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The Impact of Regulatory Interventions on the Use of Diclofenac

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ABSTRACT

The Impact of Regulatory Interventions Regarding the Use of Diclofenac

In 2013, a safety-related referral procedure concluded that diclofenac was associated with an increased cardiovascular risk and resulted in warnings, contraindications, and changes to the product information were implemented in the European Union Member States. The objective of this study was to evaluate the impact of this regulatory intervention on diclofenac by assessing the usage patterns from 2009 to 2019. This assessment was performed for diclofenac use in general as well as for patient groups with different baseline risks for cardiovascular events. Data from the Clinical Practice Research Database, a primary care database including primary care patients from the United Kingdom was used. Prevalence, incidence, discontinuation of diclofenac use, and switching to alternative analgesics were assessed by using a segmented regression of interrupted time series analysis. A total of 993.835 patients received at least a single diclofenac prescription during the study period. Prevalence fell from 5.2 to 1.5 per 100 persons and incidence fell from 1.7 to 0.4 per 100 persons during the study period, whereas the discontinuation was constant and switching to alternative analgesic had an unusual pattern. The intervention was associated with a significant decline in prevalence (-0.560, P = <.001) and incidence (-0.158, P = <.001) immediately after 2013. However, no significant changes were observed for discontinuation (-1.125, P = .435) and switching to other analgesics (0.363, P = .086). When looking specifically at different risk groups, significant changes were not seen in discontinuation and switching in patients belonging to the high-risk group immediately after the intervention, as would have been expected. In conclusion, the regulatory intervention for diclofenac had a significant impact on decreasing prevalence and incidence on diclofenac use, while there was no significant impact on the discontinuation and switch rate. The intervention had a less impact on patients with high risk for cardiovascular events.

ÁGRIP

Áhrif reglugerðaríhlutunar varðandi notkun diklófenaks

Árið 2013 var niðurstaðan af málskotsaðferð (e. referral procedure) vegna lyfjagátar að diklófenak væri tengt aukinni hættu á hjarta- og æðasjúkdómum og viðvaranir, frábendingar og breytingar á lyfjaupplýsingum, meðal annars á fylgiseðli lyfs, var framkvæmd í aðildarríkjum Evrópasambandsins. Markmið þessarar rannsóknar var að meta áhrif þessarar reglugerðaríhlutunar á notkun diklófenaks, með því að leggja áherslu á notkunarmynstur diklófenaks frá 2009 til 2019. Þetta mat var framkvæmd á almennri notkun diklófenaks og auk þess á sjúklingahópum með mismunandi grunnáhættu á hjarta- og æðasjúkdómum. Notast var við gögn frá Clinical Practice Research Datalink frá Bretlandi, sem er gagnagrunnur og þar á meðal breska sjúklingar í meðferð hjá heimilislæknum. Tíðni á algengi, nýgengi, meðferðarrofi diklófenaks og skipting yfir í önnur verkjalyf var metin með aðgreiningar aðhvarfsgreiningu frá rofinni tímaraðagreiningu. Samtals voru 993.835 sjúklingar sem fengu að minnsta kosti einn diklófenak lyfseðil á rannsóknartímabilinu. Meðan á rannsóknartímabilinu, þá féll algengi úr 5.2 í 1.5 á hverja 100 einstaklinga og nýgengi féll úr 1.7 í 0.4 á hverja 100 einstaklinga, meðan að meðferðarrof var tiltölulega stöðugt og skipti yfir í önnur verkjalyf var með einkennilegt mynstur. Reglugerðaríhlutunin tengdist marktækri lækkun á algengi (-0.560, P = <.001) og nýgengi (-0.158, P = <.001) strax eftir 2013. Hins vegar, það voru engar marktækar útkomur á tíðni meðferðarrof (-1.125, P = .435) né skiptingin yfir í önnur verkjalyf (0.363, P = .086). Þegar mismunandi áhættuhópar voru skoðaðir, þá sáust engar marktækar breytingar strax eftir íhlutunina, sem hefði mátt gera ráð fyrir, á meðferðarrofi og skiptingum hjá sjúklingunum sem tilheyrðu hópnum í mestu áhættu. Niðurstaðan var sú að reglugerðaríhlutun á diklófenaki lækkaði algengi og nýgengi á notkun diklófenaks marktækt, meðan að engin marktæk áhrif sáust á tíðni meðferðarrofs og skiptinga yfir í önnur verkjalyf. Íhlutunina hafði minni áhrif á sjúklingana með mikla áhættu á hjarta- og æðasjúkdómum.

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
COX	Cyclooxygenase
CPRD	Clinical Practice Research Database
DHPC	Direct Healthcare Professional Communication
EC	European Commission
EMA	European Medicine Agency
EU	European Union
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
GP	General Practitioner
GVP	Good Pharmacovigilance Practice
ITS	Interrupted time series
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare Product Regulatory Agency
NCA	National Competent Authority
NSAID	Non-Steroidal Anti-Inflammatory Drug
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
WHO	World Health Organization

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Declaration of Contribution

This study was conducted within an Erasmus+ traineeship agreement between University of Iceland and Utrecht University (The Netherlands). The study was conducted in the Netherlands, at the division Pharmacoepidemiology and Clinical Pharmacology in Utrecht University between November 2019 and April 2020. For this study data from the United Kingdom Clinical Practice Research Database (CPRD) was used, representing primary care patient data. The student, Jeanne, was involved in defining the research question, writing the introduction leading to the aim of the study, creating the study design, programming and performing the statistical analysis using R, designing figures and tables, interpreting the results, writing the discussion, and setting up the references and appendix. Lárus, the administrative supervisor provided feedback on the design and content of the study throughout the project period. Helga, the daily supervisor was involved in creating the study design, helping with interpreting the study results, and providing feedback on the content. Patrick, the data manager at the division, provided feedback on the study design, extracted data from the CPRD database, made the necessary transformations of the data and provided the analytical data matrix.

Declaration for disruption of study plans due to COVID-19

Due to unforeseen circumstances because of the COVID-19 outbreak, the student was forced to abruptly leave the Netherlands on the 14th of March 2020, or earlier than planned. The COVID-19 pandemic affected the functioning of the Division of Pharmacoepidemiology and Clinical Pharmacology substantially during month of March. These disruptions included staff and supporting staff having to shift their work focus to facilitate development and organisation of online educational activities for the >400 pharmacy students enrolled in the Pharmacy Education at Utrecht University. In addition, virtual data environment had to be optimized, strengthened and expanded to allow researchers at the Division to access their data and continue with their research activities remotely. This resulted in a disruption of the study plan for the student, due to temporarily limited access to supervisory resources (daily supervisor and data manager) as well as delayed data delivery. Due to limited flexibility at the home institution regarding deadlines for delivery, with only adding 10 days to account for the COVID-19 disruption, and the delays in Utrecht, the student has had less time than originally planned to analyse the data as well as to construct the discussion of the findings. These circumstances are by no means the fault of the student, which through

hard work and dedication has managed to complete the study as planned with only limited adjustments. Together with the supervisory team it was considered more meaningful and educative to provide the student with experience that aligns with the academic research cycle suitable for master's level, including an analytical phase, instead of opting for the conduct of an extra literature review.

If any further information is needed on the disruptions at Utrecht University as well as the functioning of the students under these stressful circumstances, we will be happy to provide this information.

Best wishes,

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1. INTRODUCTION

1.1 Drug Regulation

Medicines or drugs are one of the most regulated marketed products. Drugs may be lifesaving and improve quality of life, but they can also bear potential risks that can cause harm to patient health. Some drugs may cause adverse drug reactions (ADRs) that lead to hospitalisation or morbidity (Lezotre, 2014). When drugs are marketed, they have already gone through many pre-marketing clinical phases including both pre-clinical and clinical research. These aim to assure the safety and effectiveness of drugs and safeguard that market approval of drugs are only governed by a positive benefit-risk balance. However, albeit this approach it does not assume that all is known at the moment of market approval about the safety of use. Studies show that the pivotal clinical trials are often of inadequate duration to detect adverse reactions of drugs that are rare or connected with long-term use of the drug (Briggs & Levy, 2006). These clinical trials are also often limited in study size and they exclude high-risk populations (Nissen & Wolski, 2010; Psaty & Furberg, 2005; World Health Organization, 2004). Hence, pivotal clinical trials have limited statistical power to detect rare and serious ADRs and their generalisability is limited to a relatively homogenous healthy population (Singh & Loke, 2012; World Health Organization, 2004). Therefore post-marketing monitoring of their safety is needed which can occur by different means, such as by means of monitoring occurrence of ADRs or conducting observational studies where drugs are follow-up in clinical practice (Briggs & Levy, 2006). Post-marketing surveillance of drug safety is also called pharmacovigilance. In most developed countries, national regulatory agencies are responsible for ensuring the safe and efficient use of drugs by patient and by means of drug regulation.

Governments use laws, regulations, and procedures to ensure the safety, efficacy, and quality of drugs. Regulations are defined as a rule established by an agency which interprets the laws to simplify their implementation (Lezotre, 2014). In other words, drug regulation is an organised public activity that aims to correct the behaviour, activities, products or events that are seen as being harmful for public health (Demortain, 2008). They also aim to promote and protect public health and they do so by interacting or communicating with various stakeholders, such as manufacturers, traders, health professionals, researchers, consumers, and governments (Rago & Santoso, 2008). The regulation of drugs includes different functions, such as licensing, inspection of manufacturing facilities and distribution channels, assessment and

registration of a product, ADR monitoring, quality control, control of drug promotion and advertising, and control of clinical drug trials. These functions must be operated in mind of efficient and moderate drug use of patients (Ratanawijitrasin & Wondemagegnehu, 2002). Regulatory systems in the developed world have made large maturation steps in the past decades. This evolution of drug regulations has often been in parallel with the occurrence of major ADRs, sometimes called “disasters”. The modern regulatory system was not recognised until after several unfortunate ADRs catastrophe, which led to the establishment of different regulatory agencies and the development of regulatory systems, pharmacovigilance, and risk minimisation activities to safeguard the public health.

1.1.1 The History of Drug Regulation

The history of drug regulation reflects the growing involvement of governments ensuring that only safe and effective drugs are accessible and only appropriate manufacture and marketing practices are used (Strom, 2019). In the past, the development of drug regulation was often led by unfortunate events of drugs such as the disaster of thalidomide which is considered one of the most important landmarks in the evolution of drug regulation (Rago & Santoso, 2008). Thalidomide is a non-addictive sedative and hypnotic that was marketed in Germany in the late 1950s as an anti-emetic to treat morning sickness in pregnant women and it was believed to be safe for use during pregnancy. Thalidomide became one of the largest selling drugs in the world (Vargesson, 2015) and, its popularity had much to do with the drug’s wide availability as it was sold over the counter and it was relatively inexpensive. In the United States (US), the drug was never approved for marketing, despite the pressure to do so. It was due to concerns with the drug’s lack of safety data, by an FDA officer, Dr Frances Kelsey, that had been assigned to review drug applications in the US. Several reports worldwide began to surface when infants developed birth deficiencies, where limbs and bones were abnormal and other deformities (Rehman, Arfons, & Lazarus, 2011). In 1961, Dr William McBride, from Australia, wrote a short warning letter to *The Lancet*, that he had observed these birth deficiencies in infants from mothers that have taken thalidomide during pregnancy. This was marked as the first published notification of concern due to thalidomide use. However, in reality, it was Dr McBride’s nurse, Sister Sparrow, that first noticed these defects. At first, McBride did not accept her claims but after a while, he did and took all the credits when this effort got recognition. On the other hand, Dr McBride’s letter didn’t show any proof of

scientific research behind his claims, but Dr Widukind Lenz, from Germany, was the one that performed research on thalidomide use and the severe birth defects (Stafford, 2018; Swan, 2018). The aftermath of this disaster led to over 10.000 infants being affected worldwide and increased miscarriage rates, and subsequently, thalidomide was withdrawn from most of the countries where it was approved. However, due to Dr Kelsey's efforts, a major disaster was prevented in the US (Rehman et al., 2011; Vargesson, 2015). The impact of these events has led to changes in the way drugs are tested before getting market approval and led to a positive change in the drug regulation, by remodelling regulatory process, expanding patient informed consent procedures and called for more transparency from drug manufacturers (Rehman et al., 2011). A larger emphasis was placed on the safety of new drugs and more demanding regulations were put in place for manufacturers to ensure the safety, efficacy, and quality of new drugs in development. Assessment during the pre-registration phase was expanded to identify potential hazards in human trials, thus, *in vitro* models were conducted beforehand, and to avoid unnecessary animal experiments (Griffin, 2009; Willemen, 2011). Furthermore, extensive monitoring of drugs during the post-marketing phase was introduced where the safety of drugs was monitored in clinical practice. In case of identification of unknown safety issues, appropriate actions such as distributing safety warnings or drug withdrawal could be taken to try to counteract these issues (Willemen, 2011). These developments of drug regulation have catalysed the creation of proper drug guidelines and the establishment of a marketing authorisation system for drugs in the US and Europe and the arrangement of notification schemes to collect information on adverse drug events that appear in post-authorisation.

1.1.2 Regulatory Agencies

The regulation of drugs is important to prevent ineffective, poor quality, harmful use of drugs that can lead to therapeutic failure, aggravation of the disease, resistance to drugs and in worst-case death. To ensure effective regulation on manufacture, trade, and use of drugs, governments are in need to establish strong national regulatory authorities. The effectiveness of drug regulations demands the implementation of sound medical, scientific and technical knowledge and skills within a legal framework. Several aspects that make regulation effective by national regulatory authorities consist of political commitment to regulation, strong public support of drug regulation, adequate availability of accessible drugs, efficient cooperation between national

regulatory authorities and other government institutions, and qualified pharmaceutical, medical and other professionals (Rago & Santoso, 2008). Regulatory agencies are defined as stringent based on relation to good manufacturing practices (GMP) inspections (World Health Organization, 2016). Stringent regulatory authorities are considered members, observers, or associates of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The largest agencies that currently are qualified as stringent regulatory authorities are the European Medicines Agency (EMA) in Europe, the Food and Drug Administration (FDA) in the US, and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, which are all members of the ICH. Other large agencies include Health Canada in Canada, which is an ICH observer, and the regulatory authority in Australia, which is associated with an ICH member through a legally-binding mutual recognition agreements (Stop TB Partnership, 2009; World Health Organization, 2017). These regulatory agencies have the goal to ensure the safety and efficacy of drugs, but they differ in several areas. For example, the FDA is governed by a centralised process within the US, while the EMA is a decentralised agency, governed by representatives from 28 different European countries and works closely with national competent authorities (NCAs) of the 28 Member States in the European Union (EU) that collaboratively participate in drug authorisation (Van Norman, 2016).

The FDA is responsible for all drug authorisation in the US and its modern regulatory function was developed by reforming the Pure Food and Drugs act in 1906, that state marketed drugs must be pure and free of any possible contamination (The Food and Drug Administration, 2018a). The FDA commits to promoting public health by stimulating timely innovations that results in more effective, safer, and more affordable drugs. They also aim to protect public health by ensuring the safety and efficacy of human and veterinary drugs, biological products, and medical devices. This also includes ensuring the safety of food supply, cosmetics, and products that emit radiation (The Food and Drug Administration, 2018b). The EMA was established in 1995 and has worked across the EU to protect public and animal health through the evaluation and supervision of drugs. The EMA aims to promote public health by ensuring the efficacy and safety of drugs across Europe and promoting research and innovation in drug development (European Medicines Agency, n.d.-d). The EMA does not manage all drug authorisation in Europe like how the FDA does in the US. The EMA is a networking organisation that brings together scientific experts from all over

Europe. The agency forms a partnership, known as the European medicines regulatory network, with the NCAs in the EU Member States (European Medicines Agency, n.d.-e), which has the responsibility for validating nationally authorised products on their territory (Santoro, Genov, Spooner, Raine, & Arlett, 2017). The European medicines regulatory network also works together with the European Commission (EC), whose role is to make binding decisions based on the scientific recommendations given by the EMA. The EMA and the EU Member States cooperate and share knowledge on new drug assessment and drug safety, and they depend on each other for information of drug regulation. The EMA also prepares guidelines with the assistance of experts from its scientific committees and these guidelines are to safeguard that drugs are developed consistently and at its highest quality (European Medicines Agency, 2016). In general, both the FDA and the EMA have the responsibility to monitor the safety profile of drugs and observe if there are any changes in the safety profile of the post-marketing environment through a variety of mechanisms.

1.2 Post-marketing Safety Monitoring

Once a drug has been authorised and enters the market, it leaves the secure and protected scientific environment of clinical trials and is free for prescribing by health care professionals and consumption by the general population (World Health Organization, 2004). During this post-marketing phase, information about effectiveness and safety of drugs is collected throughout the drug lifecycle. Some ADRs are only detectable after the drug has been marketed, especially unforeseen, rare and series adverse effects that are unknown during clinical trials. Furthermore, drugs can also be unnecessarily prescribed and taken for a longer period and/or in higher doses than recommended or used in patients where they are contraindicated. Having a well-organised mechanism in place for evaluating and monitoring the safety of authorised drugs is essential to prevent and reduce the harm of adverse events. It also increases the chances of a more reasonable regulatory decision will be made for drugs and improves public health (Demortain, 2008).

1.2.1 Drug Monitoring in the EU

When a drug has been authorised to market in the EU, the drug's safety is constantly monitored by the EMA and the EU Member States (Figure 1). This allows them to take timely action when new information on the drug's safety indicates that it is no longer

safe or effective as it was previously thought (European Medicines Agency, n.d.-a). The EMA relies on seven scientific committees that evaluate drugs from the early stages of their development, through marketing authorisation, to monitoring safety once they are on the market (European Medicines Agency, n.d.-m). The EMA relies on these committees when it comes to scientific assessments, such as the Committee for Medicinal Products for Human Use (CHMP), which is responsible for human drugs. The CHMP plays a critical role when drugs are authorised in the EU and they also consider recommendations from the Pharmacovigilance Risk Assessment Committee (PRAC) on the safety of drugs on the market (European Medicines Agency, n.d.-b; Kaeding, Schmälter, & Klika, 2017). The PRAC was established in 2012 when the new pharmacovigilance legislation took place, and its role is to safeguard the public health and strengthen referral procedures (European Medicines Agency, n.d.-f). The PRAC is responsible for evaluating and monitoring the safety of drugs and is essential in operating the EU pharmacovigilance system. Also, it has the responsibility for assessing all the risk management plans (RMPs) for drugs on the EU market, which involves in detecting, assessing, minimising, and communicating relating to the risk of ADRs while taking into account the therapeutic effect of the drug (Figure 1). Thus, guaranteeing that drugs authorised for the EU market are ideally used by maximising their benefits and minimising their risks. Furthermore, the role of the PRAC is to design and evaluate post-authorisation safety studies and pharmacovigilance audit (European Medicines Agency, n.d.-i). The PRAC is also responsible for sending out recommendations to the CHMP relating to pharmacovigilance, risk management systems and their effectiveness (Sharrar & Dieck, 2013), and when necessary, the CHMP will forward the recommendations to the EC regarding the centralised authorisation procedure, if needing to change the drug's marketing authorisation or its suspension or withdrawal from the market (European Medicines Agency, n.d.-b; Kaeding et al., 2017). This will make sure that the EMA and the EU Member States can react quickly once a safety issue occurs, thus they can take necessary actions if needed (European Medicines Agency, n.d.-a). Data from clinical practice, which are available in various electronic health records databases, can be used to assess safety issues as well as support recommendations by the PRAC (European Medicines Agency, n.d.-j). The EMA's EudraVigilance database is an information system of collected reported ADRs. If adverse events of drugs occur in the EU, it is legally required that it must be included in the database by the Member States and marketing authorisation holders (MAHs) (Kaeding et al., 2017).

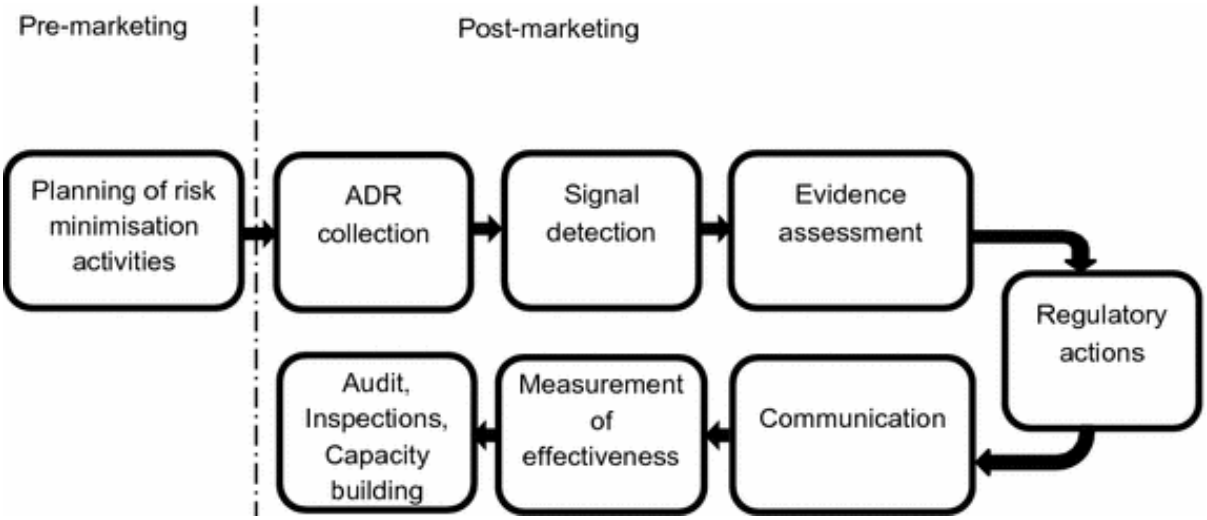

Figure 1. The EU pharmacovigilance system continuous risk minimisation activities planning from pre- to post-marketing (Santoro et al., 2017).

It is important to monitor the safety of all drugs during their use in clinical practice, that way there is good and useful evidence available for continuous assessment of a drug's benefit-risk profile. The establishment of pharmacovigilance has become a key pillar of drug regulation and has led to strengthen patient safety in drug use and support health programmes by providing dependable and solid information for the effective assessment of the benefit-risk profile of drugs (World Health Organization, 2006). Furthermore, the EU law requires the operation of a pharmacovigilance system from MAHs, NCAs and the EMA (European Medicines Agency, n.d.-j).

1.2.2 Pharmacovigilance

Pharmacovigilance is defined as the science and activities relating to detecting, assessing, understanding, and preventing ADRs or any other issues relating to drugs (World Health Organization, 2002). It is a system used by an organisation and its role is to carry out its legal tasks and responsibilities connected to pharmacovigilance. Pharmacovigilance is designed to monitor the safety of authorised drugs and detect if there will be any changes in their benefit-risk balance, and to further reduce the burden of ADRs (European Medicines Agency, 2012b). For pharmacovigilance to be effective, it requires the close cooperation of various actors, including politicians, health administrators, policy officials, healthcare professionals, the pharmaceutical industry, and the general public. Particularly, healthcare professionals have an important role in reporting adverse events of drugs for pharmacovigilance (Kaeding et al., 2017). Pharmacovigilance encourages the rational and safe use of drugs and can help to

educate and inform patients about the effectiveness and risks of drugs (World Health Organization, 2006).

1.2.2.1 The EU Pharmacovigilance Legislation

The EU pharmacovigilance system is based on a regulatory network consisted of the NCAs, the EMA, the EC and a legal framework that forms roles and responsibilities, principles and procedures (Santoro et al., 2017). Even though the EU pharmaceuticals regulation dates back to the 1960s, the risk assessment of authorised drugs after marketing was neglected until the 1990s, then the EU began to put in place legislations dedicated to pharmacovigilance (Kaeding et al., 2017). However, due to the frequency reports of adverse events, in 2005, the EC began a review of the European system of safety monitoring. This resulted in the adoption of new Directive 2010/84/EU and Regulation (EU) No 1235/2012 in 2010, which brought significant changes in the safety monitoring of drugs across the EU. In July 2012 a new pharmacovigilance legislation was established to further strengthen observation of adverse events, due to some harmful and unintended response to drugs that has caused increased death rates per year in the EU. The new pharmacovigilance legislation aims to decrease the number of ADRs in the EU. This entails collection of better data on the safety of drugs, better assessment of the issues relating to drugs' safety, effective regulatory action to deliver safe and effective drug use, empowerment of patients through participation and reporting, and increase levels of transparency and communication. Furthermore, the pharmacovigilance legislation affects the marketing authorisation applicants and holders, by giving a clearer view of their role and responsibilities, minimising duplication of effort, free up resources by rationalising and simplifying reporting on safety issues, and build a clear legal framework for monitoring post-authorisation (European Medicines Agency, n.d.-g).

