym punktem końcowym było zdarzenie złożone ze zgonu i poważnego zdarzenia sercowo-naczyniowego lub poważnego krwawienia w ciągu 12 miesięcy.

Terapia riwaroksabanem spełniła pokładane nadzieje — wystąpienie pierwszorzędowego punktu końcowego rejestrowano po średnio 347,5 dnia w grupie leczonej riwaroksabanem i po 340,1 dnia w grupie leczonej warfaryną ($p < 0{,}001$ dla równoważności — trend przewagi riwaroksabanu zarysował się w analizach pacjentów faktycznie otrzymujących dobrany w randomizacji sposób leczenia).

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Zgon z przyczyn sercowo-naczyniowych wystąpił u 3,4% pacjentów przyjmujących riwaroksaban i u 5,1% z grupy otrzymujących warfarynę (bez znamiennej różnicy; współczynnik ryzyka [HR, *hazard ratio*] 0,65; 95-proc. przedział ufności [CI, *confidence interval*]: 0,35–1,20). Riwaroksaban istotnie lepiej zabezpieczał przed udarem mózgu, który rozpoznano w trakcie obserwacji u 0,6% chorych w tej grupie, natomiast w grupie leczonej warfaryną wystąpił u 2,4% badanych (HR 0,25; 95% CI: 0,07–0,88). Poważne krwawienie odnotowano odpowiednio u 1,4% w porównaniu z 2,6% pacjentów (bez znamiennej różnicy, HR 0,54; 95% CI: 0,21–1,35).

Wyniki badania potwierdzają co najmniej pełną równoważność prostszej terapii NOAC w stosunku do dawnego standardu. Oczywiste korzyści ze stosowania NOAC, jak brak konieczności ustalania dawki pod kontrolą INR czy niższe ryzyko groźnych krwawień, zachęcają do kontynuowania badań nad zagadnieniem będącym przedmiotem badania RIVER [1].

GALACTIC-HF: *Registrational Study with Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure with Reduced Ejection Fraction*

We współczesnej terapii przewlekłej niewydolności serca w zasadzie nie korzysta się z leków o działaniu inotropowym (pewien wyjątek może stanowić digoksyna). W szczególności stosowanie leków poprawiających siłę skurczu serca poprzez wpływ na gospodarkę jonami wapnia wiązało się w badaniach klinicznych z pogorszeniem przeżycia. Poszukiwania nowych dróg dla farmakoterapii niewydolności serca trwają jednak dalej. Bezpośrednie wspomaganie molekularnego mechanizmu skurczu komórki mięśnia sercowego poprzez aktywację miozyny to postulowane działanie, jakie wykazuje omekamtiw mekarbil. Przyspiesza on powstanie mocnego wiązania „główek" miozyny z filamentem aktyny, co przekłada się na zwiększeni liczby tych wiązań i w efekcie — na zwiększenie siły skurczu włókna. Celem klinicznym działania tego leku jest poprawa kurczliwości mięśnia sercowego u chorych z niewydolnością serca z obniżoną frakcją wyrzutową bez zwiększania zapotrzebowania miokardium na tlen.

W badaniu GALACTIC-HF oceniano ryzyko wystąpienia pierwszego incydentu związanego z niewydolnością serca oraz zgonu z przyczyn sercowo-naczyniowych u chorych przyjmujących omekamtiw mekarbil lub placebo w połączeniu ze standardową terapią. Do badania włączano pacjentów z objawową niewydolnością serca i obniżoną frakcją wyrzutową lewej komory (≤ 35%). Łącznie interwencji poddano 8256 pacjentów. Średnia wieku wynosiła 64,5 roku, w wyrównanych proporcjach płci. Ponad 3/4 grupy stanowiły osoby rasy białej. Blisko 90% chorych w chwili włączenia do badania przyjmowało przewlekle antagonistę układu renina–angiotensyna–aldosteron (RAA) oraz beta-adrenolityk. Obserwacja trwała niespełna 2 lata.

