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# Consumption of diclofenac and health outcomes in outpatients with or at high risk for cardiovascular diseases in Montenegro after implementation of the innovative risk minimization digital tool

## Potrošnja diklofenaka i zdravstveni ishodi kod ambulantnih bolesnika obolelih ili sa visokim rizikom od kardiovaskularnih bolesti u Crnoj Gori nakon implementacije inovativnog digitalnog alata za minimizaciju rizika

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**Abstract**

**Background/Aim.** Risk minimization measures (RMMs) for medicines are one of the most important interventions in maintaining a positive benefit–risk ratio and ensuring their safe use. Systemic formulations of diclofenac are medicines with routine and additional RMMs in place for its well-established cardiovascular (CV) safety risk. In 2021, an innovative digital tool (IDT) was implemented in the Montenegrin Information System of Primary Health Care (PHCIS). The aim of this study was to analyze diclofenac consumption in CV risk patients who did not use diclofenac before the introduction of this new IDT for RMM (diclofenac-naïve patients), taking into account their demographic (gender and age) and clinical characteristics [CV diseases (CVD)/risk factors of CVD]. **Methods.** Patients with CVD/diseases posing a risk for CVD development (conditions that are contraindications/precautions for prescribing diclofenac) were selected after an automated screening of all diagnoses, classified in accordance with the International Classification of Diseases, 10th revision, from their electronic medical records. These patients also had medical diagnoses that served as indications for prescribing nonsteroidal anti-inflammatory drugs such as diclofenac. These patients were monitored for a period of one year after the introduction of the IDT (October 4, 2021 – October 4, 2022). Diclofenac consumption was analyzed using the standard methodology of the World Health Organization based on daily defined doses/1,000 inhabitants/day and the Anatomical Therapeutic Chemical classification of medicines, as well as the total number of prescriptions and prescribed packages of the drug, taking into account their gender, age, and high-risk CV diagnoses. **Results.** It was shown that diclofenac was prescribed more frequently to women and patients aged 45–64. Regarding medical diagnoses that are contraindications/precautions for diclofenac use, the drug was most often prescribed to patients with ischemic heart disease (38.15%) and hypertension (71.00%). Following the introduction of the drug into therapy, there was an increase in the number of patients with diagnoses (CVD) that are contraindications for diclofenac use. The largest increases were recorded in patients with diseases of arteries, small arteries and capillaries (41.77%), and congestive heart failure (28.57%). **Conclusion.** After the introduction of the IDT as a new RMM for adverse CV effects of diclofenac into the Montenegrin PHCIS, the drug was most frequently prescribed to female diclofenac-naïve patients, individuals aged 45–64 years, and those with high-risk CV diagnoses that required precautions for its use. The use of diclofenac led to an increase in the number of patients with CVD, indicating the need to introduce new measures to reduce the risk of its adverse CV effects.

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

**Apstrakt**

**Uvod/Cilj**. Mere za minimizaciju rizika (*risk minimization measures* – RMMs) za lekove su jedna od najvažnijih intervencija u održavanju pozitivnog odnosa korist–rizik i omogućavanju njihove bezbedne upotrebe. Sistemske formulacije diklofenaka su lekovi sa rutinskim i dodatnim RMMs zbog njihovog dobro utvrđenog kardiovaskularnog

