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Prescription patterns of diclofenac in patients with cardiovascular diseases or at high risk for cardiovascular diseases at primary health care level in Montenegro: retrospective, national, drug utilization study

Propisivanje diklofenaka bolesnicima sa kardiovaskularnim bolestima ili visokim rizikom od razvoja kardiovaskularnih bolesti na nivou primarne zdravstvene zaštite u Crnoj Gori: retrospektivna, nacionalna, studija upotrebe leka

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Abstract

Background/Aim. Diclofenac, a non-selective inhibitor of cyclooxygenase with analgesic, anti-inflammatory, and antipyretic effects, is one of the most prescribed nonsteroidal anti-inflammatory drugs (NSAIDs). The aim of this study was to analyze the prescription patterns of diclofenac systemic formulations at primary health care (PHC) level in Montenegro, in patients with cardiovascular (CV) diseases (CVD) and patients with risk factors for CVD, from 2016 to 2020. **Methods.** A retrospective national drug utilization study was conducted and it included patients with CVD, to whom prescribing diclofenac was contraindicated, and patients with risk factors for CVD, to whom diclofenac could be prescribed but with increased precaution. PHC information system has been used as a source of medical data for these patients. **Results.** Within the observed period, prescribing diclofenac systemic formulations, dominantly oral formulations in 75 mg dose, increased by 36.9% [from 4.6 of defined daily doses (DDD) /1,000 inhabitants/day in 2016 to 6.3 DDD/1,000 inhabitants/day in 2020]. A rising trend in prescribing diclofenac was also recorded in patients with CVD or those with risk factors for CVD, to whom diclofenac prescribing is contraindicated. Out of the overall number of patients who were prescribed diclofenac in 2016, 2017, 2018, 2019, and 2020, 16%, 18%, 24%, 15%, and 20% of them, respectively, already had a CVD or some risk factor for CVD. Most CV patients (39.7%), for whom the use of diclofenac was contraindicated, had ischemic heart disease and were prescribed 40.7% of the total amount of diclofenac prescribed for this group of patients (expressed in DDD/1,000 inhabitants/day for the given medicine). The majority (77.4%) of CV patients to whom the drug could be prescribed, but with increased precautions, had hypertension, and they were prescribed 77.2% of the total amount of diclofenac prescribed for this group of patients (expressed in DDD/1,000 inhabitants/day for the given medicine). **Conclusion.** Despite the undertaken regulatory measures aimed at a safer prescription of diclofenac to patients with CVD or at high risk of developing CVD, this medicine is still widely prescribed at the level of PHC in Montenegro, even in cases that represent a contraindication for its use.

Key words:
cardiovascular diseases; delivery of health care; diclofenac; drug utilization; montenegro.

Apstrakt

Uvod/Cilj. Diklofenak, neselektivni inhibitor ciklooksigenaze sa analgetskim, protivupalnim i antipiretičkim dejstvima, jedan je od nesteroidnih protivupalnih lekova (NSPUL) koji se najčešće propisuje. Cilj rada bio je da se istraže propisivanje i potrošnja sistemskih formulacija diklofenaka na nivou primarne zdravstvene zaštite (PZZ) u Crnoj Gori (CG), kod bolesnika sa kardiovaskularnim (KV) bolestima (KVB) i bolesnika sa faktorima rizika od KVB, u periodu od 2016. do 2020. godine. **Metode.** Sprovedena je retrospektivna, nacionalna studija upotrebe leka, koja je uključivala bolesnike sa KVB kojima je bilo kontraindikovano propisivanje diklofenaka,

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kao i bolesnike sa faktorima rizika od KVB, kojima se diklofenak mogao propisati uz pojačane mere opreza. Kao izvor podataka o bolesnicima korišćeni su podaci iz informacionog sistema PZZ. **Rezultati.** U posmatranom periodu, propisivanje sistemskih formulacija diklofenaka, dominatno oralnih, u jačini od 75 mg, povećana je za 36,9% [sa 4,6 definisanih dnevnih doza (DDD)/1 000 stanovnika/dan u 2016., na 6,3 DDD/1 000 stanovnika/dan u 2020. godini]. Zabeležen je trend rasta propisivanja diklofenaka bolesnicima sa KVB, ili onim sa faktorima rizika od KVB, kojima je propisivanje diklofenaka kontraindikovano. Od ukupnog broja bolesnika kojima je tokom 2016, 2017, 2018, 2019. i 2020. godine bio propisan diklofenak, njih 16%, 18%, 24%, 15% i 20%, redom, već je imalo KVB ili neki faktor rizika od KVB. Najviše (39,7%) KV bolesnika, kojima je bila kontraindikovana primena diklofenaka, imalo je ishemijsku bolest srca i njima je bilo propisano 40,7% od ukupno propisane količine diklofenaka za grupu KV bolesnika (izraženo u DDD/1 000 stanovnika/dan za dati lek). Najviše (77,4%) KV bolesnika kojima se lek mogao propisati, ali uz pojačane mere opreza, imalo je hipertenziju i njima je bilo propisano 77,2% ukupno propisane količine diklofenaka za grupu KV bolesnika (izraženo u DDD/1 000 stanovnika/dan za dati lek). **Zaključak.** Uprkos preduzetim regulatornim merama, čiji je cilj bezbednija primena sistemskih formulacija diklofenaka, bolesnicima sa KVB ili visokim rizikom od razvoja KVB se i dalje široko propisuje ovaj lek na nivou PZZ u CG, čak i u slučajevima koji predstavljaju kontraindikaciju za njegovu primenu.