The pharmacovigilance legislation introduced activities that fall into four main areas, which is drug information collection, better analysing and understanding of data and information, regulatory action to protect public health, and the communication with stakeholders. To collect key information on drugs, the pharmacovigilance legislation further strengthen process concerning RMPs, established a format and content for periodic safety update reports (PSURs), and further strengthen the legal basis for requesting post-authorisation safety studies (PASSs) and post-authorisation efficacy studies (PAESs). Furthermore, the legislation strengthened the process for detecting safety signals for drugs by enhancing EudraVigilance, and additional monitoring of

drugs, thus, to better analyse and understand data and information of drugs. The legislation also further strengthened the communication with stakeholders by publishing agendas and minutes on the EMA website of all committees, coordinating announcements on the safety of drugs, and organise public hearings for safety-related referral procedures (European Medicines Agency, n.d.-f). To further understand the concept of pharmacovigilance, and facilitate the performance of pharmacovigilance, it was important to develop proper guidelines and standards that described the practical details of the intended information flow (Meyboom, Egberts, Gribnau, & Hekster, 1999).

1.2.2.2 Good Pharmacovigilance Practice

The guideline on Good Pharmacovigilance Practice (GVP) was a key deliverable of the new pharmacovigilance legislation. GVP was developed to strengthen the management of pharmacovigilance in the EU and act as a guide to support the implementation of legislation (Santoro et al., 2017). GVP is a set of measures made to assist the pharmacovigilance performance in the EU. It applies to MAHs, the EMA, and medicines regulatory authorities in the EU Member States. The guideline on the GVP is divided into two different types of chapters, modules on pharmacovigilance processes and product- or population-specific considerations. The GVP includes 16 modules (I to XVI), and each module presents one major pharmacovigilance process. The GVP also provides a guideline for specific product types, such as vaccines and biological drug products, and specific population in which drugs are used, such as the paediatric population (European Medicines Agency, n.d.-c). When a report of a suspected adverse event of a drug occurs, it is important that these reports are collected and managed correctly so that it is possible to analyse the suspected ADRs and support the safe and effective use of drugs.

1.2.2.3 EudraVigilance

When monitoring the safety profile of drugs, it can be done by passive surveillance or voluntary reports, which is the collection of spontaneously reported ADRs from healthcare professionals and consumers (Sharrar & Dieck, 2013). Spontaneous reporting is a system of reported ADRs submitted by health professionals and pharmaceutical companies, and it has been demonstrated to be the main source of information for pharmacovigilance and drug regulation (Meyboom et al., 1999). Other means to monitor the safety of drugs in the post-marketing phase is through active surveillance or a proactive search of adverse events. Active surveillance often includes

use of large databases of healthcare records where association between drug use and ADRs are assessed (Sharrar & Dieck, 2013). In the EU, the term post-marketing activities is used, which gives regulators a wider range of authority over a broader number of factors (Pitts, Louet, Moride, & Conti, 2016). The EMA uses the database, EudraVigilance, which was established in 2001, a passive, voluntary reporting system and computerised information database. This database is designed to monitor the post-marketing safety profile of drugs and it collects data on ADRs from manufacturers, healthcare professionals, consumers, lawyers, and others. The database is beneficial in the sense that it collects data on ADRs that are experienced by patients who are normally not included in the clinical trials and collects data about rare adverse events of drugs, and it also identifies issues of concern to the healthcare professionals using the drug (Sharrar & Dieck, 2013). In 2017, the database EudraVigilance was revised and adopted a new access policy. The policy indicated that the EMA will provide increased access to reports on suspected ADRs that are marketed in the EU, while also ensuring the protection of personal data. The EMA and the World Health Organization (WHO) agreed to allow the daily transfer of data on suspected ADRs from EudraVigilane to the WHO Global Individual Case Safety Report database, Vigibase. This will lead to a better knowledge of the safety of drugs globally and help to better promote the safe use of drugs for the benefit of patients worldwide (European Medicines Agency, 2015; Uppsala Monitoring Centre, n.d.). Currently, Vigibase includes over 20 million reports of suspected adverse events and it is the largest database of its kind in the world (Uppsala Monitoring Centre, n.d.). Although EudraVigilance is important for safety monitoring it does not allow for determining incidence rates of adverse events experiences as knowledge of the denominator, i.e., number of patients taking the drug, is not available. Further, not all adverse events that occur are reported to EudraVigilance. Moreover, it lacks data on the comparable patient populations with similar underlying conditions and has not been treated by the drug, and it is also poor at detecting adverse events that have a long latency period (Sharrar & Dieck, 2013). It would not matter creating the best database if it is lacking in reports of adverse events. Hence, it is important that suspected adverse events must be reported to get a representative picture of reality on ADRs.

The involvement in reporting adverse events from all sectors of the healthcare system, especially healthcare professionals and patients, is essential. Furthermore, only patients taking the medication know the actual benefit and harm of the drug, so their participants in the reporting of adverse events will increase the efficiency of the

pharmacovigilance system (World Health Organization, 2002). Nevertheless, the EMA monitors the database and determines if there are changes or new risks associated with drug use, and when the safety signals from the database are identified, they have to be evaluated and characterised by pharmaceutical companies (Sharrar & Dieck, 2013).

1.2.2.4 Risk Management Plan and Safety Update Reports

Pharmacovigilance has shifted from being a reactive system responding to emerging risks, to a planned, preventive and risk proportionate approach. Pharmacovigilance activities are currently included in the life cycle of a product and should be clearly defined for a drug prior to authorisation. When applying for a drug's marketing authorisation, pharmaceutical companies are obligated by legislation to submit an RMP to regulatory authorities, to further minimise the risks associated with the post-marketing phase of a drug. The RMP aims to reduce concerns regarding a drug's safety profile at different points in its life cycle and to appropriately plan risk management activities. Whenever a request of a regulatory authority or the risk-management system is modified, a drug's RMP should be updated throughout the drug's lifetime (Santoro et al., 2017). Furthermore, pharmaceutical companies are required, by the EMA, to prepare routine safety update reports on all new drugs describing adverse events that have been reported during a certain period. So that it is possible to determine whether there have been any changes since the last evaluation of the drug's safety profile (Sharrar & Dieck, 2013). Safety update reports could be such as PASSs and PSURs, which MAHs are obliged to carry out (European Medicines Agency, n.d.-h, n.d.-k). PASSs can either be clinical trials or non-interventional studies that are carried out when there is a need to obtain further information on the safety of drugs that have been authorised or to measure the effectiveness of risk-management measures. The purpose of a PASS is to evaluate the benefit-risk and safety profile of a drug and support decision-making regarding regulatory (European Medicines Agency, n.d.-k). However, a PSUR is a report or pharmacovigilance document that describes the safety experience with a drug at a defined time after the drug is authorised. The purpose of the PSUR is to introduce a comprehensive and critical analysis of a drug's benefit-risk balance while also taking into account new or emerging information of a drug's safety. An assessment of PSUR can determine if requirements for further investigations on a specific issue is needed,

or if an action to protect public health is necessary (European Medicines Agency, n.d.-h).

Overall, pharmacovigilance activities are performed by several components, such as regulators and pharmaceutical companies, along with risk management planning, collecting and managing reports on suspected adverse reactions, signal detection and management, and post-authorisation studies that give new information about the drugs that are marketed (Pharmacovigilance Risk Assessment Committee, 2017). Thus, these pharmacovigilance activities have the purpose to facilitate decision-making of the safety profile of drugs and take regulatory action when it is necessary.

1.2.3 Regulatory Interventions

Pharmacovigilance activities are often aimed at facilitating increase in knowledge and improvement in behaviour of individuals, including consumers, patients, healthcare professionals, and caregivers, and in healthcare practice, to further protect patients and promote public health (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, 2019a). When a safety issue has been reported and evaluated, which results in a change in the benefit-risk balance of the drug use in clinical practice, the regulatory authorities have different means to safeguard this balance and can do so by applying regulatory interventions. These can include informing prescribers and/or patients of the new safety information or the new effectiveness of the drug, to counsel them to change their behaviour to prevent or minimise ADRs, to restrict the drug's accessibility when the benefit-risk profile is no longer safe for a specific group of patients, or a combination of these actions (Pharmacovigilance Risk Assessment Committee, 2017). A regulatory intervention or a referral procedure means that a drug is 'referred' to the EMA, and the PRAC is called for to assess the drug and construct recommendations on the safety or benefit-risk issue at stake on behalf of the EU (Santoro et al., 2017). Appropriate regulatory interventions are carried out to minimise the risk of drugs, such as labelling change, restriction, contraindication or withdrawal of the product (Goedecke, Morales, Pacurariu, & Kurz, 2018). As mentioned before, the PRAC evaluates particular safety signals from the EudraVigilance database and safety update reports and makes recommendations that are considered by the CHMP before they become legally binding and necessary regulatory actions can be carried out.

1.2.3.1 Examples of the PRAC recommendations

Recommendation from the PRAC may include the need for further additional information or the need for regulatory action. Some drugs may be subjected to additional monitoring, because of their changed safety profile, and a new symbol, the "black triangle", can be added on the drug's package to indicate this. For instance, the drug Tysabri (natalizumab), which is used to treat multiple sclerosis (MS) is one of those drugs that additional monitoring applies to. The PRAC advised additional monitoring for Tysabri because reports of serious adverse events represented by progressive multifocal leukoencephalopathy (PML) occurred. However, the benefit of the drug is considered to outweigh the risks related to Tysabri treatment, so the drug was not taken of the market but the black triangle symbol was added on the package and the drug is under additional monitoring (European Medicines Agency, 2019b). The black triangle symbol aims to emphasis for patients the importance of reporting suspected adverse events of drugs and thus improving their safety (Kaeding et al., 2017). When there is a need for regulatory action, it may be an update of the product's information (Summary of Product Characteristics (SmPC) and package leaflet), RMP through a variation, launch a referral procedure or urgent safety restrictions (European Medicines Agency, n.d.-l). The PRAC may recommend an update on a drug's information to give awareness on the ADRs, such as include a specific ADR, contraindications, new safety warnings or a requirement on performing patient monitoring tests (Santoro et al., 2017). For instance, the PRAC recommended that the use of Xofigo, a prostate cancer radiopharmaceutical drug, with the cancer drug Zytiga (abiraterone acetate) and prednisone/prednisolone, should be contraindicated. Because preliminary clinical trials showed that there's was an increased risk of death and fractures with this combination (European Medicines Agency, 2018c). Also, another example is that the PRAC recommended updating the measures for pregnancy prevention and included a warning on the possible neuropsychiatric disorders risk during the use of drugs containing retinoid, due to harmful effects on the unborn child and thus the drug must not be used during pregnancy (European Medicines Agency, 2018b). The PRAC may advice other measures, such as controlling the number of dosage units, restricting its administration or modifying the legal status of the drug (Santoro et al., 2017). For instance, the PRAC recommended that the use of fluoroquinolone and quinolone antibiotics should be restricted, due to a disabling and potentially long-lasting but very rare side effects. Their advice is that they should only be used when an antibiotic is essential in treating infections and other antibiotics

cannot be used for the specific clinical situation (European Medicines Agency, 2018a). The PRAC may also recommend specific communication measures, such as a Direct Healthcare Professional Communication (DHPC). However, in the most serious cases, the PRAC may recommend the suspension or withdrawal of a drug from the market when the benefit-risk balance is no longer positive, and warnings and restrictions are not sufficient enough (Santoro et al., 2017). For instance, the PRAC recommended the withdrawal of marketing authorisation for cough drugs containing fenspiride, because of the confirmed risk that the drug could cause heart rhythm problems (European Medicines Agency, 2019a). However, it is essential to monitor the impact of the regulatory interventions, so that regulators can determine if the risk minimisation measures were effective or not and if there is a need for improvement.

1.2.3.2 The PRAC Strategy

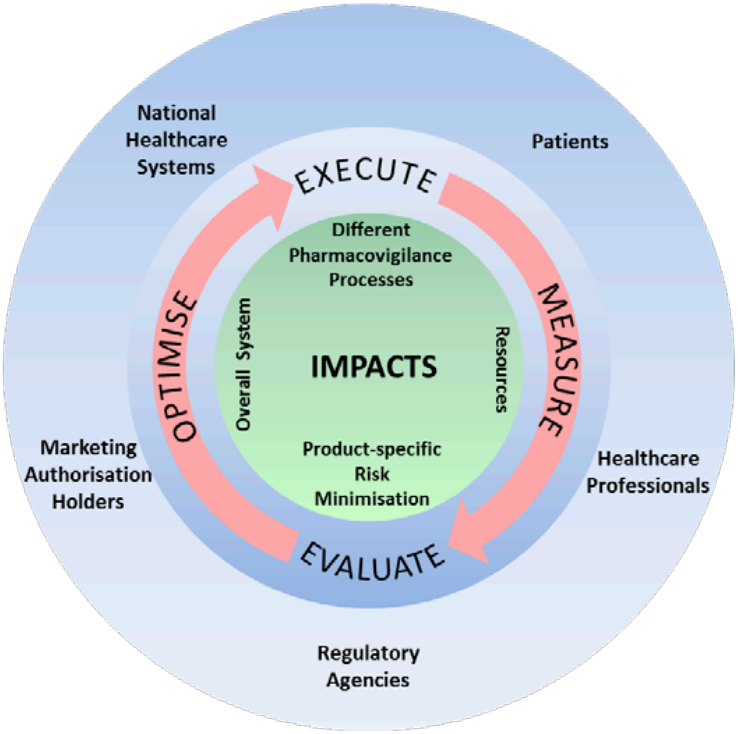

Figure 2. Conceptual approach to the PRAC strategy on measuring the impact of pharmacovigilance activities (Pharmacovigilance Risk Assessment Committee, 2017).

In January 2016, the PRAC implemented a strategy to measure the impact of pharmacovigilance activities and aims to be a long-term approach. The pharmacovigilance strategy provides information, knowledge, and data on regulatory actions and on other enabling factors. This summaries the conceptual approach, priorities, stakeholders, principles, information, data-collection planning, knowledge on translating activities into measurable health outcomes, and potentially unintended

effects in healthcare (Pharmacovigilance Risk Assessment Committee, 2017). The reduction of harmful ADRs is an example of measurable health outcomes while switching patterns and conditions left untreated could be an example of unintended consequences. The strategy emphasises on assessing patient-relevant health outcomes of major regulatory interventions and it focuses on four main areas. These areas are the effectiveness of risk minimisation activities, the effectiveness of pharmacovigilance processes, enablers of effective pharmacovigilance and stakeholder engagement, and advanced methodologies on impact research (Figure 2). Therefore, these can support product monitoring, support improvements, and enhance the performance of pharmacovigilance activities (Pharmacovigilance Risk Assessment Committee, 2017). Measuring the impact of regulatory interventions is still challenging and if measurements are insufficiently implemented or fail to accomplish their intended objectives, there will remain the possibility of unintended effects of the regulatory interventions (Goedecke et al., 2018).

1.3 Measuring the Impact of Regulatory Interventions – Diclofenac as a Case Study

1.3.1 Diclofenac

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) and it possesses analgesic, anti-inflammatory, and antipyretic properties (Gan, 2010). It is one of the most widely prescribed NSAIDs since being authorised to market and one of the largest selling drugs in the world (Gan, 2010; McGettigan & Henry, 2013). In 1974, diclofenac was first introduced in Japan and its use was indicated for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and mild to moderate pain. Diclofenac is authorised in the EU in several different formulations, such as oral, suppository, intravenous, intramuscular, transdermal patch, or gel formulations (European Medicines Agency, 2013; Gan, 2010). Diclofenac ranks low in terms of risk for gastrointestinal complications and also does not interfere with the antiplatelet effects of low-dose aspirin compare to other NSAIDs, for example, ibuprofen or naproxen (Altman, Bosch, Brune, Patrignani, & Young, 2015; Cannon et al., 2006). However, there are several potential complications with diclofenac treatment, and it has much to do with its mechanism of action (Gan, 2010).

Diclofenac can inhibit cyclooxygenase (COX) activity, such as COX-1 and COX-2 enzymes, although with higher selectivity for COX-2 than for COX-1. When the drug

inhibits these enzymes, it reduces the production of prostaglandins, prostacyclin, and thromboxane, which is believed to be the main mechanism of action of the drug's potent analgesic and anti-inflammatory properties (Altman et al., 2015). Prostaglandins are associated with causing pain and inflammation at the site of injury or tissue damage in the body, and by reducing their production, it will reduce pain and inflammation (European Medicines Agency, 2013). However, prostaglandins normally protect the gastric mucosa from injury, and if their production is reduced, it will increase the risk of gastrointestinal adverse effects, which is mediated mostly by the inhibition of COX-1 enzyme. Diclofenac is normally associated with relatively low levels of gastrointestinal adverse effects compared to other NSAIDs, because of its selectivity for COX-2 enzyme but the risk is usually dose-related (Altman et al., 2015; van Walsem et al., 2015). Therefore, the intended use for drugs that selectively inhibit the COX-2 enzyme was to limit the gastrointestinal adverse effects, however, at the same time, the drugs were associated with an increase in cardiovascular risk (Gan, 2010). The suppressing of prostacyclin is most likely the explanation for the increased cardiovascular risk. Prostacyclin restrains mediators of platelet activation, hypertension, and atherogenesis. Therefore, when choosing an anti-inflammatory agent in clinical practice, healthcare professionals need to take into consideration if the patient is at a higher risk of attaining cardiovascular and gastrointestinal events, including congestive heart failure, and other renovascular effects, gastrointestinal tolerability, and efficacy (Cannon et al., 2006). Diclofenac and other NSAIDs are one of the first choices when treating pain related to chronic conditions and the use of this drug class is likely to increase within the aging population, which increases the safety concerns of the drug when some patients are exposed to it (Gan, 2010). Several meta-analyses of randomised clinical trials and observational studies have shown that diclofenac is associated with an increased risk of cardiovascular disease (Cannon et al., 2006; Coxib and traditional NSAID Trialists' (CNT) Collaboration, 2013).

1.3.2 Regulatory Intervention of Diclofenac

In October 2012, a request came from the drug regulatory agency from the United Kingdom (UK), the Medicines and Healthcare product Regulatory Agency (MHRA), for a review of diclofenac's safety profile. The MHRA identified an increased risk of cardiovascular adverse effects with diclofenac when compared with other NSAIDs. The drug's safety profile was reviewed by the PRAC, which concluded that systematic cardiovascular risks of diclofenac were similar to selective COX-2 inhibitors. The PRAC

conclusion came from data available from several randomised clinical trials, observational studies and individual epidemiological studies. This resulted in a regulatory intervention on 28 June 2013 where new safety advice for diclofenac-containing medicinal products were endorsed that aimed at minimising the cardiovascular risk of diclofenac use. The PRAC considered that diclofenac is effective in their approved indications, but recommended that systemic formulations of diclofenac, such as oral, suppository, or injections, should have the same precautions as selective COX-2 inhibitors (European Medicines Agency, 2013). Similar as selective COX-2 inhibitors, diclofenac is associated with small increased risk of arterial thromboembolic events, such as blood clots in the arteries. However, some are at a higher risk than others, particularly patients with underlying cardiovascular risk factors. Diclofenac use has in some cases led to a heart attack or stroke, especially if the drug is used at a high dose and for a long time (Coxib and traditional NSAID Trialists' (CNT) Collaboration, 2013; European Medicines Agency, 2013). As with any other NSAIDs, the cardiovascular risk of diclofenac depends on the patient's underlying risk factors, such as cholesterol levels, high blood pressure, and any other heart or circulatory conditions. The product information of diclofenac was adjusted and now indicates that the lowest dose for the shortest period possible is preferable when using diclofenac (European Medicines Agency, 2013).

Diclofenac-containing medicinal products are all authorised nationally, therefore recommendations from the PRAC were forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which is a representative body of the EU Member States. The CMDh is responsible for ensuring harmonised safety standards for drug authorised via national procedures across the EU. The CMDh adopted a final position which was confirmed by the EC resulting in a legally binding decision throughout the EU. Communications on these measures for diclofenac are intended to guide healthcare professionals on the use of diclofenac in clinical practice (Arlett et al., 2014; European Medicines Agency, 2013). When the regulatory intervention was legally implemented, this resulted in warnings, contraindications, and other changes to the product information, also a DHPC was implemented in the EU Member States to manage the cardiovascular risks for systemic diclofenac products. Diclofenac use is currently contraindicated in patients with established congestive heart failure (NYHA II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease. In addition, if patients have certain risk factors, such as hypertension, hyperlipidaemia, diabetes mellitus, and smoking, should

only use diclofenac after careful consideration. The DHPC provided an updated prescribing advice for diclofenac on the risk of cardiovascular adverse effects, including new contraindications and warnings (European Medicines Agency, 2013). The regulatory intervention for diclofenac is important to ensure the safe use of the drug and prevent harmful adverse events. However, regulatory interventions are challenging, and it is unknown if the implementation of the regulatory intervention for diclofenac was effective. Therefore, it is important to measure the impact of the regulatory intervention for diclofenac and see if resulted in its intended effects, while taking into account potential unintended consequences.

2. AIM

The aim of the study was to evaluate the impact of regulatory interventions taken for diclofenac, a non-steroidal anti-inflammatory drug (NSAID), on the use of diclofenac in clinical practice. This was achieved by assessing usage patterns of diclofenac-containing medicinal products before and after the regulatory intervention was implemented. Impact of the regulatory intervention was also assessed for patient groups with different baseline risks for cardiovascular to give better insight into the effect in a patient population of high risk.

3. METHODS

3.1 Data Sources

Data from the UK Clinical Practice Research Database (CPRD) was used for this study. The CPRD is one of the largest research databases in the UK and it includes primary care data collected from routine general practitioners (GPs). The primary care data are linked to data from other healthcare settings to provide longitudinal and representative UK population to health datasets. Over 98% of the UK population is registered with a primary care GP and under the involvement of the National Health Service (NHS) (Ghosh et al., 2019). To date, the CPRD encompasses 45 million patients, including 13 million currently registered patients (CPRD, 2020). The CPRD has been collecting data in primary care since 1987 and covers approximately 15% of the UK population. The CPRD includes data on demographics, symptoms, diagnoses, prescriptions, clinical signs, immunisations, referrals, behavioural factors, and tests, such as clinical tests, blood tests, laboratory tests or other kind. Basic demographics consist of age, gender, comorbidities and other clinical conditions such as pregnancy (Ghosh et al., 2019). Diagnosis and prescription codes are derived from the GP system and recorded as Read codes (for medical history), Gemscript codes (for drug therapy) and BNF codes (for drug therapy).

3.2 Study Population

The study period was defined from 1 January 2009 until 31 December 2019. Adult (≥18 years) individuals were included if they received a prescription for a diclofenac-containing medicinal product (Anatomical Therapeutic Chemical (ATC) codes [M01AB05] or [M01AB55]) during the study period. The index date for each patient in the cohort was the first date of a diclofenac prescription during the study period and the index date was considered as the date for baseline measurement for each patient. Patients were eligible if they had 12 months of registration at the GP practice before the index date. The patients were followed up until the end of the study period, move outside the catchment area, death or outcome of interest. The design of the study including exclusion criteria, inclusion criteria and follow up is graphically visualised in Figure 3 (Schneeweiss et al., 2019).

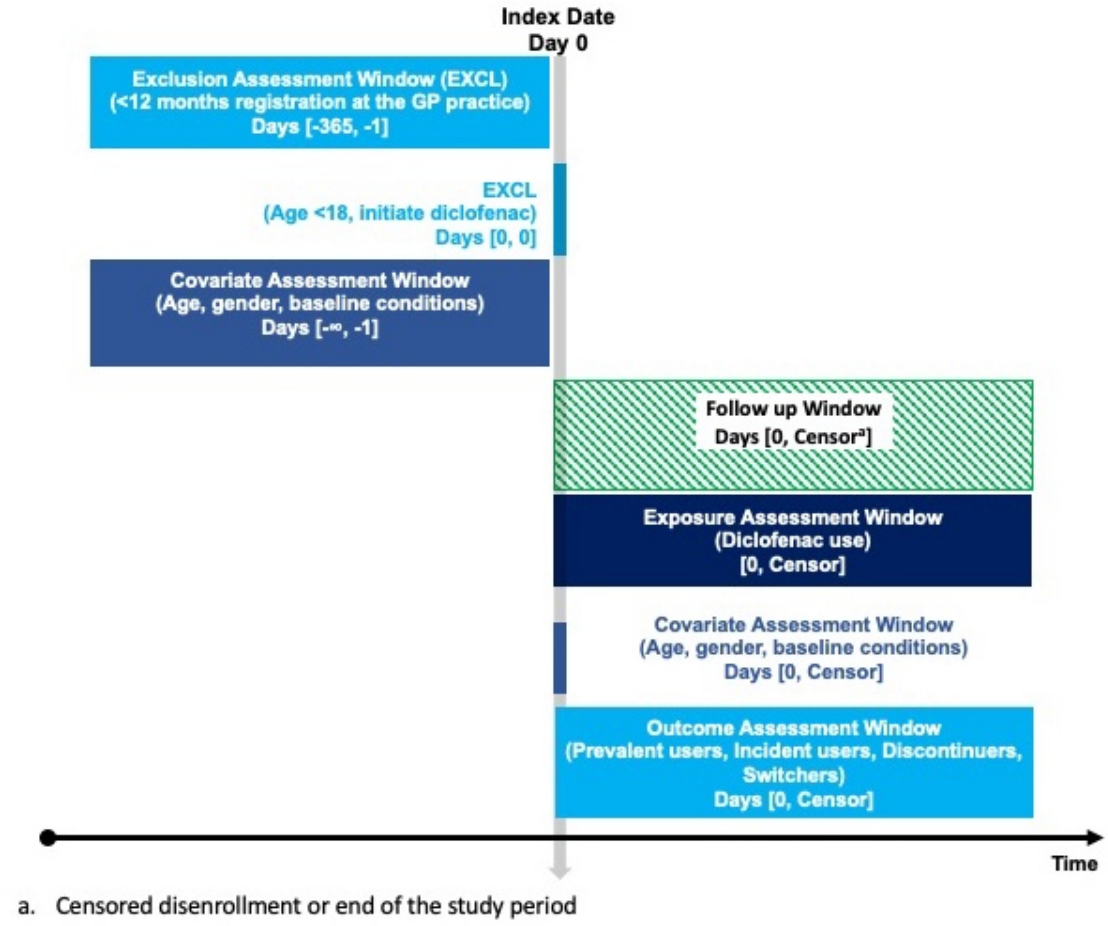

Figure 3. Graphical representation of the study design, including study population and the follow-up after the index date (Schneeweiss et al., 2019).