Główny punkt końcowy, pod postacią pierwszego incydentu związanego z niewydolnością serca (konieczność pilnej wizyty ambulatoryjnej lub hospitalizacji z powodu nasilenia objawów niewydolności serca) lub zgonu z przyczyn sercowo-naczyniowych, wystąpił u 37% pacjentów przyjmujących badany preparat, w grupie otrzymującej placebo znamiennie częściej, bo u 39,1% (HR 0,92; 95% CI: 0,86–0,99; p = 0,03). Zgon z przyczyn sercowo-naczyniowych wystąpił odpowiednio u 19,6% oraz 19,4% pacjentów (HR 1,01; 95% CI: 0,92–1,11). W grupie przyjmującej omekamtiw mekarbil odnotowano 10-procentowe obniżenie mediany stężeń N-końcowego fragmentu propeptydu natriuretycznego typu B (NT-proBNP, *N-terminal pro-B-type natriuretic peptide*), jednak subiektywna poprawa jakości życia oceniana przez pacjentów za pomocą *Kansas City Cardiomyopathy Questionnaire* nie różniła się istotnie między grupami.

Znamienne, chociaż umiarkowane, zmniejszenie częstości występowania pierwszego incydentu związanego z niewydolnością serca w grupie chorych przyjmujących badany preparat pozwala rozważyć możliwość jego zastosowania w terapii niewydolności serca u chorych z obniżoną frakcją wyrzutową. W kontekście nowej fali leków o potwierdzonej skuteczności w niewydolności serca (flozyny, riociguat) właściwe pozycjonowanie omekamtiwu mekarbilu w schematach leczenia wymaga jednak rozszerzonych badań [2].

AFFIRM-AHF: *Ferric Carboxymaltose for Iron Deficiency at Discharge after Acute Heart Failure: a Multicentre, Double-Blind, Randomised, Controlled Trial*

Punktem wyjścia badania AFFIRM-AHF było spostrzeżenie kliniczne, potwierdzone w wieloośrodkowych badaniach [3], dotyczące gorszego przebiegu przewlekłej niewydolności serca u pacjentów z niedoborem żelaza. Dożylna suplementacja kompleksu żelaza i karboksymaltozy wpływała korzystnie zarówno na jakość życia takich pacjentów, jak i na rokowanie [4, 5]. Karboksymaltoza żelaza stanowi postać farmakologiczną pozwalającą na kontrolowane dostarczanie żelaza do tkanek docelowych. W stosunkowo krótkim czasie około 80% dawki jest deponowane w szpiku kostnym, a pozostałe 20% w wątrobie i śledzionie.

W trakcie trwającej 52 tygodnie obserwacji ocenie poddano grupę 1108 pacjentów hospitalizowanych z powodu ostrej niewydolności serca, u których stwierdzono niedobór żelaza (zdefiniowany jako stężenie ferrytyny < 100 µg/l albo 100–299 µg/l z nasyceniem transferryny żelazem < 20%) i frakcję wyrzutową lewej komory poniżej 50%. Średnia frakcja wyrzutowa w badanej grupie wynosiła 33%. Uczestników przydzielano losowo do grup

otrzymujących dożylny preparat kompleksu żelaza i karboksymaltozy (FCM, *ferric carboxymaltose complex*) albo placebo. Dawki ustalano na podstawie masy ciała oraz stężenia hemoglobiny (Hb). Podanie leku następowało przed wypisaniem ze szpitala i po kolejnych 6 tygodniach. W przypadku utrzymującego się niedoboru żelaza i stężenia Hb w przedziale 8–15 g/dl chorym podawano kolejne dawki po 12 i 24 tygodniach. Leczenie podstawowe odpowiadało współczesnym standardom — pacjenci w blisko 90% przyjmowali inhibitory układu RAA, beta-adrenolityki i leki o działaniu diuretycznym.