Ključne reči:
kardiovaskularne bolesti; primarno zdravstveno zbrinjavanje; diklofenak; lekovi, korišćenje; crna gora.

Introduction

Diclofenac, a non-selective inhibitor of cyclooxygenase with analgesic, anti-inflammatory, and antipyretic effects, is one of the most prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) in treating numerous acute and chronic painful and/or inflammatory conditions [1]. It is estimated that 14 million Americans aged 45 and above take one of the NSAIDs daily, among which diclofenac is one of the leading drugs. Since the global population is growing older, it is estimated that the rising trend in consumption of these medicines will continue, taking into account the expected growth of the prevalence of inflammatory diseases with accompanying pain (osteoarthritis and other inflammatory conditions) [2]. Diclofenac was also the most used NSAID according to the results of a study that included 15 participant countries worldwide [3]. Namely, the consumption of diclofenac and etoricoxib, both of them being NSAIDs, with recognized cardiovascular (CV) risk constitutes one-third of the consumption of all NSAIDs analyzed in the study.

Reports on the consumption of drugs in Montenegro (MNE) indicate very high consumption of diclofenac [more than 40 daily defined doses (DDD)/1,000 inhabitants/day] [4]. In comparison, in Croatia (an EU member country), consumption is significantly lower, and in 2020, it amounted to 11.63 DDD/1,000 inhabitants/day [5], while in Norway, one of the leading countries in terms of rational drug use, consumption is only 5.62 DDD/1,000 inhabitants/day [6].

Considering the safety of diclofenac systemic formulations, a topic that has attracted the attention of the professional public for years, refers to the CV safety of diclofenac, which resulted in the adoption of new recommendations issued by the European Medicines Agency (EMA) regarding the systemic use of diclofenac in patients with CV diseases (CVD) or with risk factors for CVD [7]. These recommendations have been introduced into appropriate sections of the Summary of Product Characteristics (SmPC) of diclofenac. They were also adopted in MNE by the Institute for Medicines and Medical Devices of Montenegro (CInMED) [8–10]. Additionally, in 2015, CInMED implemented the additional measure of minimizing (reducing) risks of unsafe diclofenac prescribing in a way that it had notified healthcare professionals *via* letter – Direct Healthcare Professional Communication of introduced restrictions in diclofenac prescribing in patients with CVD or with risk factors for CVD [11, 12].

Systemic formulations of diclofenac are available to patients in MNE and, for years back, they have been on the list of medicines funded by mandatory health insurance in MNE, which is also one of the reasons that contribute to the wide diclofenac prescribing at the primary health care level, i.e., outpatient care settings (OCS) [13].

Pursuant to the knowledge of the safety profile of this drug concerning CV adverse reactions, high exposure of patients to diclofenac may pose a serious public health concern.

The aim of this study was to analyze prescribing diclofenac systemic formulations in patients with CVD to whom diclofenac prescribing is contraindicated and patients with risk factors for CVD to whom diclofenac may be prescribed with special warnings and precautions at the OCS in MNE from 2016 to 2020. The aim was also to assess if the primary care physicians when prescribing diclofenac take into account the latest, evidence-based information on its safety, indicated in the SmPC, revised in MNE in 2015.

Methods

Data sources

An observational, retrospective, national drug utilization study was conducted [14]. Analysis of prescribing diclofenac systemic formulations was performed in a five-year time period (January 1, 2016, to December 31, 2020) on primary health care information system (PHCIS) prescribing data. This information system is implemented in all 18 healthcare centers in MNE. Generating the diclofenac prescribing database was enabled due to the developed Data Warehouse (DW) system at the level of the entire OCS in

MNE. DW system is a central repository of integrated diclofenac prescribing data collected in real-time as well as historical data of diclofenac prescribing captured from the electronic medical records of patients. This research included the entire system of the OCS in MNE, which is why this research belongs to a group of national-based studies.