3.3 Exposure

Diclofenac use was constructed into drug treatment episodes (Gardarsdottir, Souverein, Egberts, & Heerdink, 2010). The first exposure episode started at the first diclofenac prescription within the study period. For each prescription, the duration of diclofenac use for that individual prescription was estimated based on the number of tablets prescribed and the dosing regimen, resulting in days dispensed. However, as patients might collect subsequent drug dispensing earlier (overlap) or later (gap) than the estimated date for the last dose consumed, a gap of 90 days was allowed to elapse between the theoretical end date and the prescribing date of a subsequent diclofenac prescription. When the collection of a subsequent diclofenac prescription was before the theoretical end date of the previous prescription, then the number of days overlapping was added to the theoretical end date of the subsequent diclofenac prescription. However, if the subsequent prescription within the same treatment episode included an alternative analgesic drug (see Table A2 in Appendix A), then it was regarded as the patient had switched drug therapy and discontinued diclofenac

use. A sensitivity analysis was performed using a gap length of 30 days instead of 90 days.

3.4 Outcome

3.4.1 Usage Patterns of Diclofenac-containing Medicinal Products

The objective of this study was to evaluate if there were any immediate changes in the overall baseline prescribing patterns for diclofenac as a consequence of the regulatory intervention. The risk of cardiovascular events when using diclofenac at a high dose and for a long period, resulted in the implementation of regulatory intervention on 28 June 2013. This resulted in changes to the SmPC sections on contraindication, warnings, precautions, and changes of diclofenac's package information. Evaluating changes in prescribing practices for diclofenac were assessed before and after the regulatory intervention will give a better picture if the intervention was effective or not. Different treatment patterns of diclofenac use were assessed including; the prevalence of diclofenac use, the number of diclofenac initiators, diclofenac discontinuation, and the number of patients that switched to an alternative analgesic drug. As shown in Figure 4, the outcomes were measured in quarterly time periods, which is every 3 months of the study period. Thus, the first quarter would be January, the second quarter was April, the third quarter was July, and the fourth quarter was October.

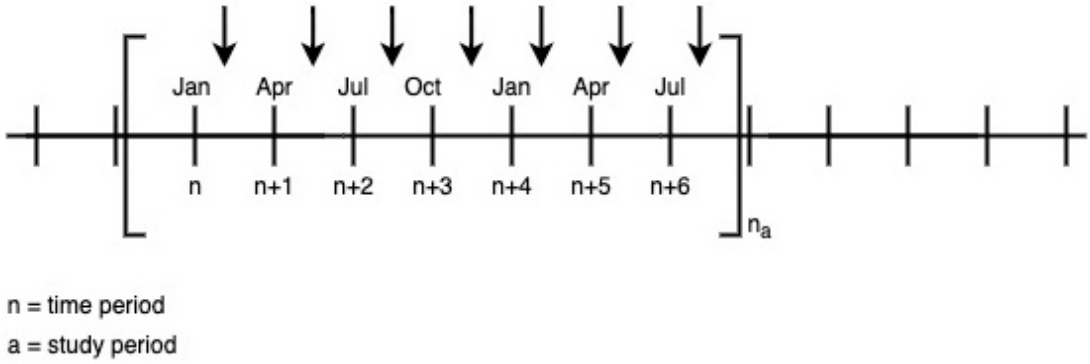

Figure 4. An example of the outcome quarterly measurements during the study period.

The overall diclofenac users (prevalence) were defined as all patients being prescribed diclofenac in a given time period (n) as shown in equation (1). The numerator was the number of patients with a prescription for diclofenac in a given time period (n). The denominator was defined as the total of patients in CPRD on the first day of the same time period (n).

$$Prevalent\ users = \frac{Diclofenac\ users\ in\ [n]}{Total\ patients\ in\ [n]} \quad (1)$$

Diclofenac initiators (incidence) were defined as patients receiving diclofenac prescription for the first time in a given time period (n) as shown in equation (2). The incident users were diclofenac users with no use of a diclofenac-containing substance during the 12 months before initiation. The numerator was the number of patients initiating diclofenac in a given time period (n). The denominator was the number of patients included in CPRD on the first day of the same time period (n).

$$Incident\ users = \frac{Diclofenac\ initiators\ in\ [n]}{Total\ patients\ in\ [n]} \quad (2)$$

The number of discontinuers was defined as the diclofenac users that discontinue diclofenac in a given time period (n), within 90 days from receiving the last diclofenac prescription in a treatment episode. As show in equation (3), the numerator was the number of patients that stopped using diclofenac in a given time period (n). The denominator was the number of diclofenac users in the same time period (n).

$$Diclofenac\ discontinuers = \frac{Diclofenac\ users\ stopped\ using\ diclofenac\ in\ [n]}{Diclofenac\ users\ in\ [n]} \quad (3)$$

Patients switching to an alternative analgesic drug were defined as patients who have stopped using diclofenac and initiate an alternative analgesic drug (see Table A2 in Appendix A). A common protocol (EUPAS24089) was used to identify the list of alternative analgesic drugs (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, 2019b). Switching to an alternative analgesic drug was defined as receiving a different analgesic prescription within 90 days from receiving the last diclofenac prescription in a treatment episode. As shown in equation (4), the numerator was the number of patients switching to an alternative analgesic drug in a given time period (n). The denominator was the number of patients prescribed for diclofenac users in the same time period (n).

$$Switchers = \frac{Alternative\ analgesic\ drug\ initiators\ in\ [n]}{Diclofenac\ users\ in\ [n]} \quad (4)$$

Product codes were used to identify the prescription patterns for diclofenac-containing medicinal products (see Table A1 in Appendix A) and the alternative analgesic drugs in CPRD.

3.4.2 Usage Patterns of Diclofenac-containing Medicinal Products in Specific Populations

Usage patterns were assessed for specific population based on their baseline risk for the outcome related to the regulatory intervention as well as based on their duration of use. Three specific patient risk groups were defined, based on the information from the EMA Summary of Product Characteristics (SmPC) chapters on contraindication, special warnings, and precautions endorsed for diclofenac when the regulatory intervention took place (European Medicines Agency, 2013). As shown in Table 1, patients were classified as in a low, moderate or high baseline risk group for cardiovascular events according to the safety advice for diclofenac. The high baseline risk group was defined as patients were diclofenac use was contraindicated. Therefore, if patients have established one or a combination of the specific comorbidities that are contraindicated for diclofenac use, then they were considered as in high baseline risk. Moderate baseline risk was defined as patients with one or a combination of significant risk factors warnings for cardiovascular events. Patients in moderate baseline risk should only use diclofenac after careful consideration. The group in low baseline risk was defined as all patients that were not included in the moderate or high baseline risk group, e.g., those were diclofenac use was not contraindicated and without any co-medication use or comorbidities related to significant warnings for diclofenac use. The following comorbidities were included (Table 1); congestive heart failure (NYHA class II-IV), ischemic heart disease, peripheral arterial disease, cerebrovascular disease, hypertension, hyperlipidaemia, and diabetes. Co-medication use was defined as patients prescribed any anti-hypertensive drugs, anti-hyperlipidaemic drugs, or anti-diabetic drugs. Anti-hypertensive drugs were defined from a study that EMA used for assessment in the regulatory intervention and another similar study (Krum et al., 2012; Qvarnström et al., 2016). The list of co-medication use can be found in Appendix A. The discontinuation and switch rate for the risk groups were calculated similar to equation (3) and (4), whereas the incidence rate for the risk groups were calculated in proportion of incident users.

Table 1. Risk groups for cardiovascular events based on the safety advice for diclofenac from the EMA.

Risk group	Covariates
Low baseline risk	*No contraindication, special warnings, and precautions for diclofenac use.*
Moderate baseline risk	*Hypertension, hyperlipidaemia, diabetes mellitus, co-medications, and current smoking.*
High baseline risk	*Contraindications: Congestive heart failure (NYHA class II-IV), ischemic heart disease, peripheral arterial disease, and cerebrovascular disease.*

Diclofenac users were also defined as one-time users or chronic users based on their treatment episode duration. Patients with treatment duration at least 60 days or longer were considered chronic users, while those with less than 60 days of use were considered one-time users. One-time users are most likely to be those with only a single prescription.

3.4.3 Time period

The event date was specified as the date when the regulatory intervention took place, which was 28 June 2013. The periods observed were divided into the pre-intervention period (January 2009 to April 2013), the intervention period (June 2013), and the post-intervention period (July 2013 to December 2019). The intervention period would assess the immediate effects of the event date.

3.5 Covariates

The study outcomes were stratified by age, gender, smoking status, comorbidities, and drug therapy at index date and every quarter measurements of the study period. Age of each patient was defined in each quarter and was categorised as 18-39 years, 40-49 years, 50-69 years and ≥70 years. The smoking status of a patient was classified as a current smoker, ex-smoker or never smoked, and the most recent record before the start of each time period was used. The assessment of covariates was based on available data during registration at the GP practice. Covariates were assessed in every quarter measurements of the study period as some patients might be categorised differently as the study period goes by. All the covariates were encoded and assessed, and then afterward patients were divided into the three risk groups.

3.6 Data Analysis

Segmented regression analysis in interrupted time series (ITS) studies, which is a statistical method for estimating intervention effects (Wagner, Soumerai, Zhang, & Ross-Degnan, 2002), was used to estimate levels and trends and the changes in level and trends. Quarterly time periods were defined between 1 January 2009 and 31 December 2019 (Figure 4) and used to assess prescribing patterns, and possible changes. The primary analysis was to determine changes in prescribing trends and levels for diclofenac before and after the intervention took place. ITS regression analysis was used to fit quarterly time trends for usage patterns of diclofenac. First, the data was visualised graphically by plotting the data and then fitted into regression models. A least-squares regression line was fitted in each segment. The regression models estimated a baseline trend before the intervention, then the level change immediately after the intervention, and a change in trend after the intervention, compared with the baseline trend before the intervention. This was done for the prevalence of diclofenac use, incidence of diclofenac use, discontinuation of diclofenac use and switching to alternative analgesic drugs. A step function was used to determine the change in level by including an indicator variable in the model. The indicator variable was coded as 0 in the months before the intervention and coded as 1 from the month after the intervention. To determine the change in trend a continuous variable was also included in the model. The continuous variable was coded as 0 before the intervention and then started counting the number of months after the intervention. The analysis was stratified by age, gender, and the EMA risk group definition. All of the regression models were tested for autocorrelation by using the Durbin-Watson statistic. All statistical analysis was performed using R studio statistical software (version 1.2.5019).

4. RESULTS

4.1 Study population

A total of 993.835 patients had at least one treatment episode of diclofenac from 1st January 2009 till 31st December 2019 (Table 2). The study population included relatively equal number of males and females. The largest age group was 50-69 years (35.6%) and the smallest was ≥70 years (17.5%). Most of the study population were non-smokers, having never smoked before (43.2%) or stopped smoking (30.7%). About a fifth of the population had a diagnosis of hypertension (21.7%) and about a fifth used statins (15.8%) or renin angiotensin-aldosterone system (RAAS) inhibitors (14.4%) on index date.

Table 2. Characteristics of the study population (n = 993.835) on index date during the study period (2009-2019).

Variables	N	%
Patient characteristics		
Gender		
Female	*448.775*	*45.2*
Male	*545.060*	*54.8*
Age		
18-39 years old	*264.954*	*26.6*
40-49 years old	*201.407*	*20.3*
50-69 years old	*353.911*	*35.6*
≥70 years old	*173.563*	*17.5*
Smoking		
Current smoker	*259.552*	*26.1*
Ex-smoker	*304.529*	*30.7*
Never smoked	*429.754*	*43.2*
Comorbidity		
Hypertension	*215.995*	*21.7*
Diabetes	*69.119*	*7.0*
Hyperlipidaemia	*58.956*	*5.9*
Ischemic heart disease	*57.822*	*5.8*
Cerebrovascular disease	*27.895*	*2.8*
Congestive heart failure	*11.252*	*1.1*
Peripheral arterial disease	*9.984*	*1.0*
Co-medication use		
Statins	*156.754*	*15.8*
RAAS inhibitors	*143.129*	*14.4*
Diuretics	*99.669*	*10.0*
Calcium channel blockers	*84.722*	*8.5*
Beta-blockers	*82.049*	*8.3*
Oral diabetic drugs	*41.409*	*4.2*
Insulin	*13.153*	*1.3*

4.2 Impact of the 2013 EMA Regulatory Intervention on Prevalence of Diclofenac Use

In 2009, the prevalence of diclofenac use was approximately 5.2 per 100 persons (Figure 5). Throughout the study period, the prevalence rate decreased almost by half from 5.2 to 2.7 per 100 persons until right before the intervention in 2013. After the intervention, the use of diclofenac dropped further by 26% to approximately 2.0 per 100 persons (level change) immediately after the intervention in 2013. During the post-intervention period, the prevalence rate kept relatively stable around 1.5 per 100 persons until 2019.

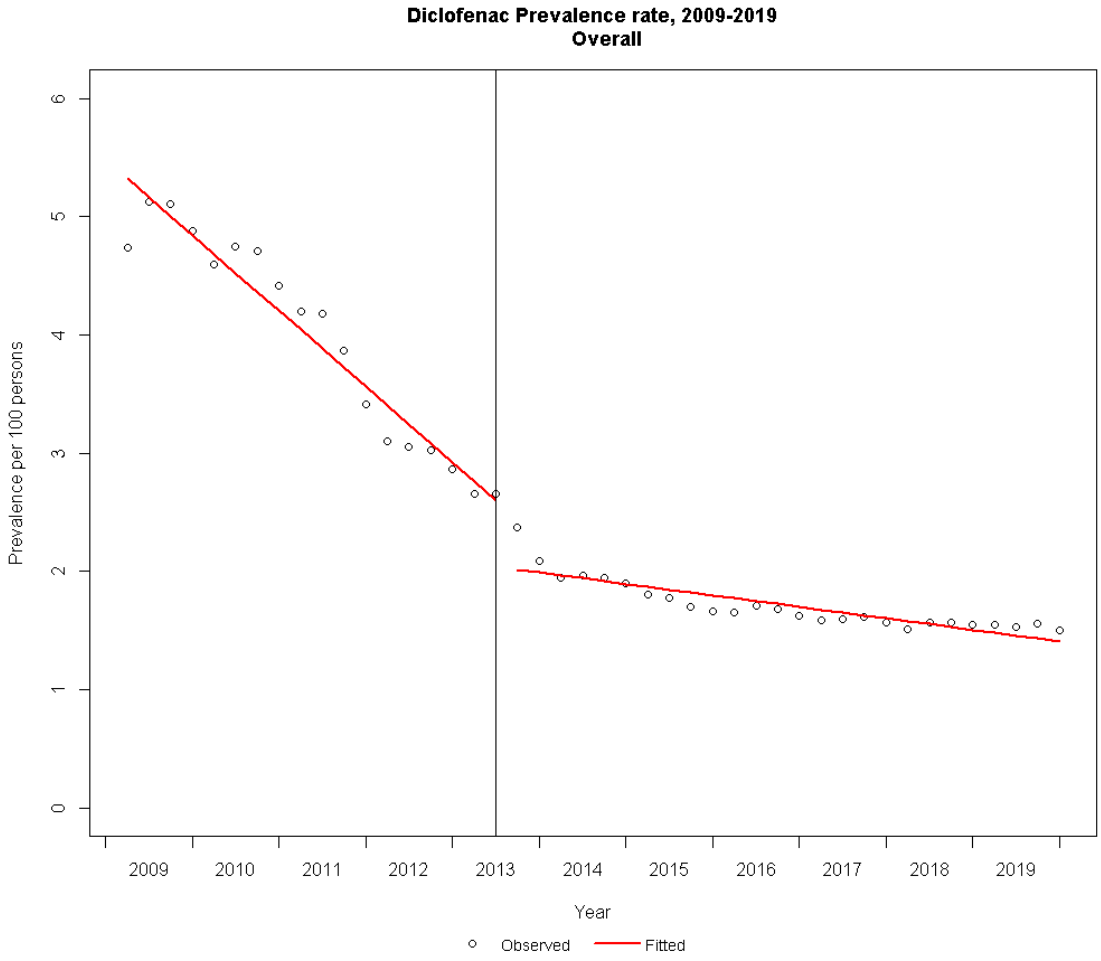

Figure 5. Prevalence rate of diclofenac use during the study period. Vertical line in 2013 indicates the date of the EMA regulatory intervention.

Before the regulatory intervention in 2013, the baseline trend on diclofenac use was significantly negative (-0.160, P = <.001) (Table 3), and with a significant immediate change in prevalence of diclofenac use (-0.560, P = <.001) when the regulatory intervention took place in 2013. During the post-intervention, the trend was

not as negative as in pre-intervention. The trend change in diclofenac prevalence was significant (0.139, P = <.001) when compared with the baseline trend in pre-intervention.

Table 3. Trend and level change results of the ITS regression analysis in the prevalence of diclofenac use

Usage patterns of prevalent users			
Variables	**Pre-intervention**	**Intervention**	**Post-intervention**
Overall	*-0.160 (-0.176, -0.145), P = <.001*	*-0.560 (-0.767, -0.353), P = <.001*	*0.136 (0.118, 0.154), P = <.001*
Gender			
Female	*-0.174 (-0.190, -0.158), P = <.001*	*-0.582 (-0.793, -0.370), P = <.001*	*0.150 (0.132, 0.168), P = <.001*
Male	*-0.147 (-0.162, -0.131), P = <.001*	*-0.539 (-0.743, -0.335), P = <.001*	*0.122 (0.105, 0.140), P = <.001*
Age			
18-39 years	*-0.080 (-0.088, -0.072), P = <.001*	*-0.271 (-0.377, -0.165), P = <.001*	*0.069 (0.060, 0.078)), P = <.001*
40-49 years	*-0.149 (-0.165, -0.132), P = <.001*	*-0.630 (-0.845, -0.415), P = <.001*	*0.119 (0.101, 0.138), P = <.001*
50-69 years	*-0.247 (-0.271, -0.223), P = <.001*	*-0.931 (-1.25, -0.611), P = <.001*	*0.204 (0.176, 0.231), P = <.001*
≥70 years	*-0.199 (-0.219, -0.178), P = <.001*	*-0.422 (-0.693, -0.152), P = .003*	*0.179 (0.156, 0.203), P = <.001*

4.2.1. Impact of the 2013 EMA Regulatory Intervention on Prevalence of Diclofenac Use Stratified by Gender and Age

The prevalence of diclofenac use was slightly higher in women than in men (Figure 6). The prevalence was approximately 5.6 per 100 persons in women and 4.6 per 100 persons in men in 2009. Right before the regulatory intervention in 2013, the prevalence rate was 3.0 per 100 persons in women and 2.3 per 100 persons in men, which dropped by 27% to 2.2 per 100 persons in women and by 26% to 1.7 per 100 persons in men immediately after the intervention in 2013. After 2013, the prevalence of diclofenac use remained rather stable with a prevalence of 1.8 per 100 persons in women and 1.2 per 100 persons in men by the end of 2019.

The baseline trend in women (-0.174, P = <.001) was slightly more negative than in men (-0.147, P = <.001) before the regulatory intervention in 2013 (Table 3). The regulatory intervention in 2013 was associated with a significant level change for both women (-0.582, P = <.001) and men (-0.539, P = <.001). After 2013, there was significant change in trend for both women (0.150, P = <.001) and men (0.122, P = <.001) when compared with the baseline trend.

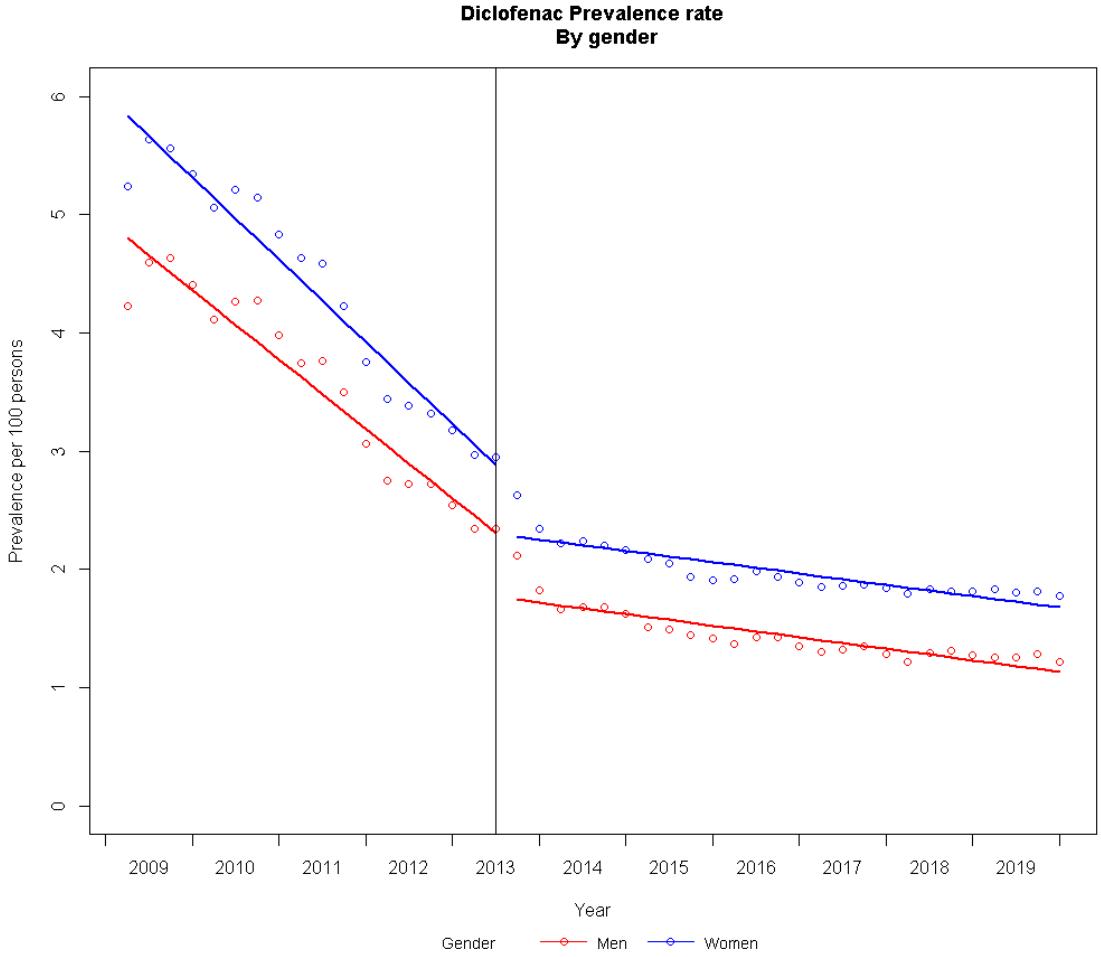

Figure 6. Trends in the prevalence of diclofenac use stratified by gender during the study period.