Głównym punktem końcowym było zdarzenie złożone pod postacią całkowitej liczby ponownych hospitalizacji z powodu niewydolności serca lub zgonu z przyczyn sercowo-naczyniowych — podczas okresu obserwacji w grupie otrzymującej FCM pierwszorzędowy punkt końcowy odnotowano w 293 przypadkach (57,2/100 chorych/rok). W grupie otrzymującej placebo zdarzenie wystąpiło nieznamiennie częściej (p = 0,059) — u 372 pacjentów. Badanie można zatem uznać za nieosiągające założonego celu; bardziej optymistyczne wątki pojawiły się w analizie złożonego drugorzędowego punktu końcowego — całkowitej liczby hospitalizacji z przyczyn sercowo-naczyniowych i zgonu z przyczyn sercowo naczyniowych: stwierdzono ją o 20% rzadziej (w 370 przypadkach) w grupie przyjmującej FCM i u 451 pacjentów w grupie otrzymującej placebo (ryzyko względne [RR, *relative risk*] 0,80; 95% CI: 0,64–1,00; p = 0,05). Suplementacja badanego leku pozwoliła także na zmniejszenie częstości hospitalizacji z powodu niewydolności serca w porównaniu z grupą otrzymującą placebo (RR 0,74; 95% CI: 0,58–0,94; p = 0,013), ale nie wykazano wpływu leczenia na zmniejszenie częstości zgonów (p = 0,81) [6].

EARLY-AF: *Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation*

cja przezskórna jest zabiegiem, który ma niekwestionowaną i ugruntowaną pozycję w leczeniu arytmii. W przypadku pierwszorazowego AF zwykle zaleca się, by przed wykonaniem ablacji podjąć próbę terapii przynajmniej jednym lekiem przeciwarytmicznym. Nie były, jak dotąd, dostępne przekonujące dane, które potwierdzałyby, że takie postępowanie jest skuteczniejsze w utrzymaniu rytmu zatokowego od ablacji jako terapii pierwszego wyboru.

Badaniem EARLY-AF objęto grupę 303 pacjentów z objawowym, dotychczas nieleczonym, napadowym AF. Chorych losowo przydzielono do grupy leczenia za pomocą krioablacji balonowej (154 chorych w wieku średnio 57,7 roku — 72,2% mężczyzn) lub do przeciwarytmicznego leczenia farmakologicznego (149 chorych w wieku średnio 59,5 roku — 68,5% mężczyzn). W okresie obserwacji trwającym 12 miesięcy wszyscy chorzy byli monitorowani za pomocą wszczepialnego rejestratora arytmii.

Pierwszorzędowy punkt końcowy określono jako AF lub AFL albo tachykardię przedsionkową w okresie od 91. dnia do końca obserwacji w przypadku grupy leczonej za pomocą ablacji lub od początku leczenia farmakologicznego do końca obserwacji. Zdarzenie to wystąpiło u 42,9% chorych leczonych ablacją oraz u 67,8% pacjentów poddanych farmakoterapii (p < 0,001). Objawowa tachyarytmia przedsionkowa nawróciła odpowiednio w przypadku 11% i 26,2% pacjentów (HR 0,39; 95% CI: 0,22–0,68). Co istotne, poważne zdarzenia niepożądane, włączając w to powikłania zabiegu ablacji, wystąpiły u 3,2% chorych leczonych zabiegowo — nie częściej niż u pacjentów leczonych zachowawczo (4%).

Badanie obejmowało względnie małą grupę pacjentów i nie określono w nim wpływu interwencji na ogólne ryzyko sercowo-naczyniowe, jednak jego wyniki dają podstawę do rozważania ablacji jako leczenia pierwszego rzutu u pacjentów z objawowym AF. *Novum* EARLY-AF polega na włączeniu pacjentów z nową diagnozą, a nie — jak w większości poprzednich badań — po nieskutecznej farmakoterapii; rangę dowodów zwiększa również wykorzystanie rejestratora zdarzeń elektrokardiograficznych do wykrywania nawrotów [7].

SAMSON: *Self-Assessment Method for Statin Side-effects Or Nocebo*

Korzystny efekt działania statyn w prewencji schorzeń układu krążenia nie ulega wątpliwości. Mimo licznych prób podważania tego stanu przez antynaukowe grupy społecznościowe rzetelne dane naukowe jednoznacznie przemawiają za koniecznością ich stosowania zarówno w prewencji pierwotnej, jak i wtórnej licznych chorób serca i naczyń. Jedną z najczęstszych przyczyn przerywania leczenia statynami przez pacjentów są działania niepożądane ze strony układu mięśniowego, choć w licznych badaniach nie wykazano obiektywnego zwiększenia częstości występowania tych objawów podczas terapii statyną w porównaniu z placebo. Ze względu na nieswoistość objawów ze strony układu ruchu i medialne nasilenie szkodliwych działań lobbystów antystatynowych leki te wydają się szczególnie narażać pacjentów je przyjmujących na efekt nocebo. Polega on na zgłaszaniu działań niepożądanych leku niezależnie od faktycznego potencjału ich wywoływania przez dany preparat. Powodem wystąpienia tych działań jest negatywne nastawienie pacjenta do terapii i w tym kontekście efekt nocebo można nazwać odwrotnością efektu placebo.