The following data were extracted and analyzed from the PHCIS: the overall number of patients who were prescribed the systemic formulations of diclofenac; the overall number of patients who were prescribed systemic formulations of diclofenac, with CVD contraindicated for diclofenac prescribing [congestive heart failure, ischemic heart disease (IHD), peripheral arterial disease, cerebrovascular disease], as well as with diseases that represent risk factors for CVD, for which there are special warnings and precautions in prescribing diclofenac (hypertension, hyperlipidemia, diabetes mellitus – DM); on all drugs on the market in MNE, that contain diclofenac as an active substance, but in different pharmaceutical form, strength (dose), and different method of use, except for diclofenac intended for local (topical) use.

Patients

The study included patients of both genders older than 18 years. Based on the data from their electronic medical records, the patients were prescribed diclofenac in the five-year time period. In the observed time period, as seen from their medical records, these patients had CVD or at least one of the risk factors for CVD, which represents a contraindication or requires special warnings and precautions for prescribing the systemic formulation of diclofenac.

As seen from their electronic medical records, these patients underwent screening of all diagnoses in order to determine whether CVD was characterized as a contraindication or whether some of the diseases with known CV risk factors were among patients' diagnoses, which required special warnings or precautions before prescribing systemic formulation of diclofenac. In PHCIS, medical diagnoses are classified according to the International Classification of Diseases (ICD) [15]. The selected diagnoses are shown in the supplement of this article.

According to SmPC [10], the use of diclofenac is contraindicated in patients with established congestive heart failure (New York Heart Association – NYHA, class II–IV), IHD, peripheral arterial disease, or cerebrovascular disease. At the same time, patients with significant risk factors for CVD (e.g., hypertension, hyperlipidemia, DM, smoking) should only be treated with diclofenac after careful consideration.

Consumption of systemic formulations of diclofenac was analyzed using the standard methodology of the World Health Organization based on DDD/1,000 inhabitants/day and Anatomic Therapeutic Chemical classification of medicines [16].

Results

Although the total number of patients who were prescribed systemic formulations of diclofenac decreased from 2016 to 2020 (from 94,269 to 79,168 patients), that trend was not noticed in the case of patients with risk factors for CVD, where, except for 2019, the trend of increase in number of patients with prescribed diclofenac was present. Concerning the total number of patients who in 2016, 2017, 2018, 2019, and 2020 were prescribed the systemic formulations of diclofenac, 16%, 18%, 24%, 15%, and 20% of them, respectively, had risk factors for CVD for diclofenac prescribing (Table 1).

Within the observed five-year time period, prescribing diclofenac systemic formulations to the target population, expressed in the number of prescribed diclofenac packaging, marked the growth trend in the first three years (2016–2018), with a decline in prescribing in 2019 and 2020 compared to 2018 (Figure 1).

The highest (39.7%) number of CV patients, who had contraindications for diclofenac prescribing, had IHD, while the highest (77.4%) number of patients to whom diclofenac could be prescribed but with increased precautions had hypertension (Table 2).

When it comes to the consumption of diclofenac systemic formulations, expressed in the number of DDD/1,000 inhabitants/day, in patients with CVD, its continuous growth was observed. Within the observed period, the consumption increased by 36.9% (from 4.6 to 6.3 DDD/1,000 inhabitants/day) (Figure 2).

Consumption of diclofenac systemic formulations in patients with CVD, who had contraindications for diclofenac prescribing, accompanied the trend of its increased prescribing. Namely, there was a noticeable increase in

Table 1

Total number of patients and number of patients with cardiovascular disease (CVD) or risk for CVD (contraindications and special warnings and precautions for use) who have been prescribed systemic formulations of diclofenac during the five-year period (2016–2020) in Montenegro

Year	Patients on diclofenac therapy, n	Patients with CVD on diclofenac therapy, n (%)
2016	94,269	15,602 (16)
2017	95,112	17,060 (18)
2018	93,598	22,923 (24)
2019	93,435	14,530 (15)
2020	79,168	15,702 (20)

n – number.

diclofenac consumption in this group of patients, while in 2019 and 2020, a mild decline in consumption was observed.

Consumption of diclofenac systemic formulations in patients with risk factors for CVD, to whom diclofenac has to be prescribed, with particular precaution, recorded a continuous increase − from 4.1 in 2016 to 5.8 DDD/1,000 inhabitants/day in 2020, which is an increase of 41.5% (Figure 2).