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(KV) bezbednosnog rizika. U crnogorski Informacioni sistem primarne zdravstvene zaštite je 2021. godine implementirana inovativna digitalna alatka (IDA). Cilj rada bio je da se analizira potrošnja diklofenaka kod bolesnika sa KV rizikom koji nisu koristili diklofenak pre uvođenja nove IDA za RMM (*diclofenac-naïve* bolesnici) uzimajući u obzir njihove demografske (pol i starost) i kliničke karakteristike [KV bolesti (KVB)/faktori rizika od KVB]. **Metode**. Oboleli od KVB/bolesti koje predstavljaju rizik od razvoja KVB (stanja koje su kontraindikacije/stanja koja zahtevaju mere predostrožnosti za propisivanje diklofenaka) odabrani su nakon automatizovanog skriniga svih dijagnoza, klasifikovanih u skladu sa Međunarodnom klasifikacijom bolesti, 10. revizija, iz njihove elektronske medicinske dokumentacije. Ovi bolesnici imali su i medicinske dijagnoze koje su bile indikacije za propisivanje nesteroidnih antizapaljenskih lekova kao što je diklofenak. Bolesnici su praćeni u periodu od godinu dana nakon uvođenja IDA (4. oktobar 2021 – 4. oktobar 2022). Potrošnja diklofenaka analizirana je po standardnoj metodologiji Svetske zdravstvene organizacije na osnovu broja definisanih dnevnih doza na 1 000 stanovnika dnevno i Anatomsko terapijsko-hemijske klasifikacije lekova, kao i ukupnog broja recepata i propisanih pakovanja leka, uzimajući u obzir pol, godine života i dijagnoze bolesnika sa visokim KV rizikom. **Rezultati.** Pokazano je da se diklofenak češće propisivao ženama i bolesnicima starosti 45–64 godina. Kada je reč o medicinskim dijagnozama koje su kontraindikacije/ zahtevaju mere predostrožnosti za primenu diklofenaka, lek je najčešće bio propisivan bolesnicima sa ishemijskom bolešću srca (38,15%), odnosno hipertenzijom (71,00%). Nakon uvođenja leka u terapiju povećao se broj bolesnika sa dijagnozama (KVB) koje su kontraindikacije za primenu diklofenaka. Najveći porast zabeležen je kod bolesnika sa bolestima arterija, malih arterija i kapilara (41,77%) i kongestivnom srčanom insuficijencijom (28,57%). **Zaključak.** Nakon uvođenja IDA kao nove RMM od neželjenih KV efekata diklofenaka u Informacioni sistem primarne zdravstvene zaštite Crne Gore, kod bolesnika sa bezbednosno rizičnim KV dijagnozama koji ga ranije nisu primali, lek se najčešće propisivao *diclofenac-naïve* bolesnicama, osobama starosti 45-64 godine i onima koji su imali dijagnoze koje su zahtevale mere opreza prilikom njegove upotrebe. Upotreba diklofenaka dovela je do povećanja broja bolesnika sa KVB što ukazuje na potrebu uvođenja novih mera za smanjenje rizika od njegovih štetnih KV efekata.

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

## Introduction

The risk management system in pharmacovigilance (PV) includes PV activities and risk minimization intervention with the ultimate goal of identifying, characterizing, preventing, or minimizing the risk of medicines use, including the evaluation of their effectiveness and impact in clinical practice. The implementation of risk minimization measures (RMMs) poses a great challenge for all stakeholders in the PV system [1]. RMMs consist of two components: RMM message and RMM tool. An RMM message is the key information about the risk and the actions intended to be taken by the healthcare professional (HCP) or the patient for minimizing the risk. An RMM tool is a tool used to disseminate RMM messages and to support or monitor adherence to the intended risk-minimization actions. It can belong to either the category of routine or additional RMM tools [2]. The medicines regulation in Montenegro (MNE) [3], like that in the European Union (EU), lays down the assessment of RMMs' effectiveness in clinical practice, as mandatory for marketing authorization holders and regulatory authorities [4–6]. One example is the assessment of the impact of imposed restrictions on the use of certain medicines on their further prescriptions and consumption [7]. There are a few examples of assessing the influence of PV intervention on patient-relevant health outcomes, which play a key role in the PV system that makes a difference to patients [8].

Systemic formulations of diclofenac (hereinafter: diclofenac) are one of the examples of medicines with routine and additional RMMs in place for its identified, well-established cardiovascular (CV) safety risk. These RMMs have been legally binding in the EU since 2013 [9–11], and were approved by the Institute for Medicines and Medical Devices (CInMED) of MNE in 2015. The routine RMMs referred to the changes in the diclofenac reference information (summary of product characteristics and the patient information leaflet). These changes mostly affected the safety sections in these documents (contraindications and precautions/warnings). However, the sections related to posology and route of administration were also modified, with new recommendations on maximum daily dose and duration of its use. Namely, established congestive heart failure, ischemic heart disease, peripheral arterial disease, and cerebrovascular diseases were introduced as new contraindications for prescribing diclofenac, while hypertension, hyperlipidaemia, and diabetes mellitus, which are risk factors for CV diseases (CVD), were introduced as new precautions/warnings for its prescribing. Besides routine measures, additional RMMs were introduced with the aim to proactively and timely inform relevant HCPs about the new CV safety restrictions for diclofenac use, through an official Dear Healthcare Professional Communication. This communication was disseminated to HCPs by CInMED and all marketing authorization holders for diclofenac *via* various traditional channels: post, e-mail, in person, and publication on CInMED web pages [12, 13].