Prevalence of diclofenac use was higher in older patients than in younger patients (Figure 7). In 2009, the prevalence of use was 7.7 per 100 persons in those over 70 years old, 7.6 per 100 persons for those 50-60 years old, 4.7 per 100 persons for those 40-49 years old, and 2.2 per 100 persons for those 18-39 years old. Similar to the overall diclofenac prevalence rate, prevalence of diclofenac use was already decreasing before the 2013 regulatory intervention in all age groups. Diclofenac use declined approximately to 4.7 per 100 persons over 70 years old, 3.8 per 100 persons at 50-69 years old, 2.4 per 100 persons at 40-49 years old, and 1.0 per 100 persons

at 18-39 years old, right before the intervention took place in 2013. Immediately after the intervention in 2013, diclofenac use dropped the most in patients 50-69 years old or by 32% to 2.6 per 100 persons. Use also dropped in the other age groups by 29% for those aged 40-49 years old, by 20% for those aged 18-39 years old, and by 17% to 3.9 per 100 persons over 70 years old. After the intervention, diclofenac use was relatively stable with a prevalence of 3.8 per 100 persons over 70 years old, 2.0 per 100 persons at 50-69 years old, 1.1 per 100 persons at 40-49 years old, and 0.5 per 100 persons at 18-39 years old in 2019.

In pre-intervention, a decline in trend was observed in all groups on diclofenac use (Table 3) with the largest trend changes in the age group 50-69 years (-0.247, P = <.001) and the least in the youngest age group, 18-39 years (-0.080, P = <.001). There was a significant level change in the prevalence rate for all age groups immediately after the regulatory intervention in 2013. The intervention had a greater level effect on older patients than younger patients, the highest on the age group 50-69 years (-0.931, P = <.001) and the lowest on the age group 18-39 years (-0.271, P = <.001). After 2013, the change in prevalence trend was significant for all age groups, when compared with the baseline trend before 2013, and the most trend change was in the age group 50-69 years (0.204, P = <.001).

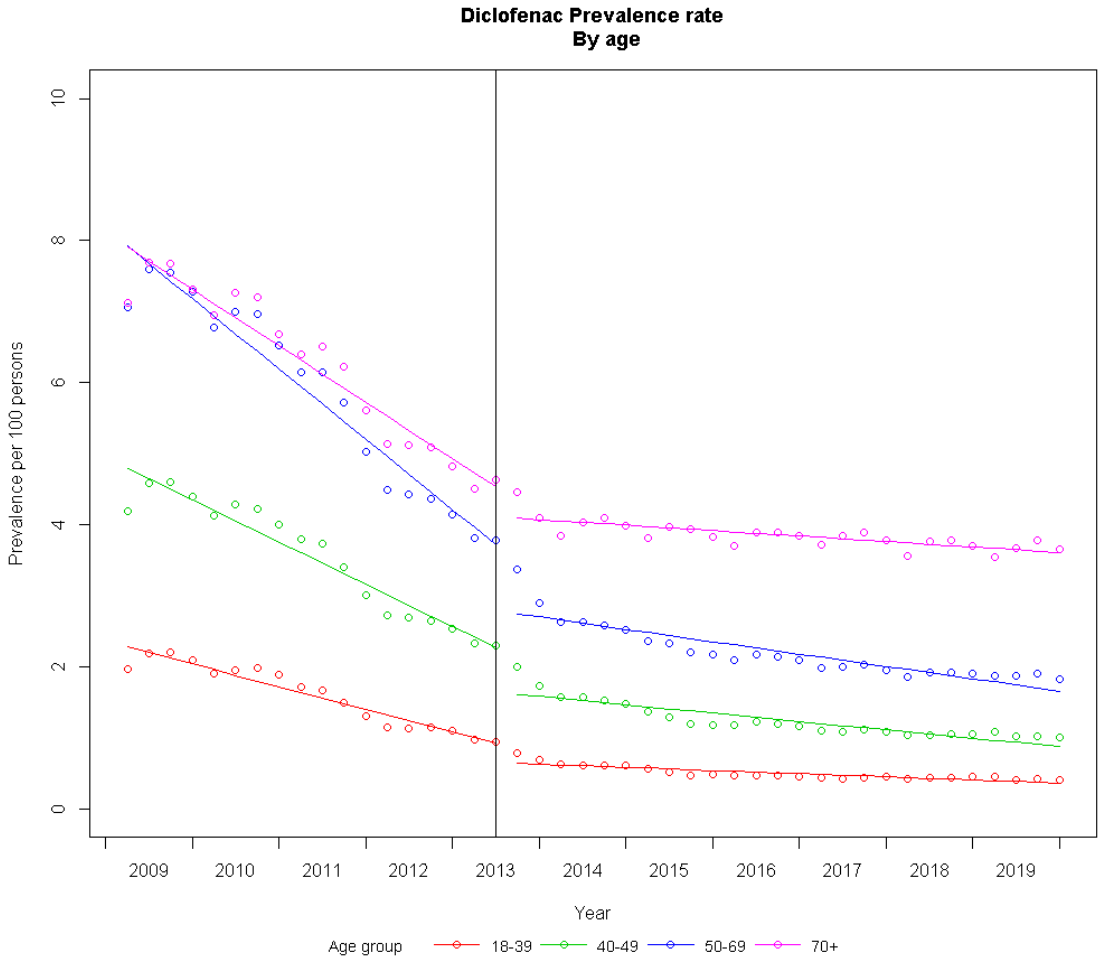

Figure 7. Trends in the prevalence of diclofenac use stratified by age during the study period.

4.3 Impact of the 2013 EMA Regulatory Intervention on the Incidence of Diclofenac Use

An overall average of 1.7 per 100 persons had initiated diclofenac use in 2009, which decreased to approximately 0.8 per 100 persons right before the intervention in 2013 (Figure 8). Then, diclofenac initiation dropped by 25% to 0.6 per 100 persons immediately after the 2013 regulatory intervention and continued to decline stably to 0.4 per 100 persons in 2019.

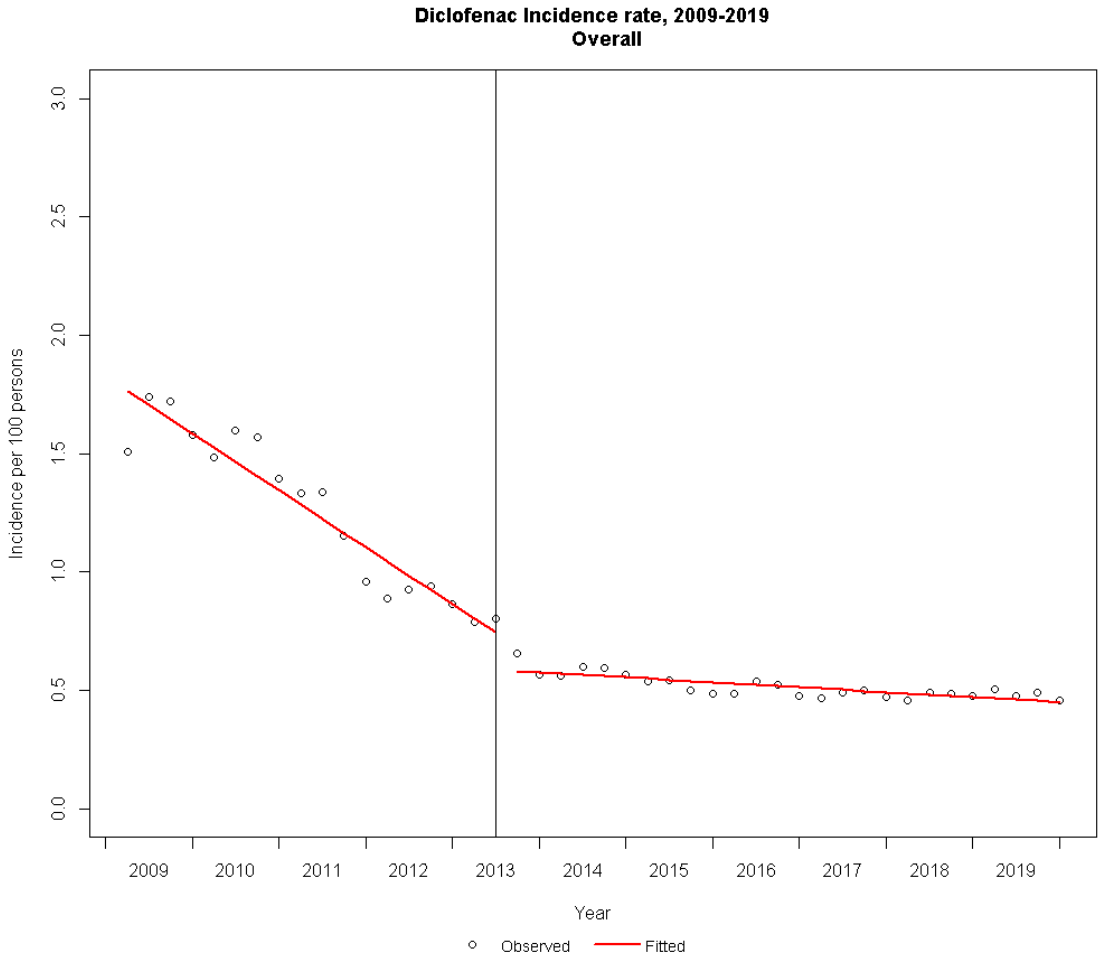

Figure 8. Incidence rate of diclofenac use during the study period.

The baseline incidence trend was negative (-0.060, P = <.001) before the 2013 regulatory intervention (Table 4). Afterwards, the intervention was associated with a significant immediate fall in diclofenac initiation (-0.158, P = <.001) immediately after 2013. In post-intervention, diclofenac initiation decreased less than the baseline trend in pre-intervention, with a significant trend change (0.055, P = <.001).

Table 4. Trend and level change results of the ITS regression analysis in the incidence of diclofenac use.

Usage patterns of incident users			
Variables	**Pre-intervention**	**Intervention**	**Post-intervention**
Overall	*-0.060 (-0.067, -0.053), P = <.001*	*-0.158 (-0.246, -0.069), P = <.001*	*0.055 (0.047, 0.062), P = <.001*
Gender			
Female	*-0.064 (-0.071, -0.058), P = <.001*	*-0.164 (-0.252, -0.075), P = <.001*	*0.059 (0.051, 0.067), P = <.001*
Male	*-0.056 (-0.063, -0.049), P = <.001*	*-0.152 (-0.243, -0.061), P = .002*	*0.050 (-0.043, 0.058), P = <.001*
Age			
18-39 years	*-0.049 (-0.053, -0.044), P = <.001*	*-0.167 (-0.234, -0.101), P = <.001*	*0.043 (0.038, 0.049), P = <.001*
40-49 years	*-0.070 (-0.078, -0.062), P = <.001*	*-0.263 (-0.366, -0.160), P = <.001*	*0.062 (0.053, 0.071), P = <.001*
50-69 years	*-0.073 (-0.082, -0.065), P = <.001*	*-0.185 (-0.296, -0.075), P = .002*	*0.067 (0.058, 0.077), P = <.001*
≥70 years	*-0.048 (-0.057, -0.039), P = <.001*	*0.041 (-0.077, 0.159), P = .486*	*0.045 (0.035, 0.056), P = <.001*

4.3.1. Impact of the 2013 EMA Regulatory Intervention on Incidence of Diclofenac Use Stratified by Gender and Age

Incidence of diclofenac use was higher in women than in men (Figure 9). In 2009, the incidence rate was approximately 1.8 per 100 persons in women and 1.6 per 100 persons in men, however, the incidence decreased to 0.8 per 100 persons in women and 0.75 per 100 persons in men right before the intervention in 2013. Immediately after the intervention in 2013, the incidence rate dropped by 25% to 0.6 per 100 persons in women and 33% to 0.5 per 100 persons in men. The incidence kept relatively stable afterwards and in 2019 around 0.5 per 100 persons in women and 0.4 per 100 persons in men were initiating diclofenac.

In pre-intervention, the trend change was negative for both genders (Table 4). However, the baseline negative trend in women (-0.064, P = <.001) was slightly higher than in men (-0.056, P =<.001) before 2013. Immediately after the intervention in 2013, there was a significant level change for both women (-0.164, P = <.001) and men (-0.152, P = .002). After the intervention in 2013, the trend in post-intervention was not

as negative as in pre-intervention, however, the trend change was significant in women (0.059, P = <.001) and men (0.050, P = <.001) when compared with the trend before the intervention.

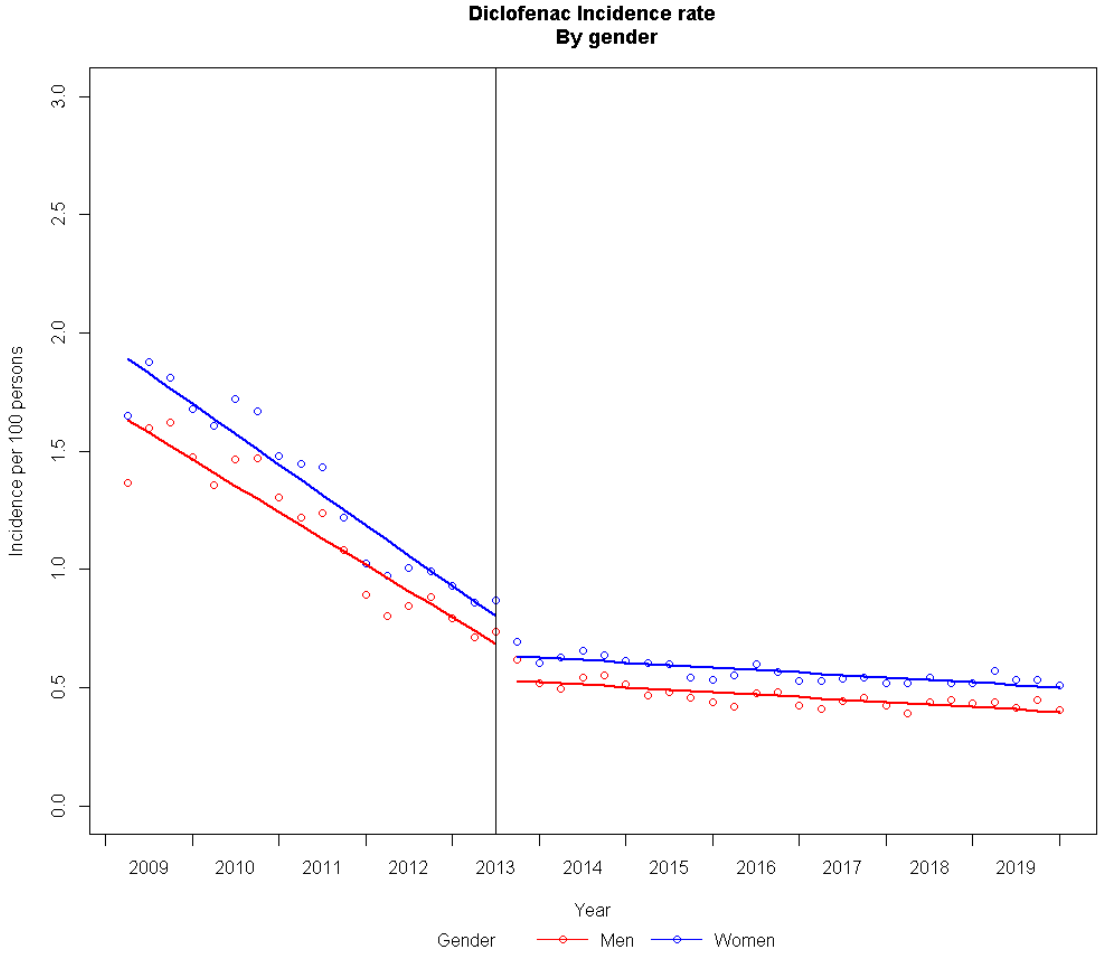

Figure 9. Trends in the incidence of diclofenac use stratified by gender during the study period.

Before 2013, the incidence of diclofenac use was greater in older patients than in younger patients, and especially high in the age groups 50-69 years and 40-49 years (Figure 10). However, after the regulatory intervention in 2013, diclofenac initiation dropped considerably for all age groups but remained the highest in the oldest age group, over 70 years. In 2009, diclofenac initiation was approximately 1.75 per 100 persons over 70 years old, 2.1 per 100 persons at 50-69 years old, 1.9 per 100 persons at 40-49 years old, and 1.3 per 100 persons at 18-39 years old. The incidence rate was already decreasing to 1.0 per 100 persons over 70 years old, 0.9 per 100 persons at 50-69 years old, 0.8 per 100 persons at 40-49 years old, and 0.4 per 100 persons at 18-39 years old, right before the intervention in 2013. Immediately after 2013, diclofenac initiation dropped the most, or by 25%, to 0.6 per 100 persons in the 40-49

years old. Incidence also dropped by 22% to 0.7 per 100 persons for those 50-69 years old, and by 13% to 0.35 per 100 persons for those 18-39 years old. However, the same did not occur in the patient group over 70 years where the incidence rate did not drop immediately after 2013 and kept relatively stable after the intervention with an incidence of 0.8 per 100 persons in 2019. For other age groups, incidence rate continued to decrease stably to 0.6 per 100 persons at 50-69 years old, 0.4 per 100 persons at 40-49 years old, and 0.25 per 100 persons at 18-39 years old in 2019.

The baseline trend in pre-intervention was negative for all groups, however, the trend was highest in the age groups 50-59 years (-0.073, P = <.001) and 40-49 years (-0.070, P = <.001) than the other age groups (Table 4). The regulatory intervention in 2013 was associated with a significant fall in incidence rate for all age groups, except in the oldest age group, over 70 years old (-0.041, P = .486). The fall was greatest in the age group 40-49 years old (-0.263, P = <.001). In post-intervention, there was a significant trend change in the incidence rate for all age groups when compared with the baseline trend in pre-intervention, with the highest trend changes in the age groups 50-69 years (0.067, P = <.001) and 40-49 years (0.062, P = <.001).

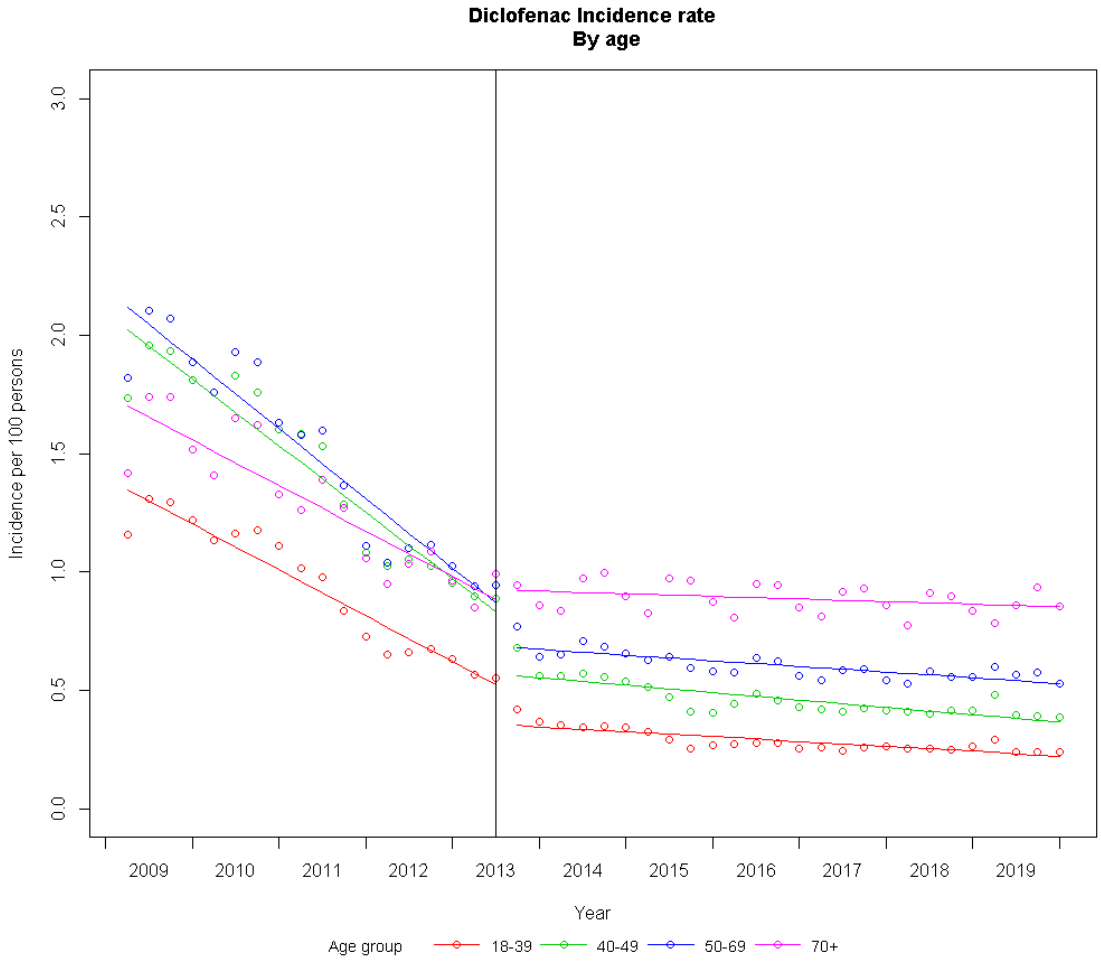

Figure 10. Trends in the incidence of diclofenac use stratified by age during the study period.

4.4 Impact of the 2013 EMA Regulatory Intervention on Discontinuation of Diclofenac Use

The overall diclofenac discontinuation rate was relatively stable throughout the study period (Figure 11). In 2009, the discontinuation rate was approximately 35 per 100 users of diclofenac and declined slightly to 34 per 100 users of diclofenac right before 2013 and did not show any change immediately after the regulatory intervention in 2013 nor in post-intervention. At the end of 2019, there was an unusual observation point with a discontinuation rate of 55 per 100 users of diclofenac

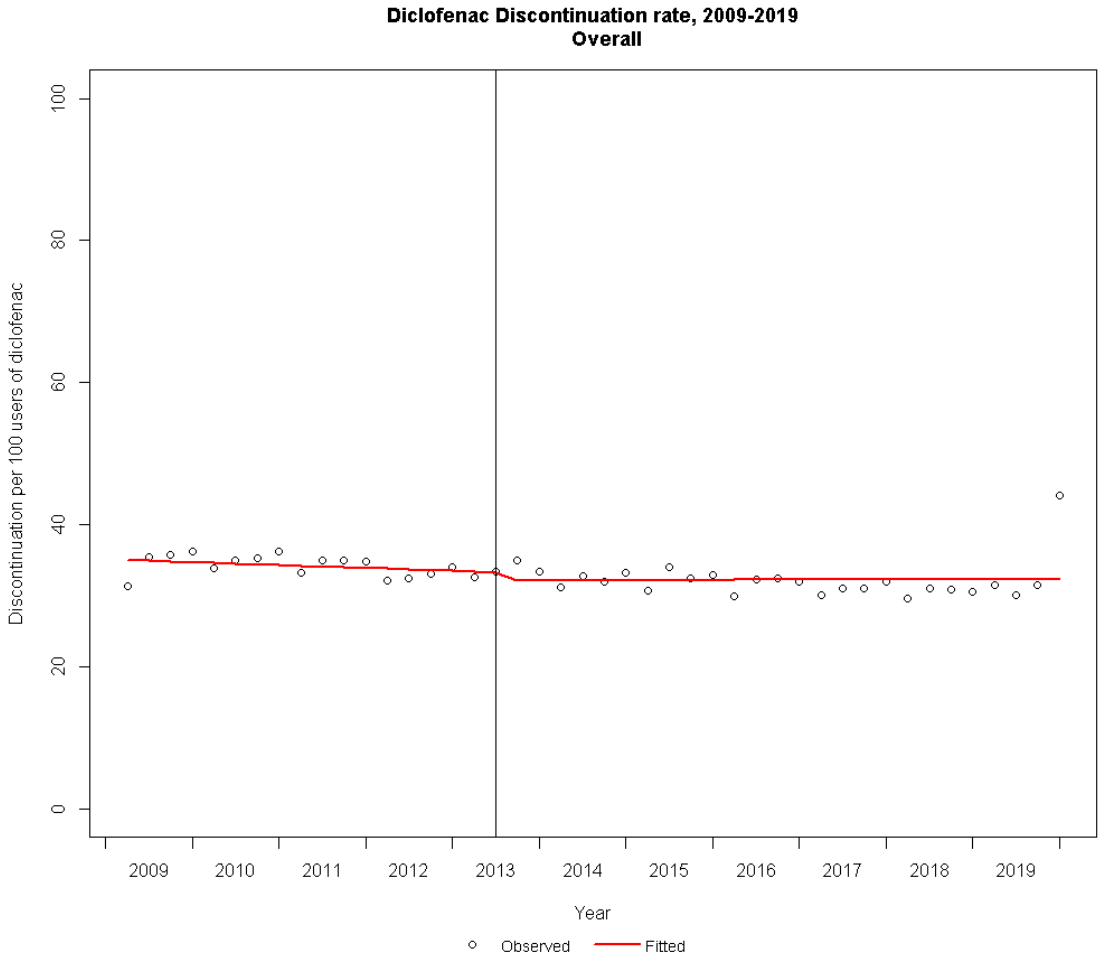

Figure 11. Discontinuation rate of diclofenac use during the study period.

The baseline trend did not have a significant trend change (-0.104, P = .336) during pre-intervention nor a significant level change (-1.125, P = .435) immediately after the intervention in 2013 (Table 5). After the intervention, there was no change in trend (0.110, P = .378), as the trend was relatively stable during the study period.