Analysis of diclofenac systemic formulations consumption concerning CVD, or diseases designated as CV risk factors, also showed that diclofenac, although contraindicated, was mostly prescribed to the patients suffering from IHD (with 40.7% of those patients), while among the diseases requiring special precautions for diclofenac prescribing, hypertension dominated (with 77.2% of those patients) (Table 3).

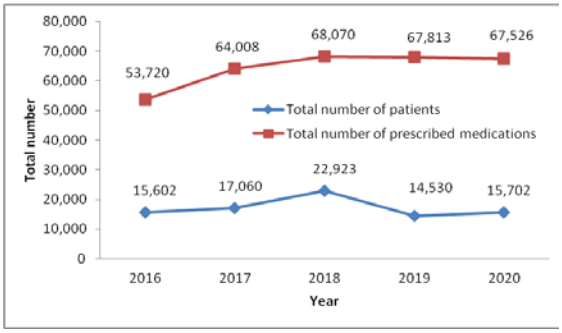

Fig. 1 – Total number of prescribed systemic formulations of diclofenac and number of patients with cardiovascular disease (CVD) or risk factors for CVD (contraindications and special warnings and precautions for use) who have been prescribed the drug during the five-year period (2016–2020) in Montenegro.

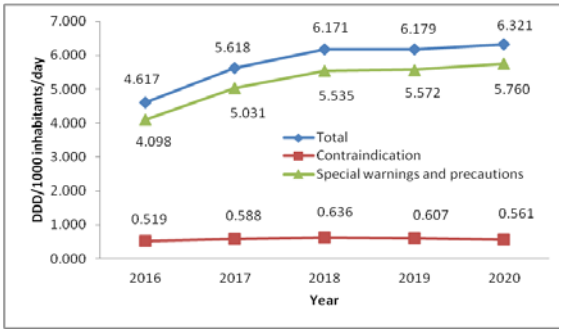

Fig. 2 – Total consumption of systemic formulations of diclofenac in patients with cardiovascular disease (CVD) or risk factors for CVD (contraindications and special warnings and precautions for use) expressed as the number of daily defined dose (DDD)/1,000 inhabitants/day during the five-year period (2016–2020).

Table 2

Number of patients with cardiovascular disease (CVD) or risk for CVD who have been prescribed systemic formulations of diclofenac during the five-year period (2016–2020) in Montenegro (according to the primary diagnosis)

Parameter	2016	2017	2018	2019	2020	Total
CVD						
congestive heart failure	95	87	102	63	40	387
ischemic heart disease	753	785	1,004	619	569	3,730
other heart diseases	507	488	597	369	330	2,291
diseases of arteries, small arteries, and capillaries	151	156	221	154	141	823
cerebrovascular disease	371	390	529	374	364	2,028
diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs	14	20	46	26	28	134
Disease as a risk factor for CVD						
hypertension	10,561	11,713	15,836	10,025	11,013	59,148
hyperlipidemia	330	350	403	263	289	1,635
diabetes mellitus	2,820	3,071	4,185	2,637	2,928	15,641
Total	15,602	17,060	22,923	14,530	15,702	85,817

Table 3

Consumption of systemic formulations of diclofenac expressed as the number of daily defined dose (DDD)/1,000 inhabitants/day during the five-year period (2016–2020) in patients with cardiovascular disease (CVD) or risk for CVD in Montenegro

Disease	2016	2017	2018	2019	2020	Total
CVD						
congestive heart failure	0.0313	0.0300	0.0283	0.0210	0.0181	0.1286
ischemic heart disease	0.2077	0.2457	0.2615	0.2466	0.2252	1.1867
other heart diseases	0.1384	0.1487	0.1519	0.1336	0.1241	0.6966
diseases of arteries, small arteries, and capillaries	0.0384	0.0420	0.0471	0.0460	0.0487	0.2222
cerebrovascular disease	0.1010	0.1175	0.1381	0.1485	0.1355	0.6407
diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs	0.0026	0.0050	0.0112	0.0122	0.0115	0.0426
Disease as a risk factor for CVD						
hypertension	3.1617	3.8670	4.2565	4.3121	4.4586	20.0613
hyperlipidemia	0.0873	0.0987	0.0966	0.0951	0.1004	0.4781
diabetes mellitus	0.8434	1.0638	1.1797	1.1636	1.1994	5.4499

If the consumption of systemic formulations of diclofenac in patients with CVD was analyzed regarding the type of systemic formulations (oral, parenteral, rectal), the continuous growth in consumption of oral formulations, the decline in consumption of parenteral formulations since 2017, and continuous decline in consumption of rectal formulations of diclofenac were observed. Oral formulations of diclofenac made up 98% of total diclofenac systemic formulations consumption (Table 4).