Zagadnienie potencjału wywoływania przez statyny objawowych działań niepożądanych było przedmiotem precyzyjnie zaprojektowanego badania SAMSON. Włączono do niego 60 chorych, którzy odstawili statyny w ciągu 2 tygodni od rozpoczęcia leczenia. Każdy otrzymał łącznie 12 fiolek, po cztery opakowania (każde na miesięczną terapię) zawierające atorwastatynę w dawce 20 mg, placebo i 4 puste fiolki na okres bez terapii. Przedmiotem randomizacji była

kolejność wykorzystywania przez pacjenta leku aktywnego lub placebo. Pacjenci korzystali z elektronicznego dzienniczka do raportowania wystąpienia objawów. Mieli również możliwość odstawienia leku w przypadku wystąpienia szczególnie dotkliwych objawów.

Pierwszorzędowym punktem końcowym było nasilenie intensywności objawów niepożądanych zależnych od efektu nocebo — stosunku intensywności objawów zgłaszanych podczas przyjmowania placebo pomniejszonej o intensywność objawów zgłaszanych w okresach bez interwencji — do intensywności objawów notowanych przez pacjentów podczas przyjmowania statyny skorygowanych w ten sam sposób.

W trakcie obserwacji 11 pacjentów zaprzestało przyjmowania statyn (4 w wyniku własnej decyzji, w 3 przypadkach była to decyzja badaczy). Średnie nasilenie objawów (w skali 0–100) podczas okresów bez leczenia wyniosło 8 (95% CI: 4,7–11,3). Podczas przyjmowania placebo chorzy ocenili nasilenie objawów średnio na 15,4 (wysoce znamienny wzrost w porównaniu z okresami bez leczenia). W trakcie faktycznego leczenia statyną średnie nasilenia objawów wyniosło 16,3 — zatem przy porównaniu nasilenia objawów w trakcie leczenia statyną i w okresach przyjmowania placebo różnice okazały się nieistotne statystycznie ($p = 0,39$). Wartość wskaźnika nocebo wyniosła 2,2 (95% CI: 62,3–66,7); wyliczenia te zaburzyły pojedyncze przypadki pacjentów, którzy zgłaszali dużą intensywność objawów niepożądanych w okresach bez terapii, co przekładało się na zaniżanie wartości użytych do kalkulacji stosunku. Zindywidualizowane wyliczenia pozwoliły ostatecznie określić wartość wskaźnika nocebo na 0,9.

Wnioski z analizy danych pozwalają jednoznacznie stwierdzić, że wpływ statyn na nasilenie intensywności objawów postrzeganych jako działania niepożądane nie jest istotnie większy niż wpływ placebo. Wyniki te mają ważne znaczenie jako argument przeciw nieprawdziwym, a popularnym poglądom o częstej nietolerancji statyn [8].

OMENI: *Omega-3 Fatty Acid Supplements in Elderly Patients after Myocardial Infarction*

Wielonienasycone kwasy tłuszczowe n-3 (PUFA, *polyunsaturated fatty acids*) są postrzegane jako niezbędny składnik zbilansowanej diety. Wiele wątpliwości budzi jednak celowość ich suplementacji jako metoda obniżenia ryzyka sercowo-naczyniowego. Autorzy badania OMENI skupili się na specyficznej grupie starszych chorych po MI, by określić wpływ suplementacji PUFA na ryzyko zdarzeń sercowo-naczyniowych w 2-letniej obserwacji.