Unfortunately, the implemented routine and additional measures to minimize the risk of adverse CV effects of diclofenac did not give the expected result. In the research that covered the period from 2016 to 2020, it was shown that diclofenac was still widely prescribed and that even 15–24% of outpatients who were prescribed diclofenac belong to the risk groups of patients with CVD or diseases that represent a high risk of CVD occurrence [14].

PV guidelines, relevant for RMMs, for the first time emphasize the possibility of using different digital tools in order to improve the effectiveness and impact of RMMs in clinical practice, as an additional method to the existing, traditional ones [2]. Based on the CInMED initiative, for the purpose of better impact of RMMs for diclofenac in clinical practice, an innovative digital tool (IDT) was implemented in the Primary Health Care (PHC) Information System – PHCIS. It was introduced at the level of diclofenac prescribing on October 4, 2021. Before the implementation of IDT in PHCIS, HCPs from PHC institutions, as prescribers of diclofenac, were educated about the functionality and purpose of this new, innovative means of RMMs dissemination. Education was organized by CInMED and included educational material and a practical demonstration of IDT.

RMMs for reducing CV risk of diclofenac remained unchanged, but a new RMM tool was introduced as a means of disseminating RMM messages.

This new digital tool for reducing the risk of adverse CV effects of diclofenac is based on the introduction of relevant safety data of this drug contained in its summary of product characteristics, into the PHCIS. These data appeared as warning messages on physicians' computer screens at the moment of their intention to prescribe diclofenac on an electronic prescription to patients with contraindications or warnings/precautions for its use. Based on the text of those warning messages, physicians were alerted of their adverse CV effects/contraindications and precautions.

Accordingly, it was expected that this IDT would lead to a greater decrease in diclofenac consumption, especially among high-risk groups of patients, and thus better prevention of its adverse CV effects. However, the study we conducted comparing the consumption of diclofenac in those patients one year before (October 4, 2020 – October 4, 2021) and one year after the introduction of the IDT (October 4, 2021 – October 4, 2022) showed that, although in a smaller extent, the drug continued to be prescribed even in patients for whom its use was contraindicated. The study also showed that the drug had been prescribed to patients with CVD/at risk for CVD who had not received it before the introduction of this new RMM (diclofenac-naïve patients) [15].

The aim of this study was to analyze in detail the consumption and health outcomes of diclofenac use in a group of patients who were diclofenac-naïve, one year before IDT implementation, but to whom diclofenac was prescribed in the year following IDT implementation (new diclofenac users).

## Methods

This study was a continuation of previous research, the results of which have already been published, where the method of patient selection was described in detail [15]. Briefly, new diclofenac users were selected after automated screening of all diagnoses in their electronic medical records, classified according to the International Classification of Diseases, 10th revision (ICD-10) [16], to detect those with CVD or diseases that increase the risk of developing CVD (a list of ICD diagnoses relevant for the study is given in the Supplement). These patients also had medical diagnoses that indicated the need for prescribing nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, but had not received the drug in the year prior to the introduction of the IDT (October 4, 2020 – October 4, 2021), which served as a new tool for RMM dissemination.

The patients were monitored for a period of one year after the introduction of the IDT (October 4, 2021 – October 4, 2022). Diclofenac consumption in patients was analyzed using the standard methodology of the World Health Organization based on defined daily doses/1,000 inhabitants/day and Anatomical Therapeutic Chemical classification of medicines [17], as well as through the total number of prescriptions and prescribed drug packages. Analysis was performed regarding the gender and age of the patients. We also analyzed diclofenac prescribing in new diclofenac users in relation to their CV diagnoses. Health outcomes in these patients were evaluated based on changes in their CV diagnoses during the year following the start of diclofenac use.

The Health Insurance Fund of MNE gave permission for using patient medical data from PHCIS (No. 04-2294, from June 4, 2020). The data of the patients were anonymous.

### *Statistical analysis*

The statistical computer program IBM SPSS version 26.0 was used for statistical data processing. The data are presented in the form of absolute and relative values. Significant differences between groups were tested using the Mann-Whitney *U* test and the Kruskal-Wallis test. Results obtained were considered statistically significant at the level of $p < 0.05$.

## Results

Diclofenac consumption in patients with CVD or risks for CVD, who were new diclofenac users in the time period of one year after implementation of the IDT, is given in Table 1. It was shown that the consumption of diclofenac was higher in women compared to men and was the highest in the youngest age group observed (45–64 years) (Table 1).