Analysis of the consumption of diclofenac systemic formulations, represented as the number of prescribed packaging of diclofenac to a targeted population, indicates the highest consumption of diclofenac in patients with IHD (40.3%) and other CV (25.8%) and cerebrovascular diseases (19.2%) of all CVD contraindications for prescribing diclofenac (Table 5), and patients with hypertension (76.6%) and DM (21.5%) of all cases of diseases as risk factors for CVD that require special warnings and precautions for using diclofenac (Table 6).

Table 4

Consumption of systemic formulations of diclofenac expressed as the number of daily defined dose (DDD)/1,000 inhabitants/day during the five-year period (2016–2020) in Montenegro in relation to the route of administration of systemic formulations of the drug

Route of administration	2016	2017	2018	2019	2020
Oral	4.523	5.520	6.079	6.091	6.262
Parenteral	0.090	0.095	0.091	0.086	0.060
Rectal	0.004	0.003	0.002	0.001	0.000

Table 5

Number of prescribed packages of diclofenac to patients with cardiovascular disease contraindications in different strengths (doses) and pharmaceutical forms during the five-year period (2016–2020)

Parameter	Route of administration (dose)					Total
	oral (mg)			parenteral (mg/mL)	rectal (mg)	
Congestive heart failure	50	75	100	75/3	50	
2016	4	188	138	20	-	350
2017	6	204	100	44	-	354
2018	5	219	59	71	-	354
2019	-	174	32	57	-	263
2020	-	153	32	5	-	190
[1]Ischemic heart disease						
2016	58	1,298	820	275	8	2,459
2017	76	1,710	763	339	10	2,898
2018	36	2,189	420	329	9	2,983
2019	2	2,026	445	297	1	2,771
2020	1	1,978	295	98	-	2,372
Other heart diseases						
2016	92	861	496	338	1	1,788
2017	50	1,078	382	373	-	1,883
2018	28	1,269	211	381	-	1,889
2019	9	1,120	195	262	1	1,587
2020	2	1,078	152	224	-	1,456
Diseases of arteries, small arteries, and capillaries						
2016	6	289	64	241	1	601
2017	15	322	68	172	1	578
2018	3	370	56	227	-	656
2019	-	325	99	199	-	623
2020	1	369	68	176	2	616
[2]Cerebrovascular diseases						
2016	24	525	272	338	6	1,165
2017	22	673	264	297	-	1,256
2018	10	848	126	323	-	1,307
2019	1	896	216	346	1	1,460
2020	1	828	173	233	-	1,235
Diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs						
2016	-	23	1	4	-	28
2017	-	37	6	9	-	52
2018	-	95	1	3	-	99
2019	-	105	10	-	-	115
2020	-	99	-	-	-	99

Note: Rectal administration of diclofenac included doses other than 50 mg only for [1] ischemic heart disease (25 mg; 50 mg) and [2] cerebrovascular diseases (12.5 mg; 25 mg; 50 mg).

Table 6

Number of prescribed packages of diclofenac to patients with risk factors for cardiovascular disease (special warnings and precautions) in different strengths (doses) and pharmaceutical forms during the five-year period (2016–2020)

Parameter	Route of administration (dose)					Total
		oral (mg)		parenteral (ng/mL)	rectal (mg)	
[1]Hypertension						
2016	971	20,816	11,563	2,719	137	36,206
2017	1,042	28,230	11,097	3,016	104	43,489
2018	529	35,487	7,635	2,748	65	46,464
2019	183	34,918	9,096	2,531	57	46,785
2020	142	38,028	7,414	1,735	16	47,335
Hyperlipidemia						
2016	27	556	342	70	3	998
2017	36	710	282	124	-	1,152
2018	10	840	120	86	-	1,056
2019	2	789	169	117	-	1,077
2020	-	864	149	90	-	1,103
[2]Diabetes mellitus						
2016	250	5,469	3,052	1,328	26	10,125
2017	294	7,816	2,901	1,326	9	12,346
2018	151	9,662	2,224	1,220	5	13,262
2019	21	9,274	2,520	1,314	3	13,132
2020	54	10,077	2,083	902	4	13,120

Note: Rectal administration of diclofenac included doses other than 50 mg for [1] hypertension and [2] diabetes mellitus (12.5 mg; 25 mg; 50 mg).