Table 5. Trend and level change results of the ITS regression analysis in the discontinuation of diclofenac use.

Usage patterns of discontinuers			
Variables	**Pre-intervention**	**Intervention**	**Post-intervention**
Overall	*-0.104 (-0.320, 0.112), P = .336*	*-1.125 (-4.006, 1.756), P = .435*	*0.110 (-0.139, 0.359), P = .378*
Gender			
Female	*-0.120 (-0.339, 0.099), P = .275*	*-1.570 (-4.492, 1.352), P = .284*	*0.109 (-0.144, 0.361), P = .389*
Male	*-0.082 (-0.297, 0.134), P = .449*	*-0.486 (-3.362, 2.390), P = .735*	*0.120 (-0.128, 0.369), P = .334*
Age			
18-39 years	*-0.066 (-0.255, 0.124), P = .489*	*-1.869 (-4.398, 0.661), P = .143*	*0.037 (-0.182, 0.255), P = .735*
40-49 years	*-0.180 (-0.384, 0.024), P = .082*	*-2.337 (-5.061, 0.386), P = .091*	*0.225 (-0.010, 0.461), P = .060*
50-69 years	*-0.016 (-0.225, 0.193), P = .878*	*-0.025 (-2.768, 2.817), P = .986*	*0.110 (-0.131, 0.352), P = .361*
≥70 years	*-0.025 (-0.213, 0.264), P = .830*	*0.591 (-2.589, 3.772), P = .709*	*0.013 (-0.262, 0.288), P = .923*

4.4.1. Impact of the 2013 EMA Regulatory Intervention on Discontinuation of Diclofenac Use Stratified by Gender and Age

Discontinuation of diclofenac was slightly higher in men than in women (Figure 12). The discontinuation was 35 per 100 users of diclofenac in women and 36 per 100 users of diclofenac in men in 2009 and decreased slightly to approximately 34 per 100 users of diclofenac in women and 35 per 100 users of diclofenac in men right before the intervention in 2013. The discontinuation rate for both genders remained stable after 2013 and by the end of 2019, there was an unusual observed discontinuation rate of 44 per 100 users of diclofenac in women and 46 per 100 users of diclofenac in men, similar to the overall discontinuation rate.

In pre-intervention, the trend change was not significant for both women (-0.120, P = .275) and men (-0.082, P = .449) (Table 5). The intervention in 2013 was not associated with a significant level change for both genders and there was no significant trend change during post-intervention. The discontinuation trends and levels were relatively constant for both genders.

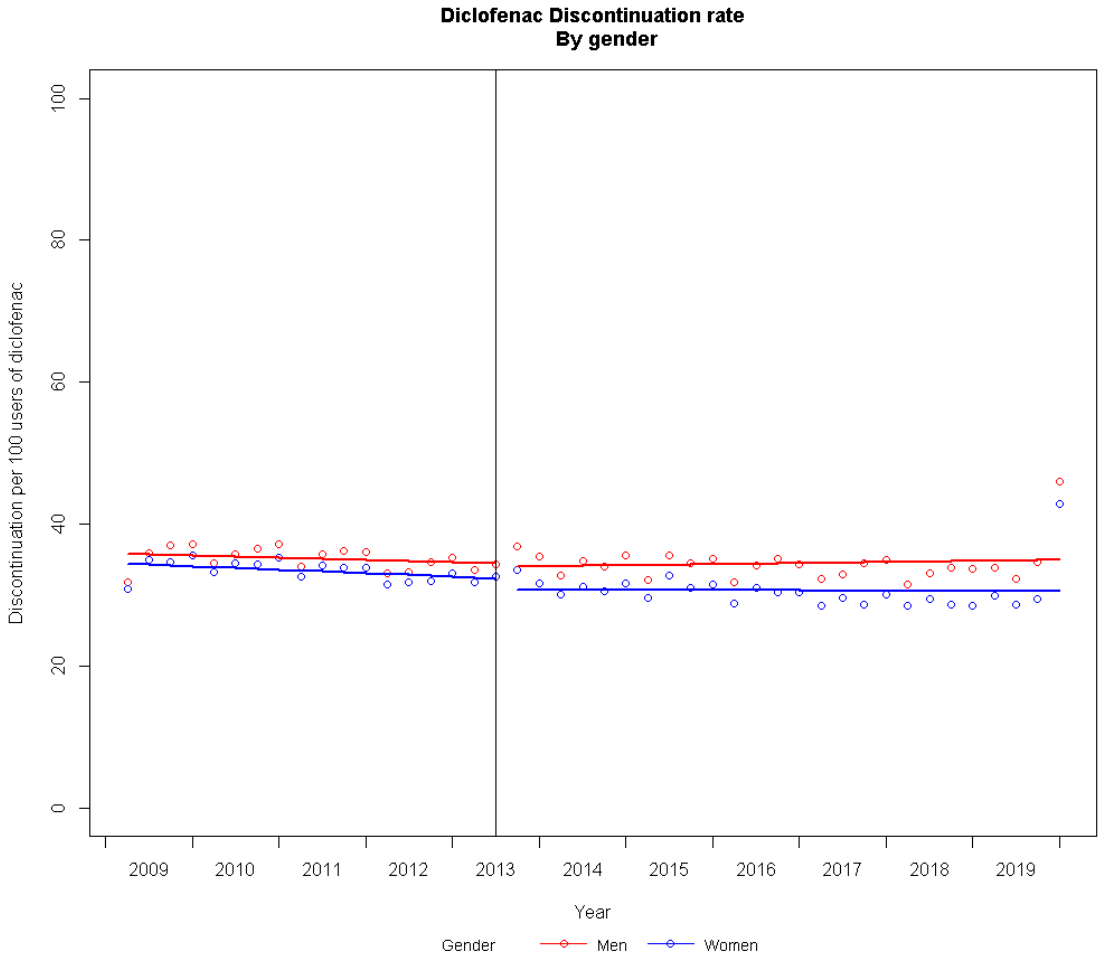

Figure 12. Trends in the discontinuation of diclofenac use stratified by gender during the study period.

The discontinuation of diclofenac use was higher in younger patients than in older patients (Figure 13). In 2009, discontinuation was 25 per 100 users of diclofenac in those over 70 years old, 30 per 100 users of diclofenac for those 50-69 years old, 42 per 100 users of diclofenac for those 40-49 years old, and 58 per 100 users of diclofenac for those 18-39 years old. Discontinuation declined slightly to 40 per 100 users of diclofenac for those aged 40-49 years old right before the intervention in 2013, however, the discontinuation rate was relatively stable for the other age groups. Immediately after 2013, discontinuation decreased slightly by 5% to 38 per 100 users of diclofenac in patients at 40-49 years old, while there was no change in the discontinuation rate for the other age groups. After the intervention, discontinuation of diclofenac use remained stable for all age groups with a discontinuation of 36 per 100 users of diclofenac over 70 years old, 31 per 100 users of diclofenac at 50-59 years old, 38 per 100 users of diclofenac at 40-49 years old, and 56 per 100 users of diclofenac at 18-39 years old in 2019. Similar to the overall discontinuation rate, there

was a sudden increased observation point at 40 per 100 users of diclofenac those in over 70 years old, 44 per 100 users of diclofenac for those 50-69 years old, 50 per 100 users of diclofenac for those 40-49 years old, and 64 per 100 users of diclofenac for those 18-39 years old, by the end of 2019.

The ITS analysis showed that there were no significant trend changes (baseline trend) for all age groups before the intervention in 2013 and also no significant level changes immediately after 2013 (Table 5). After 2013, there were also no significant trend changes for all age groups, since the discontinuation rate was relatively stable during the study period.

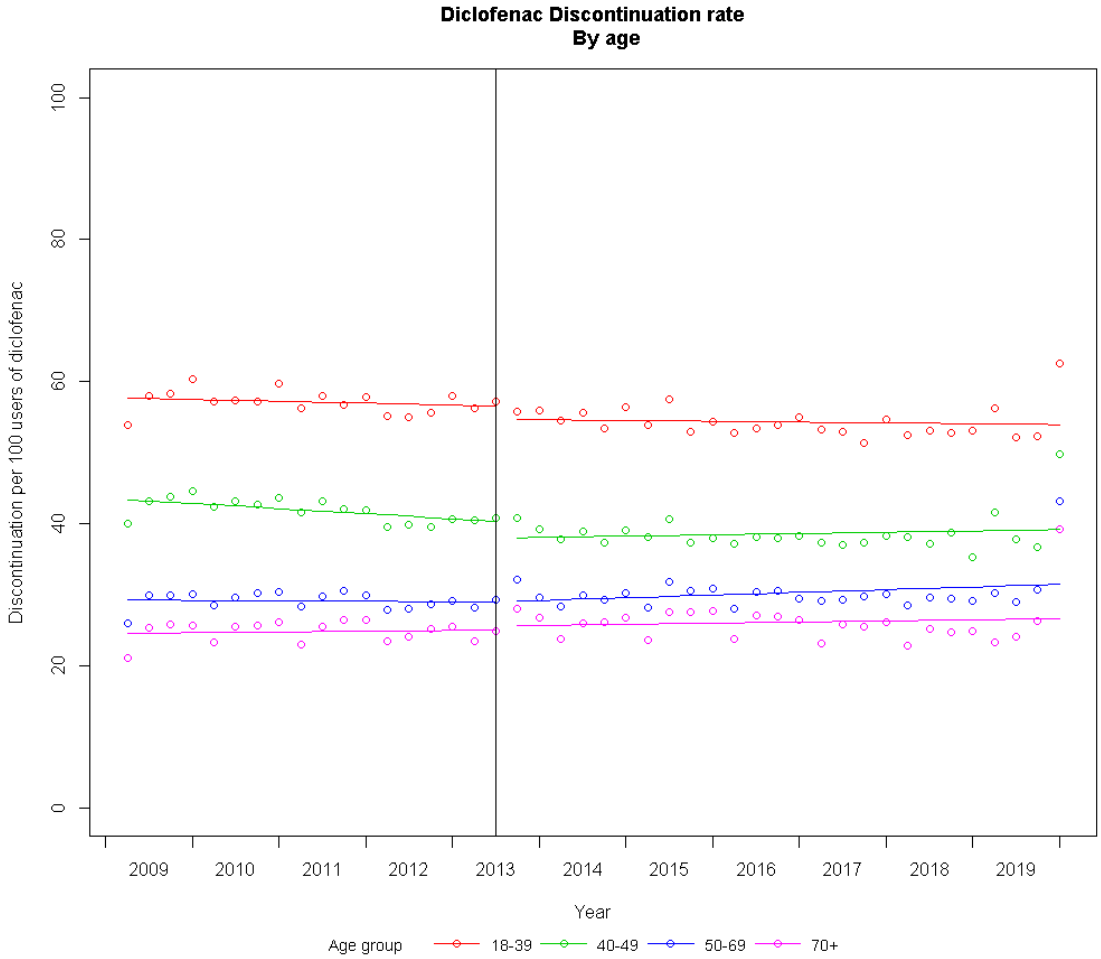

Figure 13. Trends in the discontinuation of diclofenac use stratified by age during the study period.

4.5 Impact of the 2013 EMA Regulatory Intervention on Switching to Alternative Analgesics Drugs

A total of 35.907 patients were switching to alternative analgesics from 2009 till 2019 (Table 6). The patients switching to other analgesics were mostly switching to paracetamol (39.9%) and naproxen (16.3%) during the study period.

Table 6. Top 10 out of the 36 alternative analgesic drugs that the study population were switching to during the study period (2009-2019). A total of n = 35.907 switchers.

Drug name	N	%
Paracetamol	*14.335*	*39.9*
Naproxen	*5.836*	*16.3*
Ibuprofen	*3.078*	*8.6*
Tramadol	*2.807*	*7.8*
Morphine	*1.822*	*5.1*
Codeine	*1.484*	*4.1*
Dihydrocodeine tartrate	*1.162*	*3.2*
Etoricoxib	*867*	*2.4*
Buprenorphine	*862*	*2.4*
Meloxicam	*684*	*1.9*

Patients switching to alternative analgesics were approximately 2.0 per 100 users of diclofenac in 2009 (Figure 14). Amid the pre-intervention, there was a sudden peak between 2011 and 2012, where the switch rate reached a maximum of 3.5 per 100 users of diclofenac but dropped drastically by 34% to 2.3 per 100 persons shortly after. Right before 2013, the switch rate was 2.5 per 100 users of diclofenac, which increased suddenly by 68% to 4.2 per 100 users of diclofenac immediately after the 2013 regulatory intervention. However, the switch rate dropped shorty after to 2.6 per 100 users of diclofenac, or by 38%, in 2014. After the intervention, the switch rate increased slightly to 3.0 per 100 users of diclofenac in 2015 and decreased to 2.3 per 100 users of diclofenac in 2016 and continued to decline stably to 1.7 per 100 users of diclofenac in 2019.

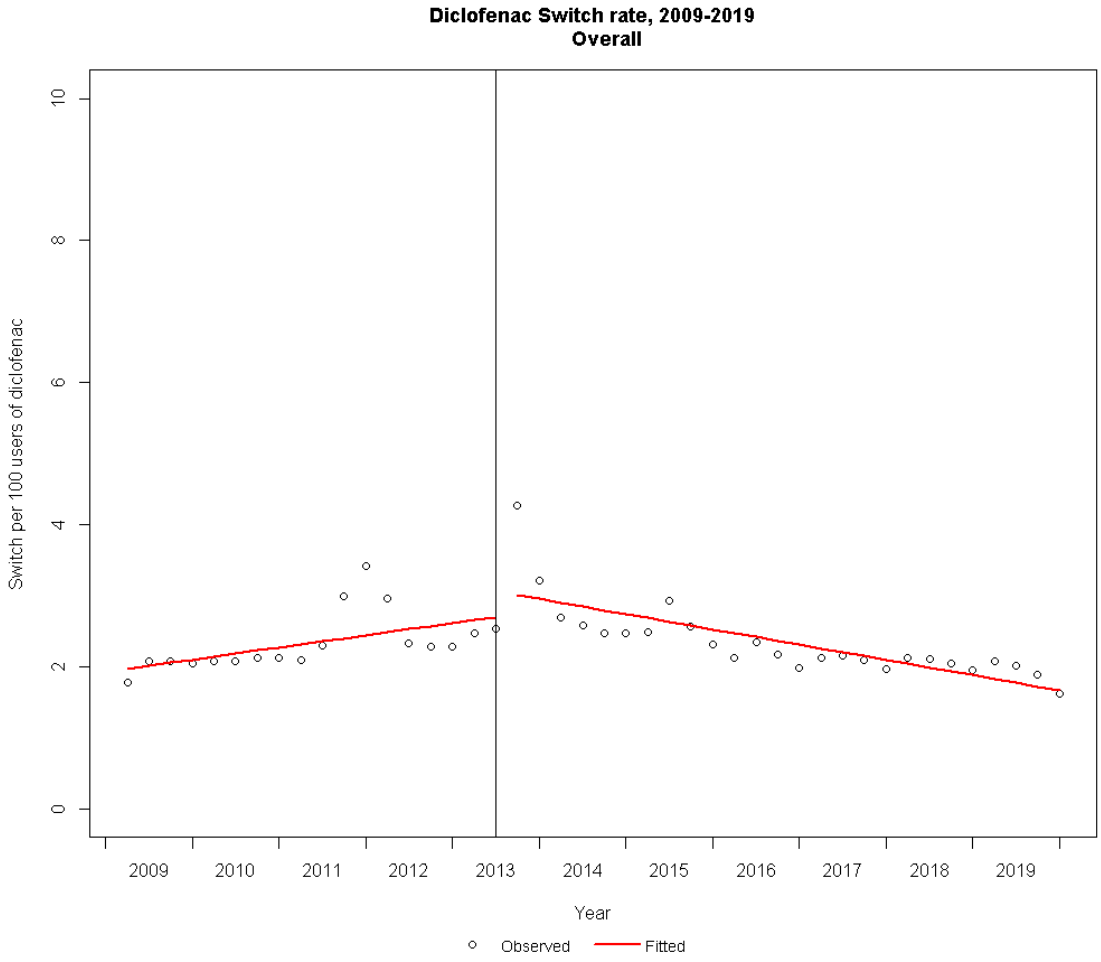

Figure 14. Switching to alternative analgesic drugs during the study period.

The baseline switch trend was significantly positive (0.043, P = .008) before the intervention (Table 7). However, the regulatory intervention in 2013 was not associated with a significant immediate level change (0.363, P = .086) for the overall switch rate. After the intervention, the trend change (-0.097, P = <.001) was significant, when it was compared with the baseline trend in pre-intervention.

Table 7. Trend and level change results of the ITS regression analysis in switching to alternative analgesic drugs.

Usage patterns of switchers			
Variables	**Pre-intervention**	**Intervention**	**Post-intervention**
Overall	*0.043 (0.012, 0.074), P = .008*	*0.363 (-0.053, 0.779), P = .086*	*-0.097 (-0.133, -0.061), P = <.001*
Gender			
Female	*0.037 (0.006, 0.068), P = .019*	*0.345 (-0.069, 0.759), P = .100*	*-0.091 (-0.126, -0.055), P = <.001*
Male	*0.050 (0.017, 0.082), P = .004*	*0.383 (-0.051, 0.817), P = .082*	*-0.104 (-0.142, -0.067), P = <.001*
Age			
18-39 years	*0.051 (0.027, 0.075), P = <.001*	*0.463 (0.141, 0.785), P = .006*	*-0.079 (-0.107, -0.051), P = <.001*
40-49 years	*0.054 (0.023, 0.084), P = <.001*	*0.512 (0.106, 0.919), P = .015*	*-0.102 (-0.137, -0.067), P = <.001*
50-69 years	*0.048 (0.006, 0.089), P = .025*	*0.589 (0.039, 1.139), P = .037*	*-0.114 (-0.161, -0.066), P = <.001*
≥70 years	*0.020 (-0.009, 0.049), P = .177*	*0.020 (-0.408, 0.368), P = .918*	*-0.065 (-0.099, -0.032), P = <.001*

4.5.1 Impact of the 2013 EMA Regulatory Intervention on Switching to Alternative Analgesics Drugs Stratified by Gender and Age

Patients switching to alternative analgesics was higher in women than in men (Figure 15). The switching was approximately 2.2 per 100 users of diclofenac in women and 1.8 per 100 users of diclofenac in men in 2009. Similar to the overall switch rate, the switching increased suddenly to 3.5 per 100 users of diclofenac in women and 3.4 per 100 users of diclofenac in men between 2011 and 2012, and dropped shortly after by 31% to 2.4 per 100 users of diclofenac in women and 38% to 2.1 per 100 users of diclofenac in men. Right before the intervention in 2013, the switch rate was 2.5 per 100 users of diclofenac in women and 2.3 per 100 users of diclofenac in men, which increased suddenly by 76% to 4.4 per 100 users of diclofenac in women and 78% to 4.1 per 100 users of diclofenac in men immediately after the intervention. However, the switch rate decreased shortly after to 2.6 per 100 users of diclofenac in women and 2.4 per 100 users of diclofenac in men in 2014. Then, in 2015, the switch rate increased slightly to 3.0 per 100 users of diclofenac in women and 2.8 per 100 users of diclofenac

in men but decreased shortly after by 23% and 18% to 2.3 per 100 users of diclofenac for both genders in 2016. The switching continued to decline slightly to 1.6 per 100 users of diclofenac in women and 1.5 per 100 users of diclofenac in men by the end of 2019.

The baseline trend change was positive for both women (0.037, P = .019) and men (0.050, P = .004) before the intervention (Table 7). Immediately after the intervention, there was no significant level change for both genders but in post-intervention, there was a significant trend change for both women (-0.091, P = <.001) and men (-0.104, P = <.001), when the trend changes were compared with the baseline trends in pre-intervention.

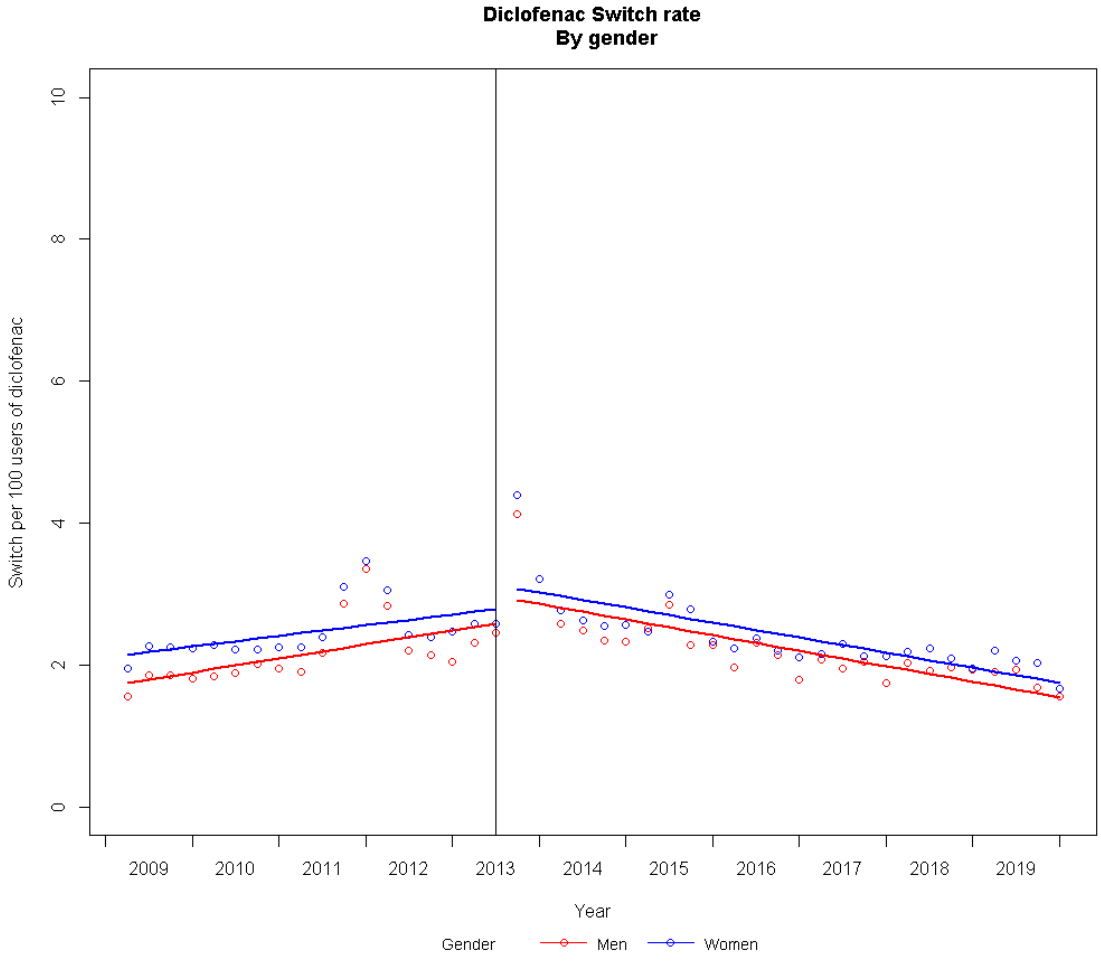

Figure 15. Trends in switching to alternative analgesic drugs stratified by gender during the study period.

Switching to alternative analgesics was highest in the oldest age group before the intervention, but after the intervention the switching was highest in the youngest age group (Figure 16). In 2009, the switching was 2.5 per 100 users of diclofenac in those over 70 years old, 2.0 per 100 users of diclofenac for those 50-69 and 40-49

years old, and 1.9 per 100 users of diclofenac for those 18-39 years old. Similar to the overall switch rate, switching increased suddenly to 3.4 per 100 users of diclofenac over 70 years old, 3.6 per 100 users of diclofenac at 50-69 years old, 3.4 per 100 users of diclofenac at 40-49 years old, and 3.0 per 100 users of diclofenac at 18-39 years old between 2011 and 2012. However, the switch rate dropped shortly after to 2.5 per 100 users of diclofenac over 70 years old, 2.1 per 100 users of diclofenac at 50-69 years old, 2.2 per 100 users of diclofenac at 40-49 years old, and 2.4 per 100 users of diclofenac at 18-39 years old in 2012. Right before the intervention in 2013, switching was approximately 2.3 per 100 users of diclofenac for those 18-39 years old and 2.5 per 100 users of diclofenac for the other age groups. Immediately after the intervention in 2013, switching increased the most in patients 50-69 years old, or by 100% to 5.0 per 100 users of diclofenac. Switching also increased in the other age groups by 52% to 3.8 per 100 users of diclofenac for those aged over 70 years old and 40-49 years old, and by 43% to 3.3 per 100 users of diclofenac for those 18-39 years old. Shortly after, the switch rate decreased again, to 2.3 per 100 users of diclofenac over 70 years old, 2.8 per 100 users of diclofenac at 50-69 years old, 2.9 per 100 users of diclofenac at 40-49 years old, and 2.5 per 100 users of diclofenac at 18-39 years old in 2014. Amid post-intervention, the switching increased to 3.2 per 100 users at 50-69 years old, 3.5 per 100 users of diclofenac at 40-49 years old, and 3.7 per 100 users of diclofenac at 18-39 years old in 2015 but decreased shortly after. The switch rate continued to decline slightly to 1.7 per 100 users of diclofenac in those over 70 years old, 1.5 per 100 users of diclofenac for those 50-69 years old, 1.7 per 100 users of diclofenac for those 40-49 years old, and 2.2 per 100 users of diclofenac for those 18-39 years old by the end of 2019.