Specific comorbidities of the patients in this analysis were medical diagnoses (in the Supplement of this article), which are contraindications and precautions/warnings for prescribing diclofenac. Considering contraindications, diclofenac was most commonly prescribed to patients with ischemic heart diseases (i.e., angina pectoris, infarct myocardi), other heart diseases (i.e., cardiomyopathy), and cerebrovascular diseases (i.e., hemorraghia, infarctus cerebri, apoplexia cerebri). Considering the precautions/warnings for its prescribing, diclofenac was most commonly prescribed to patients with hypertension. In most cases, the drug was more often prescribed to female patients (Table 2) and those younger than 75 years (Table 3). Exceptionally, the drug was most frequently prescribed to the oldest patients (≥ 75) who had congestive heart disease and other CVD (Table 3).

**Table 1**

**Consumption of diclofenac in new diclofenac users with CVD/risks for CVD who were prescribed diclofenac, by gender and age**

| Consumption | Group | | | *p** | Age, years | | | *p*** |
|---|---|---|---|---|---|---|---|---|
| | total | male | female | | 45–64 | 65–74 | ≥ 75 | |
| DDD/1,000 inhabitants/day | 2.36 | 0.94 | 1.42 | 0.067 | 1.02 | 0.82 | 0.51 | < 0.001 |
| Number of prescriptions | 20,361 | 8,080 | 12,281 | 0.119 | 9,008 | 7,033 | 4,320 | < 0.001 |
| Number of packages | 24,401 | 9,727 | 14,674 | 0.056 | 10,603 | 8,472 | 5,326 | < 0.001 |

**CVD – cardiovascular diseases; DDD – daily defined dose.**
**All values are given as numbers.**
*** – Mann-Whitney *U* test was used; ** – Kruskal-Wallis test was used.**

**Table 2**

**Number of new diclofenac users with CVD/risk for CVD who were prescribed diclofenac, by gender**

| Conditions | Group | Number of patients |
|---|---|---|
| Contraindications | | |
| congestive heart failure | total | 28 |
| | male | 16 |
| | female | 12 |
| ischemic heart diseases | total | 460 |
| | male | 235 |
| | female | 225 |
| other heart diseases | total | 277 |
| | male | 130 |
| | female | 147 |
| diseases of arteries, small arteries and capillaries | total | 158 |
| | male | 84 |
| | female | 74 |
| cerebrovascular diseases | total | 211 |
| | male | 94 |
| | female | 117 |
| diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs | total | 39 |
| | male | 15 |
| | female | 24 |
| Precautions | | |
| hypertension | total | 5,916 |
| | male | 2,258 |
| | female | 3,658 |
| hyperlipidemia | total | 701 |
| | male | 253 |
| | female | 448 |
| diabetes mellitus | total | 1,510 |
| | male | 743 |
| | female | 767 |

**CVD – cardiovascular diseases.**

Analysis of the number of new diclofenac users with CVD, which contraindicates its use, showed an increase during the year after the drug was introduced into their therapy. The greatest increase was recorded in the number of patients with diseases of arteries, small arteries and capillaries (41.77%), and congestive heart failure (28.57%), then in the number of patients with cerebrovascular diseases (12.80%) and ischemic heart diseases (10.65%), and the least in the number of patients with diseases of the heart of pulmonary origin and diseases of blood vessels of the lungs (5.13%) and other heart diseases (3.25%) (Table 4).

**Table 3**

**Number of new diclofenac users with CVD/risk for CVD who were prescribed diclofenac, by age**

| Conditions | Age, years | Number of patients | Total patients |
|---|---|---|---|
| Contraindications | | | |
| congestive heart failure | 45–64 | 5 | 28 |
| | 65–74 | 7 | |
| | ≥ 75 | 16 | |
| ischemic heart diseases | 45–64 | 196 | 460 |
| | 65–74 | 166 | |
| | ≥ 75 | 98 | |
| other heart diseases | 45–64 | 37 | 277 |
| | 65–74 | 86 | |
| | ≥ 75 | 154 | |
| diseases of arteries, small arteries and capillaries | 45–64 | 64 | 158 |
| | 65–74 | 65 | |
| | ≥ 75 | 29 | |
| cerebrovascular diseases | 45–64 | 81 | 211 |
| | 65–74 | 73 | |
| | ≥ 75 | 57 | |
| diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs | 45–64 | 18 | 39 |
| | 65–74 | 14 | |
| | ≥ 75 | 7 | |
| Precautions | | | |
| hypertension | 45–64 | 2,648 | 5,916 |
| | 65–74 | 2,043 | |
| | ≥ 75 | 1,225 | |
| hyperlipidemia | 45–64 | 442 | 701 |
| | 65–74 | 198 | |
| | ≥ 75 | 61 | |
| diabetes mellitus | 45–64 | 623 | 1,510 |
| | 65–74 | 597 | |
| | ≥ 75 | 290 | |