Diclofenac was most frequently prescribed to the target population in formulations for oral use, in a dose of 75 mg (63.7% compared to other systemic formulations and doses of diclofenac). However, diclofenac was also prescribed in a dose of 100 mg where, in case the patients took it twice a day, the total daily dose exceeded the maximum permitted one of 150 mg. The contribution of diclofenac 100 mg oral formulations compared to other diclofenac doses and formulations amounted to 18.8% (Table 5).

Similarly, prescribing diclofenac 75 mg and 100 mg oral formulations in patients with risk factors for CVD amounted to 70.7% and 21.1%, respectively, compared to other systemic formulations and doses of diclofenac (Table 6).

Discussion

In a comprehensive multi-annual analysis of CV safety of diclofenac, the EMA concluded that the data on prescribing diclofenac systemic formulations are mainly unavailable and restricted and do not represent actual patients' exposure to diclofenac. That is why the EMA recommended that, in countries in which diclofenac is on the market, research is conducted according to the design of drug utilization study, aiming at gathering information on prescribing diclofenac, with special attention to the population taking this drug (age, gender, contraindications, given doses, length of use). Based on the results, the goal was to recommend efficient measures of reducing risks from diclofenac serious CV adverse reactions [14].

Taking into account the EMA recommendation, we wanted to analyze the prescription patterns of diclofenac systemic formulations by physicians at the OCS in MNE, to patients with CVD or with risk factors for CVD, in the five-year period (2016–2020). This time period followed the update of the SmPC of diclofenac with information on new contraindications and special warnings and precautions in 2015, approved by CInMED and based on the EMA recommendation. Additional motive and reason for conducting this study in MNE was the information on growing consumption of diclofenac and significantly higher values of DDD/1,000 inhabitants/day in MNE compared to the European Union (EU) countries and countries with high standards of healthcare, like the Scandinavian countries, which were used for comparison [4].

The largest study conducted so far in Europe, in which the prescription patterns of diclofenac to patients with CVD were investigated, was the study conducted by Morales et al. [17]. This study researched the impact of the EMA recommendations on CV contraindications (IHD, congestive heart failure, peripheral arterial disease, cerebrovascular diseases) and special warnings and precautions (hypertension, hyperlipidemia, DM) introduced in EU SmPC for diclofenac on prescribing this drug to patients with CVD or with risk factors for CVD. The study was conducted in four European countries: Denmark, the Netherlands, England, and Scotland. In all these countries, the implementation of SmPC with new CV safety information resulted in a decrease in diclofenac prescribing. In the first three months after introducing the EMA recommendation, the results showed a significant immediate absolute decrease in prescribing diclofenac to the following patients: those with IHD, peripheral arterial disease, and hyperlipidemia in all countries; patients with hypertension and diabetes in the Netherlands, England, and Scotland; patients with congestive heart failure and cerebrovascular disease in England and Scotland. Within the time period after three months

following the adoption of the EMA recommendation (post-intervention), a significant decrease has been noted in prescribing diclofenac to patients with IHD, peripheral arterial disease, hypertension, hyperlipidemia, and diabetes in the Netherlands and to patients with congestive heart insufficiency, IHD, peripheral arterial disease, and hypertension in Scotland. In England, the rates of prescribing diclofenac gradually decreased, while in Denmark, the changes in prescribing diclofenac had been more prominent after the earlier analysis of the EMA on CV safety risks of the systemic use of diclofenac in 2012. Although there has been a significant decrease in prescribing diclofenac, the authors indicate that some patients with CVD, which is a contraindication for the drug, continued having it prescribed, the extent of which varied by country and CVD.

A study was also conducted in Germany to investigate the impact of the EMA-recommended restrictions on the prescription of systemic formulations of diclofenac, with an emphasis on patients who have CV contraindications for diclofenac prescription or to whom diclofenac can be prescribed but with precaution. It was concluded that the overall decline in diclofenac initiation between 2011 and 2014 was largely independent of the presence or absence of new CV contraindications. The proportion of diclofenac initiators with a new contraindication remained at a high level (more than one in ten patients), indicating the need for research at the prescriber level (e.g., interventional studies) and additional measures to improve patient safety [18].