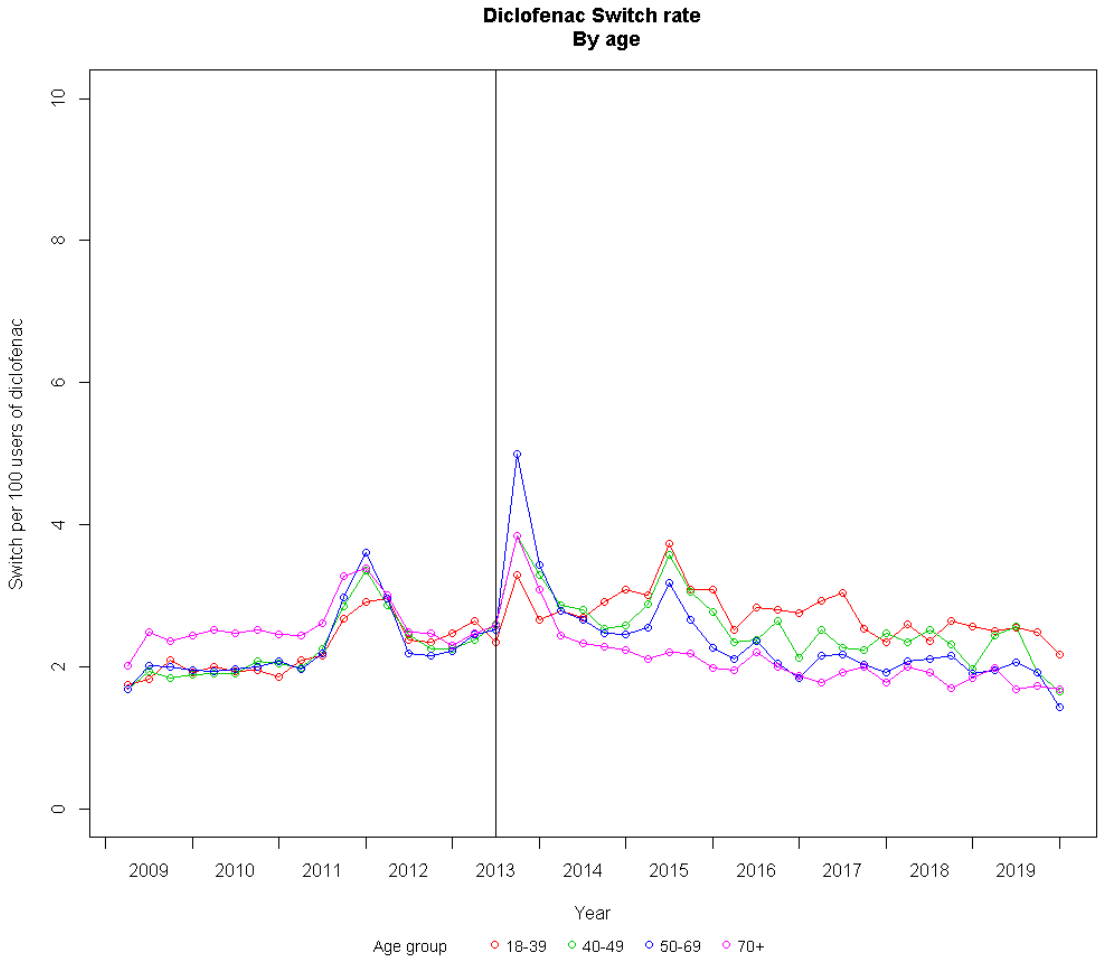

Figure 16. Switching to alternative analgesic drugs stratified by age during the study period.

In pre-intervention, there was a significant trend change in all age groups, except for those aged over 70 years old (0.020, P = .177), where there was no significant change in the baseline trend (Figure 17 and Table 7). Immediately after the intervention in 2013, there was no significant level change for those aged over 70 years old (0.020, P = .918), while the other age groups had a significant immediate change in level after 2013. In post-intervention, all age groups were with a significant trend changes when compared with the baseline trends in pre-intervention.

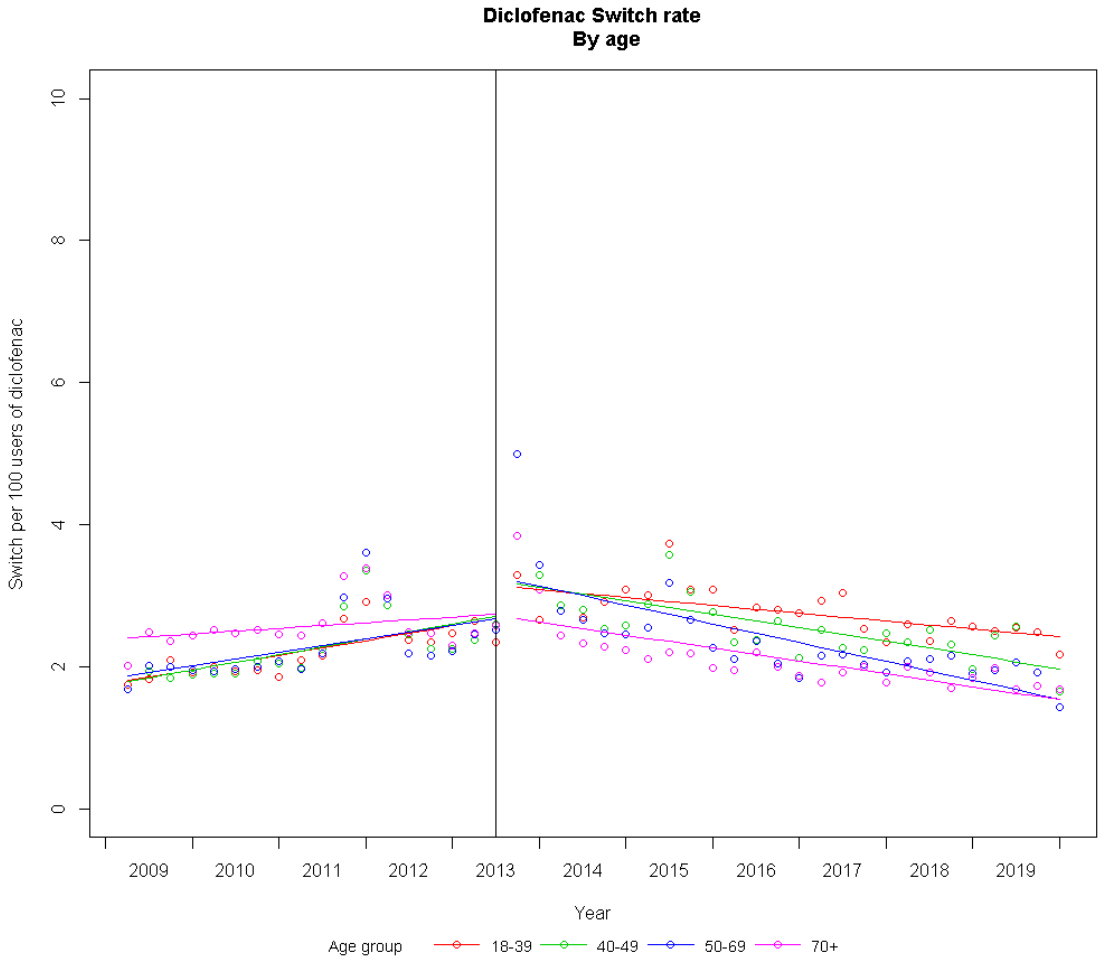

Figure 17. Trends in switching to alternative analgesic drugs stratified by age during the study period.

4.6 Impact of the 2013 EMA Regulatory Intervention on Diclofenac Use Stratified by Risk Groups

4.6.1 Impact of the 2013 EMA Regulatory Intervention on the Incidence of Diclofenac Use Stratified by Risk Groups

Diclofenac initiation was highest in patients that were at moderate and low risk for cardiovascular events (Figure 18). In 2009, the proportion of incident users in users of diclofenac was approximately 8% of total incident users at high risk, 45% of total incident users at moderate risk, and 47% of total incident users at low risk. Immediately after the intervention in 2013, the proportion of incident users started to decline in the low-risk group whereas it slightly increased for the high-risk group. In 2019, the proportion of incident users was 15% of total incident users at high risk and 40% of total incident users at low risk. The proportion of incident users at moderate risk was relatively stable during the study period

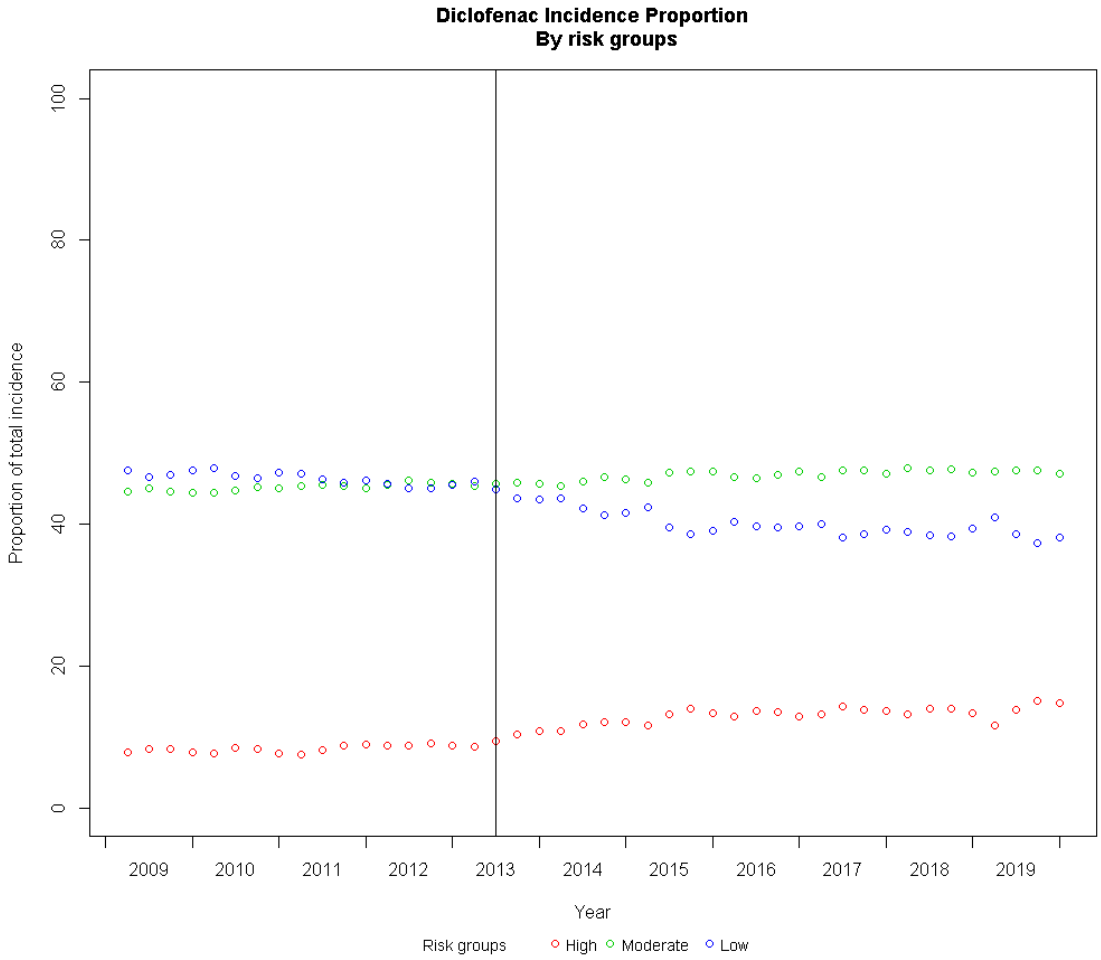

Figure 18. Incidence proportion of diclofenac use stratified by risk groups during the study period.

4.6.2 Impact of the 2013 EMA Regulatory Intervention on Discontinuation of Diclofenac Use Stratified by Risk Groups

The largest population based on their baseline risk that discontinued diclofenac use belonged to the low-risk group (Figure 19). However, discontinuation rate was relatively stable throughout the study period for all of the risk groups. In 2009, discontinuation was 24 per 100 users of diclofenac for those at high risk, 30 per 100 users of diclofenac for those at moderate risk, and 40 per 100 users of diclofenac for those at low risk. Before the regulatory intervention in 2013, the discontinuation rate declined slightly to 28 per 100 users of diclofenac for those at moderate risk and 38 per 100 users of diclofenac for those at low risk right, while discontinuation for those at high risk was rather stable. Immediately after the 2013, discontinuation did not change for all of the risk groups and remained stable throughout the end of the study period.

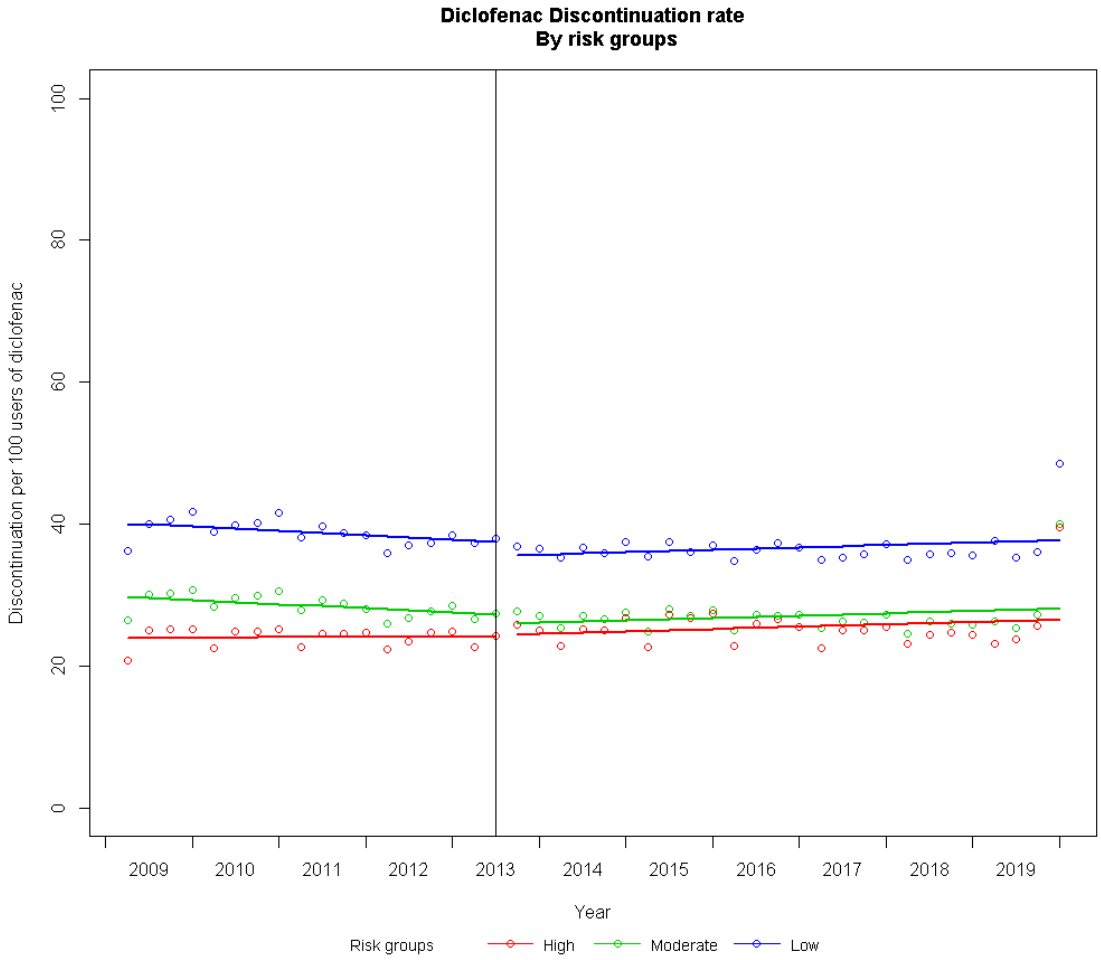

Figure 19. Trends in the discontinuation of diclofenac use stratified by risk groups during the study period.

Before the intervention in 2013, the baseline trend did not have a significant trend change for all risk groups (Table 8), where the discontinuation rate was relatively stable. There was also no significant level change for all risk groups immediately after the intervention and no significant trend change in post-intervention.

Table 8. Trend and level change results of the ITS regression analysis in the discontinuation of diclofenac use stratified by risk groups.

Usage patterns of discontinuers			
Risk groups	**Pre-intervention**	**Intervention**	**Post-intervention**
Low baseline risk	*-0.108 (-0.312, 0.095), P = .288*	*-1.557 (-4.272, 1.157), P = .253*	*0.146 (-0.089, 0.381), P = .216*
Moderate baseline risk	*-0.101 (-0.318, 0.117), P = .355*	*-0.930 (-3.834, 1.973), P = .521*	*0.119 (-0.132, 0.370), P = .342*
High baseline risk	*0.028 (-0.217, 0.273), P = .818*	*0.418 (-2.852, 3.688), P = .798*	*0.008 (-0.275, 0.290), P = .956*

4.6.3 Impact of the 2013 EMA Regulatory Intervention on Switching to Alternative Analgesic Drugs Stratified by Risk Groups

Switching to alternative analgesics was relatively higher among patients that were at high risk (Figure 20). Switching in 2009 was approximately 2.1 per 100 users of diclofenac for those at high risk, 1.9 per 100 users of diclofenac for those at moderate risk, and 1.6 per 100 users of diclofenac for those at low risk. The switching rate increased suddenly in between 2011 and 2012 and reached a maximum of 3.8 per 100 users of diclofenac for those at high and moderate risk, and 3.0 per 100 users of diclofenac for those at low risk. However, shortly after, the switching decreased by 42% to 2.2 per 100 users of diclofenac at high risk, 39% to 2.3 per 100 persons at moderate risk, and 33% to 2.0 per 100 persons at low risk. The switch rate was approximately 3.8 per 100 users of diclofenac at high risk, 3.7 per 100 users of diclofenac at moderate risk, and 2.2 per 100 persons at low risk right before the intervention in 2013. Immediately after the intervention, switch suddenly increased by 32% to 5.0 per 100 users of diclofenac at high risk, 24% to 4.6 per 100 users of diclofenac at moderate risk, and 63% to 3.6 per 100 users of diclofenac at low risk. But, switching dropped shortly after to 2.7 per 100 users of diclofenac at high risk, 2.8 per 100 users of diclofenac at moderate risk, and 2.5 per 100 users of diclofenac at low risk in 2014. In 2015, the switch rate increased slightly to 3.1 per 100 users of diclofenac for those at moderate and low risk and dropped shortly after. For all of the risk groups switching decreased slightly to 2.0 per 100 users of diclofenac at high risk, 1.7 per 100 users of diclofenac at moderate risk, and 1.6 per 100 users of diclofenac at low risk by the end of 2019.

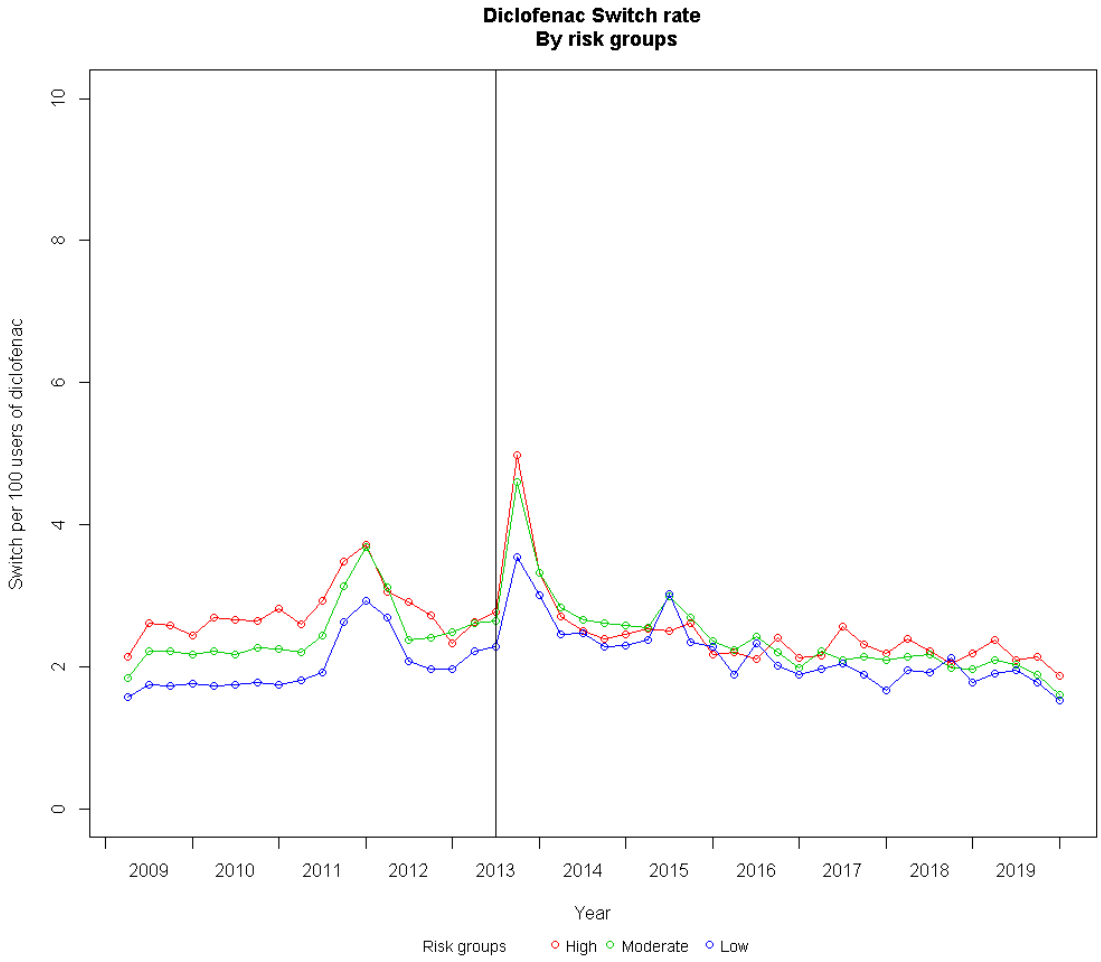

Figure 20. Switching to alternative analgesic drugs stratified by risk groups during the study period.

In pre-intervention, the baseline trend was significantly positive for the moderate-risk (0.045, P = .011) and low-risk groups (0.044, P = .002), however, there was no significant trend change in the high-risk group before the intervention in 2013 (Figure 21 and Table 9). Immediately after the intervention, there was a significant level change in the low-risk group (0.429, P = .021), but not for the other risk groups. In post-intervention, all risk groups were with a significant trend change when compared with the baseline trend in pre-intervention.