**CVD – cardiovascular diseases.**

**Table 4**

**Number of new diclofenac users with cardiovascular diseases (for which diclofenac use is contraindicated) before and after introducing the drug into their therapy**

| Diagnoses | Number of patients | | Change in number of patients, (%) |
|---|---|---|---|
| | before using diclofenac | after using diclofenac | |
| Congestive heart failure | 28 | 36 | + 28.57 |
| Ischemic heart diseases | 460 | 509 | + 10.65 |
| Other heart diseases | 277 | 286 | + 3.25 |
| Diseases of arteries, small arteries and capillaries | 158 | 224 | + 41.77 |
| Cerebrovascular diseases | 211 | 238 | + 12.80 |
| Diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs | 39 | 41 | + 5.13 |

## Discussion

The results of the impact study conducted earlier in MNE [15] showed that the introduction of the IDT in the PHCIS, as a new tool for RMM for diclofenac adverse CV effects, made an impact in the cohort of patients with CVD/risk for CVD who were prescribed diclofenac one year before the introduction of the IDT. The prescribing of diclofenac one year after the introduction of the IDT decreased by 38.79%, 37.62%, and 29.85% in patients with other heart diseases (mostly cardiomyopathy), cerebrovascular diseases, and ischemic heart diseases, respectively, which are contraindications for its prescribing. Diclofenac was less prescribed, by 22.86%, 23.61%, and 26.32% in patients with hypertension, hyperlipidemia, and diabetes mellitus, respectively, which are warnings/precautions for prescribing the

drug. It was also shown that, among new diclofenac users, diclofenac was prescribed significantly less often compared with patients who had received the drug before the introduction of the IDT.

In this study, diclofenac consumption in new diclofenac users during the year following the introduction of the IDT in the PHCIS was analyzed in more detail, taking into account gender and age of these patients as well as their specific comorbidities (medical diagnoses/diseases) that were supposed to limit its use. Additionally, the impact of initiating diclofenac therapy on these patients and CV morbidity was assessed as an indicator of its potential adverse CV effects.

Our analysis revealed that diclofenac was more commonly prescribed to women than men, and it was most frequently prescribed in the 45–64 age group, followed by the 65–74 age group, and least frequently in the ≥ 75 age group.

Regarding CVD, which are contraindications for diclofenac use, the drug was the most commonly prescribed in patients with ischemic heart disease (38.15%), other heart disease, mostly cardiomyopathy (21.44%), and cerebrovascular diseases (17.84%). For diseases listed as precautions or warnings, diclofenac was most often prescribed to patients with hypertension (71.00%).

For CVD (contraindications), diclofenac was slightly more frequently prescribed to men than women with diseases of arteries, small arteries and capillaries, ischemic heart disease, and congestive heart failure. In contrast, for other diseases, women received diclofenac more often than men. For conditions listed under precautions/warnings, women had higher prescription rates across all comorbidities (hypertension, hyperlipidemia, and diabetes mellitus). Regarding age groups and CVD (contraindications) for prescribing diclofenac, the drug was most commonly prescribed to patients aged 45–64 with ischemic heart diseases, cerebrovascular diseases, and diseases of the heart of pulmonary origin and diseases of the blood vessels of the lungs, those aged 65–74 who had diseases of arteries, small arteries and capillaries, and to patients aged ≥ 75 who had congestive heart failure and other heart diseases. Concerning all precautions/warnings, the highest prescription rate was in the youngest age group observed (45–64 years).

Other studies have also shown that drugs from the NSAID group are most often prescribed to women and younger people [18–20].

In a non-interventional retrospective cohort study investigating patterns of use for selected NSAIDs, including diclofenac, data were obtained from healthcare databases in the United States of America (MarketScan) and the United Kingdom (Clinical Practice Research Datalink – CPRD). The aim was, among other issues, to describe the demographic characteristics and specific comorbidities of patients who were on NSAID therapy [18, 19].

In both observed populations, the prevalence of use of all selected NSAIDs was higher in women, compared to men, in all age groups. For instance, in the MarketScan population of new diclofenac users, the proportion of women was 55.2% and men 44.8%. In the CPRD population, this ratio was 51.7% for women and 48.3% for men. Regarding the specific type of comorbidity in patients taking diclofenac, in the MarketScan population, the most common comorbidities were circulatory disorders, followed by ischemic heart disease and cerebrovascular diseases.[18]. The results were similar in the CPRD population, as well [19].