Contrary to the countries that were the subject of the above-mentioned study, in Lithuania, in the same period, diclofenac was the most frequently prescribed NSAID. In 2016, the contribution of diclofenac to the overall consumption of NSAIDs amounted to 30.0% [16]. Lithuania is an EU country also bound by the EMA recommendation and decisions of the European Commission. In the eleven years of the time period (2005–2016), the consumption of drugs that belong to pharmacotherapeutic groups N02B (other pain killers and antipyretics) and M01A (anti-inflammatory medicines and anti-rheumatics, non-steroidal) was increased in Lithuania by 22.8%, and from 58.4 in 2005 to 71.68 DDD/1,000 inhabitants/day in 2016, respectively. It can be indicated that despite the restrictions in prescribing diclofenac recommended by the EMA, consumption of diclofenac, as well as COX-2 inhibitors and piroxicam, was still high and growing within the observed period, while consumption of safer therapeutic alternatives (paracetamol, naproxen) was relatively low compared to the Scandinavian countries which have a prominent significant trend of decline in consumption of diclofenac and increase in consumption of paracetamol and naproxen [19].

In general, prescription databases provide an excellent infrastructure base for research in pharmacoepidemiology and pharmacovigilance. They contain information about patients, their medical and other characteristics, and all prescribed drugs, which gives the possibility of researching potential interactions between drugs, with a focus on clinically significant interactions. However, the continuous improvement of these databases, especially in implementing standardized coding systems and medical dictionaries, will provide a better understanding of the effectiveness and safety of drugs in routine clinical practice [20–25].

In Denmark, a study was conducted to examine the potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs, including diclofenac. It was concluded that the possibility of identifying NSAID use from prescription registries in Denmark is high. Low-dose aspirin and nonaspirin NSAID use varied substantially between 1999 and 2012. Notably, the use of cyclooxygenase-2 inhibitors nearly ceased, the use of diclofenac decreased markedly, and naproxen use remained unaltered [26].

Analysis of the data on prescribing systemic formulations of diclofenac in MNE from 2016 through 2020 shows that, despite new contraindications and precautions when prescribing diclofenac to patients with CVD as risk factors for CVD, this drug was widely prescribed to these patients. Namely, out of the overall number of patients who were prescribed diclofenac in that period, on average, almost every fifth patient had one of the CVD posing a contraindication or requiring special precaution in diclofenac prescribing. In the observed time period, diclofenac consumption was increased by 36.9% in patients with CVD or with risk factors for CVD. The highest (39.7%) number of CV patients to whom diclofenac was contraindicated but prescribed had IHD, while the highest (77.4%) number of patients to whom diclofenac can be prescribed but with increased precaution had hypertension. IHDs (*angina pectoris, infarctus myocardii, morbus cordis ischaemicus, cardiomyopathia ischaemica*) constitute serious clinically significant conditions which in the patients taking diclofenac may lead to an increase in their morbidity and mortality and increase the costs of healthcare due to the necessary treatment of these patients [27].

Our research showed that oral formulations of diclofenac in the dose of 75 mg were the most commonly prescribed diclofenac formulations at the OCS in MNE (63.7%) compared to other systemic formulations of diclofenac and doses. However, oral 100 mg formulations of diclofenac also made a significant contribution, which is potentially a risk factor for the progression of CVD when taking into account that the maximum daily dose of diclofenac is 150 mg. The diclofenac SmPC indicates that the risk of its serious adverse effects may be reduced using the lowest effective dose in the shortest possible period of time necessary for controlling the symptoms [10]. Bearing in mind the high consumption of diclofenac in MNE, as well as its safety risk in patients with CVD, as a routine measure to minimize (reduce) the risks, CInMED approved all systemic formulations of diclofenac to be dispensed only on prescription, with the aim of getting necessary physician's supervision over the use of diclofenac [28]. Despite that, however, it is obvious that diclofenac is irrationally prescribed at the OCS in MNE, even in patients contraindicated for diclofenac prescribing, which may result in serious health consequences for individual patients and the entire population. Therefore, it is necessary to take additional

measures (regulatory and educational) in order to raise the awareness of healthcare workers about the need to comply with the EMA and CInMED recommendations when prescribing diclofenac to patients with CVD. That refers not only to diclofenac but also to other medicines with recognized safety risks.

The main advantage of this study is that it included the entire system of primary health care in MNE, providing comprehensive insight into the prescribing practice of diclofenac – a drug with established CV risk at the level of healthcare that is mostly prescribed.