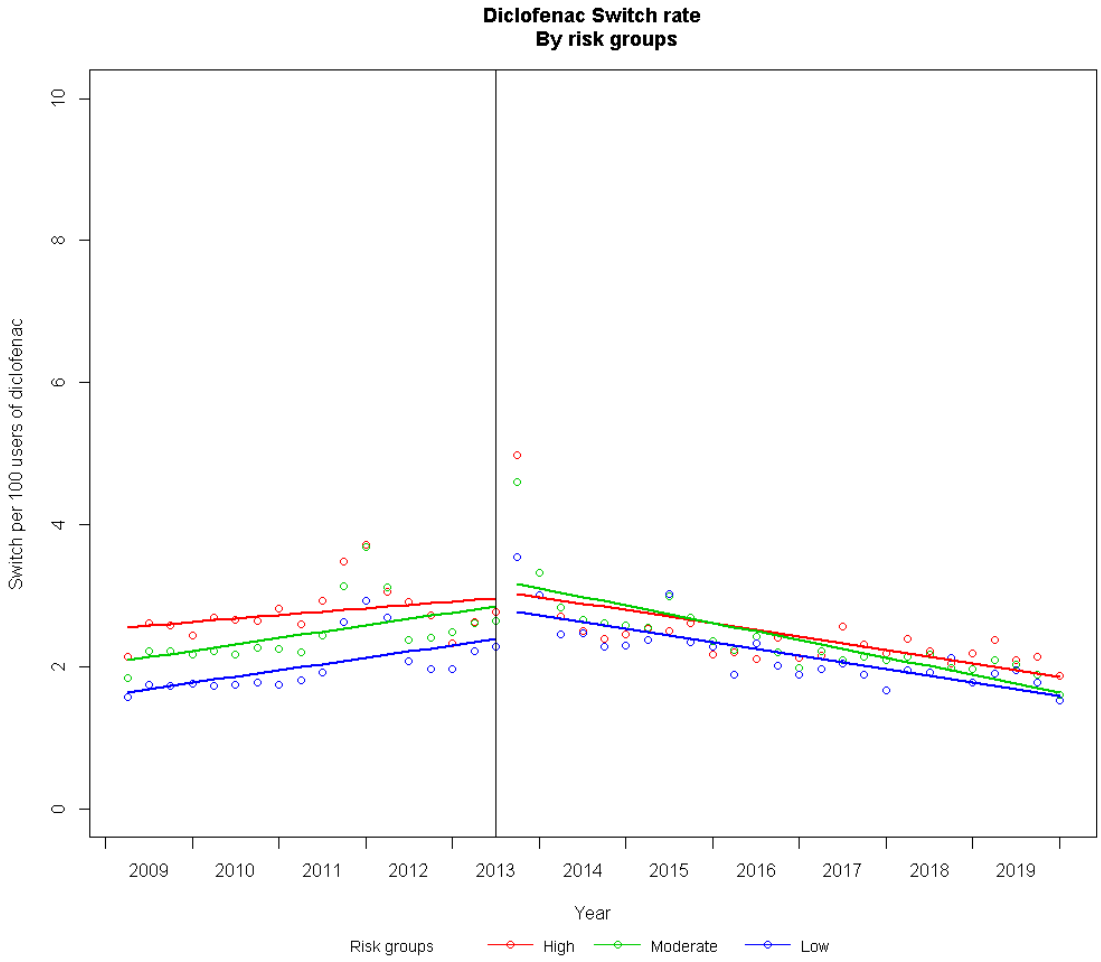

Figure 21. Trends in switching to alternative analgesic drugs stratified by risk groups during the study period.

Table 9. Trend and level change results of the ITS regression analysis in switching to alternative analgesic drugs stratified by risk groups.

Usage patterns of switchers			
Risk groups	**Pre-intervention**	**Intervention**	**Post-intervention**
Low baseline risk	*0.044 (0.017, 0.071), P = .002*	*0.429 (0.067, 0.791), P = .021*	*-0.091 (-0.123, -0.060), P = <.001*
Moderate baseline risk	*0.045 (0.011, 0.079), P = .011*	*0.375 (-0.080, 0.829), P = .103*	*-0.106 (-0.145, -0.067), P = <.001*
High baseline risk	*0.024 (-0.016, 0.064, P = .227*	*0.108 (-0.425, 0.641), P = .685*	*-0.071 (-0.117, -0.025), P = .003*

4.7 Sensitivity Analysis

The sensitivity analysis did not change much the outcome patterns, but only increased or decreased the outcome rates.

4.7.1 Applying a Gap Length of 30 Days when Constructing Treatment Episodes

A sensitivity analysis was performed using a more conservative gap length of 30 days to construct treatment episodes. The results of these analysis did not diverge much from the outcome patterns seen when using a 90-day gap length (Appendix C). The overall prevalence rate decreased slightly compared with the gap length of 90 days, however, the prevalence rate with a gap length of 30 days didn't not change much during the study period (Figure C1). The prevalence decrease was noticeable in 2009, where the prevalence decreased by 8% to 4.8 per 100 persons. Similar with the overall incidence rate, where the incidence only decreased slightly when compared with the 90 days gap analysis (Figure C2). Also, in 2009, the incidence decreased by 6% to 1.6 per 100 persons. The overall discontinuation rate increased but the pattern was the same, where discontinuation was stable during the study period (Figure C3). Overall, the discontinuation increased approximately by 26%. The overall switch rate increased also with the gap length of 30 days (Figure C4) and for example in 2009, the switch rate increased to 4.4 per 100 persons whereas the switch rate was 2.0 per 100 persons when the gap length was 90 days (Figure 14).

4.7.2 Assessment of Usage Patterns Based on Duration of Use

Assessment in patients with an episode duration of 60 days or more showed an overall decrease in discontinuation rate decreased (Figure 22) whereas an increase in switch rate for this group of patients (Figure 23). The discontinuation rate was relatively stable throughout the study period, but discontinuation decreased overall when compared with the main analysis (Figure 11). The discontinuation decreased by 71% to 10 per 100 users of diclofenac and remained stable throughout the study period. The sensitivity analysis in patients with a duration episode of 60 days or more showed no significant trend change in pre-intervention and no significant level change immediately after the intervention (Table 10). In post-intervention, there was also no significant trend change when compared with the baseline trend.

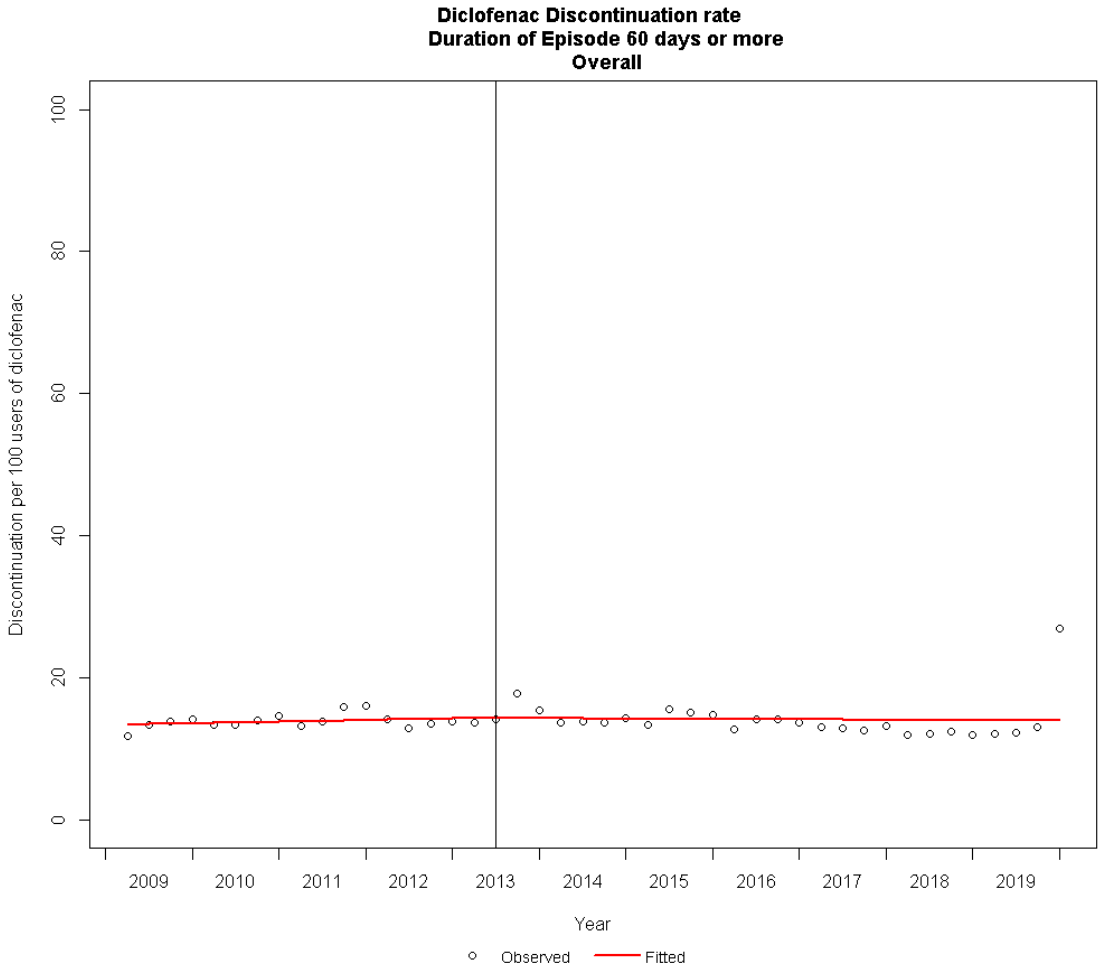

Figure 22. Sensitivity analysis with a duration episode of 60 days. Discontinuation of diclofenac use during the study period.

Table 10. Sensitivity analysis with a duration episode of 60 days or more. Trend and level results of the ITS analysis in discontinuation and switching.

Sensitivity analysis with a duration episode of 60 days or more			
Outcomes	**Pre-intervention**	**Intervention**	**Post-intervention**
Discontinuation rate	*0.056 (-0.165, 0.277), P = .610*	*-0.067 (-3.019, 2.885), P = .964*	*-0.070 (-0.325, 0.185), P = .583*
Switch rate	*0.050 (0.008, 0.092), P = .022*	*0.429 (-0.134, 0.993), P = .132*	*-0.122 (-0.171, -0.073), P = <.001*

The overall switch rate for patients with a duration episode of 60 days or more increased throughout the study period (Figure 23). For example, in 2009, the switch increased by 50% to 3.0 per 100 users of diclofenac, when compared with the switch rate in the main analysis (Figure 14). However, the switching pattern was similar to the main analysis. The sensitivity analysis showed a significant baseline trend in pre-

intervention but there was no significant level change immediately after the intervention in 2013 (Table 10). But the post-intervention trend change was significant when compared with the baseline trend in pre-intervention.

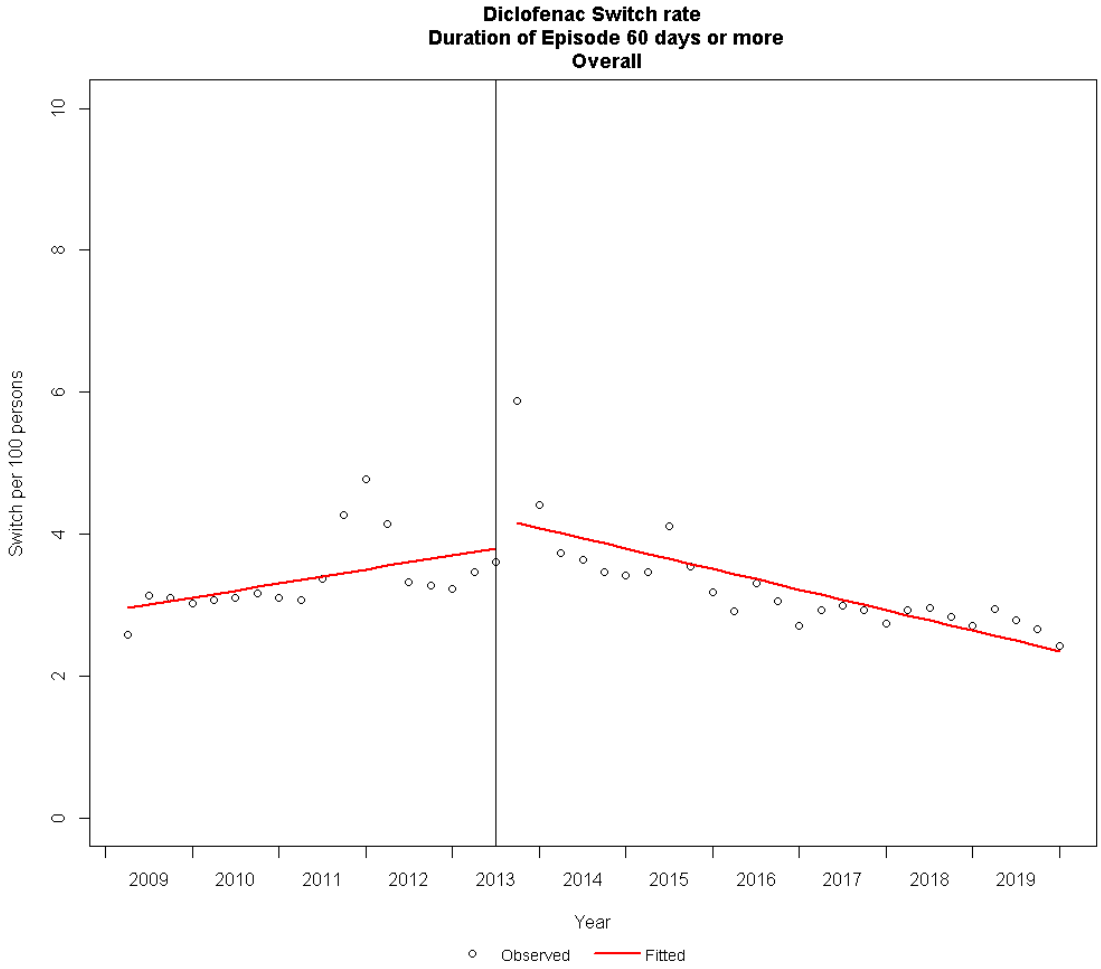

Figure 23. Sensitivity analysis with a duration episode of 60 days. Switching to alternative analgesic drugs during the study period.

5. DISCUSSION

In this study, we showed that the 2013 EMA regulatory intervention had a significant impact on prescribing patterns of diclofenac. While the overall prevalence and incidence of diclofenac use decreased during the study period, the regulatory intervention in 2013 was not associated with a significant change in the overall discontinuation of diclofenac use or overall switching to alternative analgesics. Interestingly, we observed that the overall prevalence and the overall incidence were already declining from 2009 until the intervention took place. In our study, the proportion of the three risk groups within the total incident users showed a decrease of proportion in the low-risk group while there was an increase of proportion in the high-risk group after the intervention in 2013. Also, the intervention did not have any significant effect on the discontinuation or switch rate for patients that belong to the high-risk group for cardiovascular events. When usage patterns for chronic diclofenac users with a duration episode of 60 days or longer were assessed, the overall discontinuation and switch rate did not change significantly due to the intervention, but the discontinuation decreased, whereas the switch rate increased overall.

Our results are in line with what was reported by Morales and colleagues that examined diclofenac prescribing in four different countries, including the UK (Morales et al., 2020). The switch rate was similar to the study from Morales et al, however, the same patterns for diclofenac discontinuation were not observed as in the study by Morales et al. From our analysis it seems that other factors might already have an impact on the prescribing patterns of diclofenac, even before the regulatory action in 2013 was implemented.

5.1 Regulatory Actions and Events that Might Impact Use of Diclofenac

This is an occurrence of events that might have had an impact of usage patterns of diclofenac over time (Table 11). The 2005 EMA regulatory action taken for the drug class COX-2 inhibitors might be one of the reasons that diclofenac use declined before the regulatory intervention in 2013. In 2005, the EMA concluded from its review on COX-2 inhibitors, that the drug class identified an increased risk of heart attacks and strokes. Questions about the safety of other types of NSAIDs were raised, whether the same safety concern was relevant for conventional NSAIDs as COX-2 inhibitors, remained unclear. As a result, the EMA recommended healthcare professionals and

patients to monitor use of NSAIDs and follow instructions in the product information (European Medicines Agency, 2005). Another possible reason for the pre regulatory intervention decline in diclofenac use could be that in 2006, the EMA reviewed the safety of non-selective NSAIDs and concluded that their use remained favourable, although the CHMP mentioned that they could not exclude whether or not there was an increased risk of thrombotic events. The CHMP concluded that the use of non-selective NSAIDs should be at the lowest effective dose and for short-time use only (European Medicines Agency, 2006). Therefore, these actions might have led the patients that previously used NSAIDs, including diclofenac, as a long-time use, however, decided to discontinue due to recommendations from the regulatory agency.

In 2012, the MHRA identified a similar increased risk of cardiovascular events in COX-2 inhibitors as in diclofenac and as a result they requested that the safety of diclofenac should be reviewed. The review concluded that heart attacks due to diclofenac use in patients with moderate risk would be expected to increase by 3 cases per year for every 1.000 people using diclofenac (Coxib and traditional NSAID Trialists' (CNT) Collaboration, 2013; European Medicines Agency, 2013). As discussions on this safety issue might already have been occurring in clinical practice prior to the MHRA conducting the review, these as well as the request for safety review of diclofenac might already had an impact on diclofenac use before the 2013 regulatory intervention.

In January 2015, the MHRA announced that diclofenac would no longer be sold over the counter (OTC), hence only sold with a prescription (Medicines and Healthcare products Regulatory Agency, 2015a). In June the same year, they also published a reminder for the existing prescribing advice for all NSAIDs in the June edition of Drug Safety Update (Medicines and Healthcare products Regulatory Agency, 2015b). These actions are likely to have affected diclofenac use in 2015.

Table 11. Timeline of regulatory activities and other activities that might have an impact on the use of diclofenac and other NSAIDs.

Date	Activities
2005	*The EMA reviewed COX-2 inhibitors and identified an increased risk of thrombotic events on the use of these types of NSAIDs (European Medicines Agency, 2005).*
2006	*The EMA concluded that a small increased risk of thrombotic events on the use of non-selective NSAIDs, including diclofenac, could not be excluded (European Medicines Agency, 2006).*
October 2012	*A request from the UK regulatory agency, MHRA, that the EMA reviews the safety of diclofenac use in response to findings from the 2012 review of NSAIDs (European Medicines Agency, 2013).*
28 June 2013	*The 2013 regulatory intervention took place. The EMA reviewed diclofenac and recommended updates to the treatment advice for diclofenac (European Medicines Agency, 2013). Updated contraindications and prescribing advice for diclofenac were highlighted in the June 2013 edition of Drug Safety Update (Medicines and Healthcare products Regulatory Agency, 2013).*
14 January 2015	*The MHRA press release; diclofenac tablets will no longer be sold OTC, hence only purchased with a prescription from a doctor (Medicines and Healthcare products Regulatory Agency, 2015a).*
June 2015	*The MHRA gave out new prescribing advice on the use of ibuprofen and reminded on existing prescribing advice for all NSAIDs in the June 2015 edition of Drug Safety Update (Medicines and Healthcare products Regulatory Agency, 2015b).*

5.2 Prevalence and Incidence of Diclofenac Use

Our results showed that the prevalence declined by 48% from 2009 to 2013 while incidence declined by 53%. One of the possible reasons for this decline of prevalence and incidence of diclofenac could be related to the discussion in the UK about diclofenac in 2011 and 2012, when the MHRA requested that the EMA should review the safety of diclofenac in response to findings from the 2012 review of NSAIDs (European Medicines Agency, 2012a, 2013). This review showed that around 8 in 1.000 patients using diclofenac and with moderate risk for heart disease were likely to have a heart attack over a year, which could have resulted in reluctancy in using diclofenac by clinical practitioners. Furthermore, another possible reason for this decline before the 2013 regulatory intervention, that in 2006 the EMA concluded that a small increased risk of thrombotic events could not be excluded when using non-selective NSAIDs. A study showed that patients using diclofenac for a long time

showed thrombotic event rates of 1.30 per 100 patient-years when compared with etoricoxib. Therefore, the EMA advice that diclofenac should be used at the lowest dosage and shortest duration possible (Cannon et al., 2006; European Medicines Agency, 2006). Also, the 2005 EMA regulatory intervention for COX-2 inhibitors (European Medicines Agency, 2005) might have had unintended effects on the use of diclofenac, which might resulted the decline of diclofenac use before the 2013 regulatory intervention, though it remains unclear whether this was a possible reason or not.

In our study, the use of diclofenac was most prevalent in older patients when compared to the youngest patients. In 2009, the prevalence rate was 7.7 per 100 persons for the oldest age group, while the rate was 2.2 per 100 persons for the youngest age group. Although diclofenac use decreased during the study period, the oldest age group were still with a higher diclofenac use than the youngest age group by the end of 2019. These difference between the age groups could be because older patients with chronic pains were using diclofenac more often than the younger patients who were likely to use diclofenac as a one-time use. Also, a study on analgesic use in Germany showed a similar prevalence in diclofenac use among adult patients, where diclofenac use increased with age from 2008 to 2011. Their study showed that the prevalence was highest (8.8%) in the oldest age group (≥65 years) and lowest (1.2%) in the youngest age group (18-29 years) (Sarganas et al., 2015). Also, our results indicated that the regulatory intervention had a higher impact on older patients than younger patients, which might imply that older patients were likely to have a higher risk for cardiovascular events. As a result, it was important to not increase that risk for older patients, hence, why the intervention had a bigger influence in older patients than younger patients.

5.3 Discontinuation of Diclofenac Use

Interestingly, in our study, we did not find any impact of the regulatory intervention on the diclofenac discontinuers. The discontinuation rates were 35 per 100 users of diclofenac and remained relatively stable throughout the study period. This is contrary to what the study from Morales et al, which showed that the diclofenac discontinuation rates were already falling before the intervention. Morales and colleagues showed a fall in discontinuation rates from 40% of exposed patients in 2006-2011 to 35% of exposed patients in 2013 and after the intervention to 20% of exposed patients (Morales et al., 2020). The reason for this difference in our findings might related to the

difference in the selected study population. The study of Morales et al, included all ages, whereas in our study only adult (≥18 years old) patients were included. Furthermore, diclofenac use in younger patients are more likely to be short time use rather than long time use. As shown in our study, discontinuation was higher in younger patients than in older patients, which might indicate that younger patients were usually using diclofenac for a short time, hence, leading to a higher discontinuation rate. Diclofenac prescription in children are, however, usually unlicensed and off labelled due to control for intra- and/or post-operative acute pain (Conroy & Peden, 2001). This might be the difference in rate between these two studies, however, it is unclear whether the inclusion criteria would have a big impact on the results of this study. Morales et al also pointed out from a previous systematic review that healthcare professionals tend to adopt the safety advisory of an intervention more quickly to new patients requiring treatment rather than the existing patients continuing drug treatment use (Dusetzina et al., 2012; Morales et al., 2020). This might likely apply for younger patients since diclofenac initiation or new users tended to be younger patients than older patients (Schmidt, Sørensen, & Pedersen, 2018). Also, it might be that most patients in this study were using diclofenac as a temporary pain medication and not as much as for chronic pain.

5.4 Switching to Alternative Analgesic Drugs

Our results showed three sudden increase in switching to alternative analgesics in 2011-2012, 2013, and 2015, where the overall switch rate increased suddenly by 75% in 2011-2012, 68% in 2013, and 15% in 2015 and dropped shortly after each time. The peak in between 2011-2012 gives us a clearer picture that when the MHRA requested that the EMA should review diclofenac in 2012, that might have affected diclofenac use before the actual intervention was implemented. Patients using diclofenac at that time might have felt the need to switch to another analgesic, especially, when the safety of diclofenac use was questionable. Also, when the regulatory intervention for diclofenac was implemented in 2013, the sudden increase in switching might have made healthcare professionals and patients more aware of the risk of diclofenac use and decided to switch to another analgesic. In 2015, when diclofenac tablets would no longer be sold OTC in the UK (Medicines and Healthcare products Regulatory Agency, 2015a), and the MHRA gave out new prescribing advice for ibuprofen and reminder of the existing prescribing advice for all NSAIDs (Medicines and Healthcare products Regulatory Agency, 2015b). These statements might have impacted the use of

diclofenac in 2015 and might explain the sudden increase in the overall switch rate in 2015, where healthcare professionals and patients were reminded of the prescribing advice for diclofenac. Our results showed that patients were mostly switching to paracetamol, which is in many ways a safer option, especially for those at high risk for cardiovascular events when using diclofenac. However, several patients were switching to opioids, which can be a concern. Especially, when awareness of opioid has been going on globally, to prevent an increase in death rates due to opioid abuse.

Interestingly, our results from the ITS analysis on the switch rate showed no significant level change immediately after the intervention in 2013, even though there was an obvious increased peak in switch rate immediately after 2013. This might be because the increase of switching in 2013 did not have enough observations, where the rate decreased drastically the next time point, hence, the statistical analysis was not able to capture this change properly and making it insignificant. In our study, older patients were switching more often than younger patients, which indicates that older patients that were likely to have specific contraindications for diclofenac were already switching before the intervention in 2013.

5.5 The Risk Groups

Assessment of the risk groups as defined by the EMA safety warnings was important to see if the impact varied depending on the underlying risk for cardiovascular events. A study from Schmidt et al showed that diclofenac initiators with a history of myocardial infarction or heart failure were at the highest absolute risk for major adverse cardiovascular events when compared with patients in low and moderate baseline risk (Schmidt et al., 2018). In our study, we investigated the group of diclofenac initiators to see how the patients in the risk groups were divided over this group. Our results showed that lowest proportion of diclofenac users included patients in high risk for cardiovascular events throughout the study period. However, the proportion of the high-risk group showed a slight increase in diclofenac initiation during the study period, where the proportion incidence was 8% in 2009 and increased to 15% in 2019. Whereas, the incidence proportion for the low-risk group decreased throughout the study period.