Ocenie wpływu interwencji poddano 1027 chorych w wieku 70–82 lat, którzy przebyli kliniczny incydent spełniający kryteria MI w okresie 2–8 tygodni wcześniej. Współpracę pacjentów kontrolowano poprzez określanie osoczowego stężenia kwasów tłuszczowych. Główne punkty końcowe stanowiły: MI niezakończony zgonem, nieplanowana rewaskularyzacja, udar mózgu, zgon z jakiejkolwiek przyczyny, hospitalizacja z powodu niewydolności serca. Drugorzędowym punktem końcowym było nowe rozpoznanie AF.

Częstość wystąpienia pierwszorzędowego punktu końcowego nie różniła się istotnie między grupą przyjmującą przyjmują PUFA — 108 (21,4%), a chorymi przyjmującymi placebo — 102 (20%) ($p = 0,06$). Podobną zależność zaobserwowano w przypadku drugorzędowego punktu końcowego — odpowiednio 28 i 15 pacjentów ($p = 0,06$). Wyniki badania jednoznacznie wykazały, że suplementacja PUFA n-3 nie przynosi korzyści klinicznej w prewencji wtórnej MI ani w kontekście ograniczenia szerszego pojęcia ryzyka sercowo-naczyniowego w grupie starszych pacjentów po MI. Dane te są spójne z licznymi już danymi z zakończonych prospektywnych badań tego zagadnienia [9].

HARP-MINOCA: *Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of MINOCA in Women*

Współczesne definicje MI w każdej z kolejnych modyfikacji są oparte na oznaczeniu stężenia troponiny sercowej. Pozostałe zawarte w definicji wyznaczniki kliniczne stanowią kryteria wspomagająca i zamienne. Mimo spójnej definicji etiologia MI może być zróżnicowana, a jej trafne określenie pozwala wybrać najkorzystniejszy dla pacjenta sposób leczenia. Zdecydowanie najczęstszą przyczyną zawału jest okluzja naczynia wieńcowego spowodowana pęknięciem blaszki miażdżycowej. Wykonanie koronarografii i angioplastyka wieńcowa są więc dla większości pacjentów z MI postępowaniem z wyboru. Statystyki rejestrów medycznych wskazują, że u 6–15% pacjentów, w zdecydowanej większości kobiet, koronarografia nie ujawnia istotnych zwężeń w naczyniach wieńcowych mimo spełniania kryteriów MI i braku innej niż wieńcowa przyczyny tej diagnozy.

Autorzy badania HARP-MINOCA poddali dalszej diagnostyce 170 kobiet, u których rozpoznano zawał serca bez istotnych zwężeń w naczyniach wieńcowych (MINOCA, *myocardial infarction with non-obstructive coronary arteries*). Poza koronarografią wykonano obrazowanie metodą wewnątrzwieńcowej optycznej tomografii koherentnej (OCT, *coronary optical coherence tomography*) oraz rezonansu magnetycznego serca (CMR, *cardiac magnetic resonance*). Uzyskano odpowiednio 145 oraz 116 przypadków, które z przyczyn technicznych mogły być poddane pełnej analizie daną metodą. Dzięki badaniu OCT wykryto 67 (46,2%) przypadków zmian mogących odpowiadać za wystąpienie MI (pęknięcia blaszki miażdżycowej, wylewy do blaszek

miażdżycowych). W przypadku 62 pacjentek (53,4%) W CMR potwierdzono niedokrwienne tło zawału, a w przypadku 24 chorych (20,7%) — inne niż niedokrwienne (zapalenie mięśnia sercowego, zespół takotsubo).

Zastosowanie dwóch metod identyfikacji przyczyn MINOCA pozwoliło zwiększyć skuteczność każdej z nich w postawieniu ostatecznej diagnozy, dając wartość 84,5% rozpoznań. W 63,8% przypadków potwierdzono przyczynę niedokrwienną, a w 20,7% inną niż niedokrwienną. Zakładając, że bez weryfikacji diagnozy większość chorych poddano by terapii typowej dla niedokrwiennej postaci zawału, można uznać, że zastosowana interwencja diagnostyczna pozwoliła w ponad 20% przypadków na wdrożenie adekwatnego leczenia, którego w przeciwnym razie chorzy mogliby być pozbawieni [10]. Wyniki badania potwierdzają rosnące zainteresowanie tematyką MINOCA i wskazują na potencjalne implikacje terapeutyczne precyzyjnej procedury diagnostycznej w tej nierzadkiej jednostce chorobowej.

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