Nevertheless, the study has some limitations, such as the fact that it did not include the period before the adoption of regulatory measures by CInMED. That restricted the use of systemic formulations of diclofenac in patients with CVD. Therefore, it is unknown whether the obtained data on prescribing/consuming the drug in the observed five-year time period after the adoption of those measures indicate a decrease or increase compared to the previous period. PHCIS, which enabled the generation of data necessary for this study, was implemented in all healthcare centers in MNE after 2015. Because of that, obtaining data from the previous years was impossible. However, diclofenac consumption in MNE has been high for years, with no major oscillations. It may be assumed, therefore, that in the period before the adoption of regulatory measures regarding the increased CV risk from systemic use of diclofenac, this drug had also been prescribed to patients with CVD or with risk factors for CVD in approximately the same quantity, or probably more, than after those measures were adopted. In addition, one of the limitations of the existing PHCIS is that for some diagnoses which are risk factors for CVD, like smoking, reliable data on patients' exposure to this risk factor could not be generated from PHCIS. Healthcare professionals generally do not enter data on smoking in PHCIS as a diagnosis with the appropriate ICD code. If it is entered at all, it is done as a text field that cannot be parameterized and used for statistical analysis. For this reason, when it comes to risk factors for CVD, the focus of this article is on diagnoses (hypertension, DM, and hyperlipidemia) which are the most often precautionary measures for prescribing diclofenac.

Conclusion

The drugs containing diclofenac, intended for systemic use, are widely prescribed at the OCS in MNE, even in patients with contraindications and precautions for diclofenac prescribing, such as CV patients and patients with certain CVD risk factors. Due to high prescription and, consequently, consumption of diclofenac, designing efficient measures at the OCS is necessary in order to rationalize diclofenac prescribing. These measures would reduce CV risks from its irrational use and ultimately significantly improve public health.

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Supplement – ICD diagnosis of relevance for research conducting

ICD-10: I20
Diagnosis: Angina pectoris
ICD-10: I21
Diagnosis: Infarctus myocardii acutus
ICD-10: I22
Diagnosis: Infarctus myocardii recidivus acutus
ICD-10: I23
Diagnosis: Complicatio acuta post infarctum cordis acutum
ICD-10: I24
Diagnosis: Morbi cordis ishaemici acuti alli
ICD-10: I25
Diagnosis: Morbus cordis ischaemicus chronicus
ICD-10: I26
Diagnosis: Embolia pulmonis
ICD-10: I27
Diagnosis: Morbi cordis pulmonales alii
ICD-10: I28
Diagnosis: Morbi vasorum pulmonis alii
ICD-10: I42
Diagnosis: Cardiomyopathia
ICD-10: I43
Diagnosis: Cardiomyopathia in morbis aliis
ICD-10: I50
Diagnosis: Insufficientia cordis
ICD-10: I60
Diagnosis: Haemorrhagia subarachnoidalis
ICD-10: I61
Diagnosis: Haemorrhagia cerebri
ICD-10: I62
Diagnosis: Haemorrhagia intracranialis non traumatica, alia
ICD-10: I63
Diagnosis: Infarctus cerebri
ICD-10: I64
Diagnosis: Apoplexia cerebri ut haemorrhagia sive infarctus non specificata
ICD-10: I65
Diagnosis: Occlusio arteriae praecerebralis et stenosis arteriae praecerebralis sine infarctus cerebri
ICD-10: I66
Diagnosis:Occlusio arteriae cerebri et stenosis arteriae cerebri sine infarctu
ICD-10: I67
Diagnosis: Morbi cerebrovasculares alli
ICD-10: I68
Diagnosis: Morbi cerebrovasculares in morbis aliis
ICD-10: I69
Diagnosis: Sequelae morbi cerebrovascularis
ICD-10: I70
Diagnosis: Atherosclerosis
ICD-10: I71
Diagnosis: Aneurysma aortae et dissectio aortae
ICD-10: I72
Diagnosis: Aneurysmata alia
ICD-10: I73
Diagnosis: Morbi vasorum periphericorum alii
ICD-10: I74
Diagnosis: Embolia ateriarum et thrombosis arteriarum
ICD-10: I77
Diagnosis: Morbi arteriales et arteriolares alli

ICD-10: I79
Diagnosis: Morbi arteriales, arteriolares et capillares in morbis aliis
ICD-10: I10
Diagnosis: Hypertensio arterialis essentialis (primaria)
ICD-10: I11
Diagnosis: Morbus cordis hypertensivus
ICD-10: I12
Diagnosis: Morbus renalis hypertensivus
ICD-10: I13
Diagnosis: Morbus cordis et morbus renis hypertensivus
ICD-10: I15
Diagnosis:Hypertensio arterialis, secundaria
ICD-10: E10
Diagnosis: Diabetes mellitus ab insulino dependens
ICD-10: E11
Diagnosis: Diabetes mellitus ad insulino independens
ICD-10: E12
Diagnosis: Diabetes mellitus malnutritionalis
ICD-10: E13
Diagnosis: Diabetes mellitus alius,specificatus
ICD-10: E14
Diagnosis: Diabetes mellitus,non specificatus
ICD-10: E78
Diagnosis: Disordines metabolismi lipoproteiniet lipidaemiae alii