Morales et al. [20] analyzed diclofenac prescribing practice in the period after the EU made the prescribing limitations legally binding. Four countries were included: Denmark, the Netherlands, England, and Scotland. Results showed that women were more often prescribed diclofenac than men, and the decrease in prescribing the drug had the strongest impact on the elderly population.

It can be assumed that the greater use of NSAIDs in women is a consequence of the greater prevalence of rheumatic diseases and other painful conditions for which these drugs are indicated in that gender [21–23].

Based on the results of our study, it can be concluded that diclofenac was least prescribed to the oldest patients, which is understandable considering that they represent an extremely vulnerable group. Obviously, even physicians who, despite warnings about the use of diclofenac, prescribed the drug to such patients, keep these facts in mind because they mostly prescribed it to patients in the youngest age group observed. In addition, the results of our study showed that diclofenac was almost seven times more prescribed to patients with diagnoses that require caution in its use than to patients with CVD in whom diclofenac should not be used. This also leads to the conclusion that the introduction of the IDT influenced HCPs to be more careful in prescribing diclofenac to high-risk patient groups.

However, the fact that the drug was prescribed even to patients for whom its use was contraindicated, and that the number of CVD patients increased only one year after its introduction in the treatment of new diclofenac users, is worrying. This suggests that the RMMs undertaken in MNE in the case of diclofenac are still insufficient and should be strengthened. One of the solutions could be the improvement of the existing IDT, as a new tool for RMM dissemination, with data on the use of safer NSAIDs (e.g., naproxen and ibuprofen) in the indications in which diclofenac is most often prescribed. Besides, one cycle of education of HCPs from PHC that preceded the introduction of IDT in PHCIS did not prove efficient in their adherence to the RMM for diclofenac. More intensive work on educating HCPs in PHC about the safe use of diclofenac and other drugs is necessary. Results of a study in Norway showed that an educational program for HCPs in PHC on the rational prescribing of NSAIDs aimed to promote the use of naproxen as the first choice among NSAIDs. The message of the program was that diclofenac should be avoided due to adverse CV effects, which led to a significant decrease in diclofenac prescribing immediately after the education. [24].

The advantage of this study is that it included the entire MNE primary healthcare system, where diclofenac is predominantly used based on its “prescription-only” status. Additionally, this is the first MNE study with the aim of measuring the effectiveness of a digital regulatory intervention introduced at the level of drug prescribing on patient health outcomes.

The limitation of this study is certainly its short duration (one year), although there are data that the effects of undertaken RMMs, as above-mentioned, are most pronounced immediately after their introduction [20, 24]. Besides, this research started immediately after the new IDT was implemented, while changes in healthcare, including changes in HCPs behavior, need time to be understood and implemented in clinical practice. According to the relevant Good Pharmacovigilance Practice guideline, an initial evaluation of RMM should be conducted within 12–24 months after regulatory implementation, to allow the possibility of necessary changes in healthcare. A comprehensive effectiveness evaluation should follow within four years of implementation, which, where applicable, can also inform the assessment for marketing authorization renewal. Therefore, it would be of utmost interest to continue researching this problem. Moreover, diclofenac dispensing data were not used, and consequently, there is a potential underestimation of real diclofenac use, as prescription data were used to measure drug utilization. Additionally, our research was conducted during the coronavirus disease 2019 pandemic, which could also have influenced the results obtained.

## Conclusion

After the introduction of the innovative digital tool as a new measure to reduce the risk of adverse cardiovascular effects of diclofenac into the PHCIS of Montenegro, the drug was still prescribed to patients who had not received it before. Some of these patients had existing cardiovascular diseases, making diclofenac contraindicated. Others could use diclofenac, but with increased caution, because they had diseases that increased the risk of developing cardiovascular diseases. In these patients, diclofenac was most often prescribed to women, people aged 45–64, and those with diagnoses that required caution when using it. The increase in the number of patients with cardiovascular diseases during one year from the beginning of diclofenac use indicates that new and/or improved digital interventions are needed for reducing its adverse cardiovascular effects.

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## SUPPLEMENT – International Classification of Diseases 10th revision (ICD-10) diagnoses of relevance for the study

**ICD-10: I20**
Diagnosis: Angina pectoris
**ICD-10: I21**
Diagnosis: Infarctus myocardii acutus
**ICD-10: I22**
Dijagnosis: 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 et 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