The discontinuation of diclofenac use was the greatest in the low-risk group when compared with the other risk groups. Those that were in the low-risk group consist mostly of patients that have less health-issues than those that were in the moderate and high-risk groups. Thus, it might be possible that the low-risk groups were

often using diclofenac as a one-time use and leading to a higher discontinuation rate than the other risk groups. Whereas, the moderate and high-risk group, that were with more health-issues than the low-risk group, could be using diclofenac more chronically, leading to a lower discontinuation rate. The regulatory intervention in 2013 did not affect the discontinuation rate in the high-risk group patients, and it remained constant during the whole study period. Although one would expect those in the high-risk group to have frequently stopped using diclofenac after the EMA concluded that the use of diclofenac was associated with the risk of cardiovascular events for those specific patients in the high-risk group, we did not find changes in the discontinuation rate. The overall switch rate showed that the high-risk group were switching more than the other risk groups. The switching in all the risk groups showed the same pattern as the overall switch rate. Switching was the highest immediately after the intervention in the high-risk group, where it increased by 32%. As stated above, patients were mostly switching to paracetamol, which is a safer analgesic for those that are in high risk for experiencing cardiovascular events, and especially, if they need to continue pain treatment. These changes in use might lead to an unintentional impact on use of paracetamol after the regulatory intervention of diclofenac in 2013, where the use of paracetamol increased.

5.6 Sensitivity Analysis

To assess our definitions and the impact of these we conducted a sensitivity analysis to see if there were any changes in the overall outcome rates. A more conservative gap length of 30 days provided similar results as the main analysis. The analysis using 30-day gap length showed that the prevalence and incidence of diclofenac use decreased a little bit before the intervention in 2013, while the discontinuation and switch rate increased overall. The sensitivity analysis did not change the prescribing pattern seen but more increased or decreased the general rates. These changes are most visible in the overall discontinuation and switch rate when compared with the main analysis, where more patients were discontinuing diclofenac use and switching more to alternative analgesics.

5.7 Impact of Seasonality on Drug Use Patterns and Dealing with Autocorrelated Data

Drugs are usually not used at random and for many, a certain seasonality can be visible in their usage pattern. Most of the results in this study showed seasonal fluctuations and this was especially visible in the prevalence and incidence rate when stratified by age. Where the oldest age group (≥70 years old) showed a more distinct seasonality pattern when compared with the other age groups. One of the reasons for this might be because older patients tend to be more sensitive to pain in wintertime, where they experience more stiffness and joint pain in cold weather (Timmermans et al., 2015; Timmermans et al., 2014). That might explain the seasonality pattern for this age group, where it is more common for them to be prescribed pain medication in wintertime. From a statistical point of view, in the analysis, seasonal autocorrelation can be adjusted when an ARIMA model for time series modelling would have been applied. However, this study only had 44 observation points for all outcomes, which is insufficient for conducting an ARIMA model analysis. Also, monthly data points would be preferable when adjusting for seasonal autocorrelation (Wagner et al., 2002).

Autocorrelation of data can be a common problem when conducting time series analysis, as time series tend to be correlated in time. Autocorrelation means that observations are correlated to one another, where observations are similar to one another than those that are further apart. Also, autocorrelation is often related to seasonality, where observations in one month can be similar within the same time of year, hence, leading to autocorrelation (Bernal, Cummins, & Gasparrini, 2016). This is specifically important in studies that aim to predict future outcomes, where previous values are used for a prediction of the next value. Also, if autocorrelation is not corrected then the standard errors may be underestimated, and the significant effects of an intervention may be overestimated (Wagner et al., 2002). In our study, a linear regression model was used for the statistical analysis and the variables were not adjusted for autocorrelation. However, the Durbin Watson test indicated that there was autocorrelation present. When checking the overall incidence rate, the segment before the intervention was likely autocorrelated, while the segment after the intervention was not, indicating that the observations were independent of each other. The reason for not adjusting for autocorrelation in this study was because usually adjustment for autocorrelation would be preferred when making predictions for future values, which was not the scope of this study. As stated above, applying an ARIMA model analysis was not feasible due to low number of data points (44 points in total).

5.8 Understanding the Results in the Clinical Context

In this study, usage patterns of a single drug were assessed, however, importantly drug patterns related to regulatory interventions should never be assessed in silos as every intervention has an intended or unintended impact that could lead to the use of a different type of drug. The best way to assess this would be to have a control group that is similar to the study group and followed up throughout the study period that is not expected to be impacted by the intervention (Wagner et al., 2002). For example, in this study, it would been interesting to observe the prescribing patterns of naproxen, another type of NSAID, and compared it with the prescribing patterns of diclofenac. Recent studies indicate that naproxen and low-dose ibuprofen have the lowest risk of cardiovascular effects to a problematic extent when compared with all the other NSAIDs (Coxib and traditional NSAID Trialists' (CNT) Collaboration, 2013; Salvo et al., 2014). Also, in the guidelines from the National Institute for Health and Care Excellence (NICE), they considered naproxen and low-dose ibuprofen to have the most favourable thrombotic cardiovascular safety profile when compared with all NSAIDs, and they are usually recommended as the first-line pain medication (National Institute for Health and Care Excellence, 2018). It would have been interesting to see if the regulatory intervention for diclofenac affected the prescribing of naproxen. Thus, if patients that were discontinuing diclofenac use and switching over to naproxen instead. Especially, when our results show that patients were often switching to naproxen. If the intervention for diclofenac had an unintended effect on naproxen then theoretically the prescribing of naproxen would have increased during the study period, while the prescribing of diclofenac decreased. Although this is what could have been expected an unintended effect, this could also be an increase in safety risks related to naproxen use, such as gastrointestinal effects. There is always a balance when treating patients which means weighting risks and benefits of clinical practice.

These analyses were originally planned for this project but due to the COVID-19 pandemic outbreak and the related delays in data delivery we are unable to extract this data and conduct this part of the study.

5.9 Strengths and Limitations

One of the strengths of this study was the large data source that was used representing real clinical practice in primary care. We also applied a time-series design for assessing

the impact which is one of the strongest, quasi-experimental design to estimate the impact and effects of interventions when randomised settings are not conducted. Besides, randomised controlled trials on interventions are rarely feasible to measure the impact of interventions (Wagner et al., 2002; Zhang, Wagner, & Ross-Degnan, 2011).

This study has several limitations, for example, the data source in this study was not able to capture diclofenac use or the alternative analgesics use OTC since the data source only collects primary care data from GPs. Also, sometimes GPs don't register all the information on patient characteristics and also this study was not able to capture if patients were using the drugs that they got prescribed. Although ITS analysis is a robust study design to evaluate the impact of regulatory interventions, it has some limitations, such as it requires sufficient number of data points. In addition, other factors that were occurring in clinical practice during the study period might affect the prescribing behaviours (Goedecke et al., 2018; Wagner et al., 2002). By creating a timeline of important clinical evidence and regulatory decisions, we tried to account for these and interpret our findings within this context. Another limitation would be that not adjusting for autocorrelation might lead to misinterpreting the results in the statistical analysis although this would not have had an impact on the absolute values. These showed for some of the patterns striking differences over time.

6. CONCLUSIONS

In conclusion, the 2013 EMA regulatory intervention was associated with a significant impact on the prevalence and incidence of diclofenac use. Although diclofenac use was already found to be declining prior to the intervention, we found a significant decline when the intervention was implemented in 2013. The intervention had a less significant impact on the discontinuation of diclofenac and switching to alternative analgesics. Also, there was no significant impact of the intervention on patients with high baseline risks for cardiovascular events.

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APPENDIX

Appendix A

The following are list of product codes for diclofenac-containing medicinal products that were used to extract data in this study. Also, a list of the alternative analgesic drugs and the covariates that were used for extraction.

Table A1. List of products codes for diclofenac-containing medicinal products used for extracting data in the CPRD.

Product code	Product name	Drug substance name
33669	Diclofenac 50mg Gastro-resistant tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
32601	Econac 100mg suppositories (AMCo)	Diclofenac sodium
14678	Defanac sr 100mg Modified-release tablet (Ranbaxy (UK) Ltd)	Diclofenac sodium
21444	Volraman 25mg gastro-resistant tablets (LPC Medical (UK) Ltd)	Diclofenac sodium
50602	Diclofenac potassium 50mg tablets (Alliance Healthcare (Distribution) Ltd)	Diclofenac potassium
29037	Valdic 100 Retard tablets (Fannin UK Ltd)	Diclofenac sodium
2387	Arthrotec 75 gastro-resistant tablets (Pfizer Ltd)	Diclofenac sodium/Misoprostol
17532	Dicloflex Retard 100mg tablets (Kent Pharmaceuticals Ltd)	Diclofenac sodium
57006	Diclofenac sodium 25mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	Diclofenac sodium
51293	Diclofenac potassium 50mg tablets (Phoenix Healthcare Distribution Ltd)	Diclofenac potassium
9465	Diclotard 100 100mg Modified-release tablet (Galen Ltd)	Diclofenac sodium
2386	Voltarol Retard 100mg tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
612	Dicloflex 25mg gastro-resistant tablets (Dexcel-Pharma Ltd)	Diclofenac sodium
48059	Diclofenac potassium 50mg tablets (A A H Pharmaceuticals Ltd)	Diclofenac potassium
50058	Voltarol 50mg dispersible tablets (DE Pharmaceuticals)	Diclofenac sodium
49059	Voltarol 50mg dispersible tablets (Lexon (UK) Ltd)	Diclofenac sodium
27055	Diclofenac sodium 50mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)	Diclofenac sodium
73109	Diclofenac 75mg/ml solution for injection ampoules	Diclofenac sodium
67220	Diclofenac sodium 100mg modified-release tablets (Phoenix Healthcare Distribution Ltd)	Diclofenac sodium
18151	Voltarol Pain-eze 1.16% Emulgel (GlaxoSmithKline Consumer Healthcare)	Diclofenac diethylammonium
5085	Voltarol Rapid 50mg tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac potassium
49132	Voltarol 1.16% Emulgel (Necessity Supplies Ltd)	Diclofenac diethylammonium
42793	Diclofenac 100mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
11522	Pennsaid 1.50% Cutaneous solution (Provalis Healthcare Ltd)	Diclofenac sodium
64595	Misofen 50mg/200microgram gastro-resistant tablets (Morningside Healthcare Ltd)	Diclofenac sodium/Misoprostol
16286	Lofensaid Retard 75 tablets (Opus Pharmaceuticals Ltd)	Diclofenac sodium
73131	Diclofenac 25mg Gastro-resistant tablet (Almus Pharmaceuticals Ltd)	Diclofenac sodium

54021	Voltarol Retard 100mg tablets (Sigma Pharmaceuticals Plc)	Diclofenac sodium
14084	Diclovol 75mg SR tablets (Arun Pharmaceuticals Ltd)	Diclofenac sodium
59880	Diclofenac sodium 75mg modified-release capsules (Waymade Healthcare Plc)	Diclofenac sodium
54660	Diclofenac sodium 50mg capsules	Diclofenac Sodium
928	Diclofenac sodium 25mg tablets	Diclofenac Sodium
18798	Lofensaid 50mg gastro-resistant tablets (Opus Pharmaceuticals Ltd)	Diclofenac sodium
61762	Diclofenac 10mg/5ml oral suspension	Diclofenac sodium
9886	Dicloflex 50mg Gastro-resistant tablet (Ratiopharm UK Ltd)	Diclofenac sodium
17491	Dicloflex sr 75mg Tablet (Ratiopharm UK Ltd)	Diclofenac sodium
25283	Valenac ec 50mg Gastro-resistant tablet (Shire Pharmaceuticals Ltd)	Diclofenac sodium
14884	Voltarol Gel Patch 1% medicated plasters (Novartis Consumer Health UK Ltd)	Diclofenac epolamine
10978	Voltarol 25mg Suppository (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
5200	Voltarol 50mg suppositories (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
71064	Diclofenac sodium 75mg modified-release capsules (Waymade Healthcare Plc)	Diclofenac sodium
162	Arthrotec 50 gastro-resistant tablets (Pfizer Ltd)	Diclofenac sodium/Misoprostol
4506	Volsaid Retard 75 tablets (Chiesi Ltd)	Diclofenac sodium
62636	Diclofenac sodium 25mg gastro-resistant tablets (Sterwin Medicines)	Diclofenac sodium
34744	Diclofenac 100mg Modified-release capsule (Sandoz Ltd)	Diclofenac sodium
74048	Diclomax Retard 100mg capsules (Mawdsley-Brooks & Company Ltd)	Diclofenac sodium
31944	Diclofenac sodium 25mg gastro-resistant tablets (Mylan)	Diclofenac sodium
69477	Voltarol Rapid 50mg tablets (DE Pharmaceuticals)	Diclofenac potassium
56898	Rhumalgan SR 75mg capsules (Actavis UK Ltd)	Diclofenac sodium
17126	Fenactol SR 75mg tablets (Discovery Pharmaceuticals)	Diclofenac sodium
60443	Diclofenac sodium 75mg modified-release capsules (DE Pharmaceuticals)	Diclofenac sodium
40756	Dicloflex 25mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	Diclofenac sodium
47501	Rhumalgan SR 75mg capsules (Almus Pharmaceuticals Ltd)	Diclofenac sodium
62851	Voltarol 1.16% Emulgel (Mawdsley-Brooks & Company Ltd)	Diclofenac diethylammonium
48218	Dicloflex sr 100mg Tablet (Teva UK Ltd)	Diclofenac sodium
20395	Flamatak MR 75mg tablets (Actavis UK Ltd)	Diclofenac sodium
2293	Voltarol 25mg/ml Injection (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
51237	Voltarol 1.16% Emulgel (Waymade Healthcare Plc)	Diclofenac diethylammonium
33645	Diclofenac 75mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
1984	Diclofenac sodium 100mg modified-release tablets	Diclofenac Sodium
31383	Dexomon 75mg SR tablets (Hillcross Pharmaceuticals Ltd)	Diclofenac sodium
3421	Diclomax sr 75mg Modified-release capsule (Provalis Healthcare Ltd)	Diclofenac sodium
39823	Dicloflex 50mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	Diclofenac sodium
33559	Diclofenac 50mg Tablet (C P Pharmaceuticals Ltd)	Diclofenac sodium
74028	Diclomax SR 75mg capsules (Waymade Healthcare Plc)	Diclofenac sodium
34362	Diclofenac 25mg Gastro-resistant tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
20384	Flamatak MR 100mg tablets (Actavis UK Ltd)	Diclofenac sodium
31787	Econac SR 75mg tablets (AMCo)	Diclofenac sodium

55913	Voltarol 50mg suppositories (Lexon (UK) Ltd)	Diclofenac sodium
26631	Rhumalgan XL 100mg capsules (Sandoz Ltd)	Diclofenac sodium
14707	Defanac Retard 100mg tablets (Ranbaxy (UK) Ltd)	Diclofenac sodium
37688	Diclofenac sodium 1% gel	Diclofenac Sodium
597	Diclofenac potassium 50mg tablets	Diclofenac potassium
44112	Voltarol Joint Pain 12.5mg tablets (Novartis Consumer Health UK Ltd)	Diclofenac potassium
11540	Diclofenac 16mg/ml topical solution	Diclofenac sodium
5401	Voltarol Rapid 25mg tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac potassium
34271	Diclofenac sodium 100mg modified-release tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium
29330	Diclofenac sodium 50mg gastro-resistant tablets (Sandoz Ltd)	Diclofenac sodium
34212	Diclofenac 75mg Modified-release tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
30923	Diclofenac 100mg suppositories (A A H Pharmaceuticals Ltd)	Diclofenac sodium
69683	Diclofenac 2.32% gel (Colorama Pharmaceuticals Ltd)	Diclofenac diethylammonium
50317	Voltarol 75mg SR tablets (Lexon (UK) Ltd)	Diclofenac sodium
52229	Voltarol 1.16% Emulgel (Sigma Pharmaceuticals Plc)	Diclofenac diethylammonium
6881	Solaraze 3% gel (Almirall Ltd)	Diclofenac sodium
57045	Voltarol 50mg dispersible tablets (Waymade Healthcare Plc)	Diclofenac sodium
33994	Diclofenac sodium 25mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
17030	Rhumalgan SR 75mg capsules (Sandoz Ltd)	Diclofenac sodium
17029	Rhumalgan CR 75 tablets (Sandoz Ltd)	Diclofenac sodium
1233	Diclofenac sodium 75mg modified-release tablets	Diclofenac Sodium
53345	Voltarol Rapid 50mg tablets (Lexon (UK) Ltd)	Diclofenac potassium
74835	Diclomax Retard 100mg capsules (DE Pharmaceuticals)	Diclofenac sodium
65007	Voltarol 140mg medicated plasters (GlaxoSmithKline Consumer Healthcare)	Diclofenac sodium
26351	Rheumatac Retard 75 tablets (AMCo)	Diclofenac sodium
8062	Motifene 75mg modified-release capsules (Daiichi Sankyo UK Ltd)	Diclofenac sodium
32854	Diclofenac sodium 75mg modified-release capsules (A A H Pharmaceuticals Ltd)	Diclofenac sodium
48871	Diclofenac potassium 25mg tablets (Accord Healthcare Ltd)	Diclofenac potassium
25361	Diclovol 25mg gastro-resistant tablets (Arun Pharmaceuticals Ltd)	Diclofenac sodium
64759	Diclofenac 50mg/5ml oral solution	Diclofenac sodium
45814	First Resort Double Action Pain Relief 12.5mg tablets (Actavis UK Ltd)	Diclofenac potassium
19382	Slofenac 75mg SR tablets (Sterwin Medicines)	Diclofenac sodium
499	Diclofenac 50mg suppositories	Diclofenac sodium
6115	Diclofenac sodium 3% gel	Diclofenac sodium
11168	Volsaid Retard 100 tablets (Chiesi Ltd)	Diclofenac sodium
11215	Voltarol 25mg suppositories (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
30942	Diclofenac 50mg Tablet (Regent Laboratories Ltd)	Diclofenac sodium
54906	Diclofenac 50mg/5ml oral suspension	Diclofenac sodium
52389	Voltarol 50mg suppositories (Sigma Pharmaceuticals Plc)	Diclofenac sodium
1115	Diclofenac sodium 100mg modified-release capsules	Diclofenac sodium

61596	Diclofenac sodium 75mg modified-release capsules (Phoenix Healthcare Distribution Ltd)	Diclofenac sodium
74451	Diclofenac sodium 25mg gastro-resistant tablets (Waymade Healthcare Plc)	Diclofenac sodium
65783	Diclofenac potassium 50mg tablets (DE Pharmaceuticals)	Diclofenac potassium
51099	Voltarol Rapid 50mg tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac potassium
66577	Diclofenac sodium 75mg modified-release capsules (Sigma Pharmaceuticals Plc)	Diclofenac sodium
51808	Diclofenac 12.5mg/5ml oral solution	Diclofenac sodium
30297	Diclofenac 50mg Gastro-resistant tablet (Pharmacia Ltd)	Diclofenac sodium
39876	Mobigel 4% spray (Mercury Pharma Group Ltd)	Diclofenac sodium
4095	Voltarol 12.5mg Suppository (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
38817	Diclofenac potassium 12.5mg tablets	Diclofenac potassium
24121	Diclofenac sodium 25mg gastro-resistant tablets (Actavis UK Ltd)	Diclofenac sodium
34487	Diclofenac sodium 50mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
39708	Diclofenac 4% cutaneous spray	Diclofenac sodium
1116	Diclofenac 100mg suppositories	Diclofenac sodium
58071	Voltarol Rapid 50mg tablets (Waymade Healthcare Plc)	Diclofenac potassium
47350	Voltarol Active 4% spray (Novartis Consumer Health UK Ltd)	Diclofenac sodium
56078	Rhumalgan XL 100mg capsules (Almus Pharmaceuticals Ltd)	Diclofenac sodium
21824	Flamrase 50 EC tablets (Teva UK Ltd)	Diclofenac sodium
40086	Acoflam 50mg gastro-resistant tablets (Mercury Pharma Group Ltd)	Diclofenac sodium
28553	Diclofenac sodium 50mg gastro-resistant tablets (Teva UK Ltd)	Diclofenac sodium
42455	Dicloflex Retard 100mg tablets (Teva UK Ltd)	Diclofenac sodium
72396	Diclofenac sodium 50mg gastro-resistant tablets (Medreich Plc)	Diclofenac sodium
51343	Voltarol Rapid 25mg tablets (DE Pharmaceuticals)	Diclofenac potassium
45213	Diclofenac 10mg dispersible tablets	Diclofenac sodium
580	Diclofenac sodium 75mg modified-release tablets	Diclofenac sodium
18921	Fenactol 25mg gastro-resistant tablets (Discovery Pharmaceuticals)	Diclofenac sodium
74348	Voltarol 100mg suppositories (Sigma Pharmaceuticals Plc)	Diclofenac sodium
24236	Slofenac 100mg Modified-release tablet (Sterwin Medicines)	Diclofenac sodium
4806	Voltarol 100mg suppositories (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
28390	Valenac ec 25mg Gastro-resistant tablet (Shire Pharmaceuticals Ltd)	Diclofenac sodium
18371	Digenac xl 100mg Modified-release tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
30282	Diclofenac 75mg Modified-release tablet (Galen Ltd)	Diclofenac sodium
27200	Diclovol Retard 100mg tablets (Mylan)	Diclofenac sodium
10792	Voltarol 50mg Suppository (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
25362	Defanac 25mg gastro-resistant tablets (Ranbaxy (UK) Ltd)	Diclofenac sodium
56282	Diclofenac 2.32% gel	Diclofenac diethylammonium
157	Voltarol 100mg Suppository (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
1096	Diclofenac sodium 25mg gastro-resistant tablets	Diclofenac Sodium
16272	Lofensaid Retard 100 tablets (Opus Pharmaceuticals Ltd)	Diclofenac sodium
50269	Arthrotec 75 gastro-resistant tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac sodium/Misoprostol

42406	Diclofenac 50mg Gastro-resistant tablet (Almus Pharmaceuticals Ltd)	Diclofenac sodium
25790	Rhumalgan 25mg Tablet (Lagap)	Diclofenac sodium
31950	Diclofenac sodium 50mg gastro-resistant tablets (Sterwin Medicines)	Diclofenac sodium
3416	Diclofenac sodium 100mg modified-release tablets	Diclofenac sodium
14901	Diclofenac 1% transdermal patches	Diclofenac epolamine
36486	Econac XL 100mg tablets (AMCo)	Diclofenac sodium
70468	Voltarol Rapid 50mg tablets (Sigma Pharmaceuticals Plc)	Diclofenac potassium
4692	Dicloflex 50mg gastro-resistant tablets (Dexcel-Pharma Ltd)	Diclofenac sodium
68354	Diclofenac sodium 100mg modified-release capsules (Actavis UK Ltd)	Diclofenac sodium
17128	Fenactol 50mg gastro-resistant tablets (Discovery Pharmaceuticals)	Diclofenac sodium
8789	Dicloflex retard tabs 100 100mg Modified-release tablet (Dexcel-Pharma Ltd)	Diclofenac sodium
21807	Flamrase 25 EC tablets (Teva UK Ltd)	Diclofenac sodium
71117	Diclomax SR 75mg capsules (DE Pharmaceuticals)	Diclofenac sodium
72546	Diclofenac sodium 100mg modified-release capsules (A A H Pharmaceuticals Ltd)	Diclofenac sodium
71100	Diclofenac sodium 50mg gastro-resistant tablets (Sigma Pharmaceuticals Plc)	Diclofenac sodium
47820	Voltarol Pain-eze Extra Strength 25mg tablets (Novartis Consumer Health UK Ltd)	Diclofenac potassium
60666	Diclofenac sodium 75mg modified-release capsules (Actavis UK Ltd)	Diclofenac sodium
497	Voltarol 25mg gastro-resistant tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
18448	Voltarol 12.5mg suppositories (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
54518	Diclofenac sodium 50mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	Diclofenac sodium
9500	Diclotard 75mg modified-release tablets (Galen Ltd)	Diclofenac sodium
26888	Difenor xl 100mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
57545	Voltarol 1.16% Emulgel (Dowelhurst Ltd)	Diclofenac diethylammonium
52956	Voltarol 1.16% Emulgel (Stephar (U.K.) Ltd)	Diclofenac diethylammonium
53384	Voltarol 50mg dispersible tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac sodium
25358	Defanac 50mg gastro-resistant tablets (Ranbaxy (UK) Ltd)	Diclofenac sodium
676	Diclofenac 75mg/3ml solution for injection ampoules	Diclofenac sodium
65179	Diclofenac 140mg medicated plasters	Diclofenac sodium
43045	Diclofenac potassium 50mg tablets (Accord Healthcare Ltd)	Diclofenac potassium
31589	Diclofenac sodium 75mg modified-release tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium
35893	Dicloflex Retard 100mg tablets (Almus Pharmaceuticals Ltd)	Diclofenac sodium
38948	Diclomax Retard 100mg capsules (Galen Ltd)	Diclofenac sodium
11322	Flamrase sr 75mg Modified-release tablet (APS Berk)	Diclofenac sodium
55099	Acoflam 100mg Retard tablets (Mercury Pharma Group Ltd)	Diclofenac sodium
30849	Valdic 75 Retard tablets (Fannin UK Ltd)	Diclofenac sodium
7667	Diclofenac 12.5mg suppositories	Diclofenac sodium
70438	Arthrotec 50 gastro-resistant tablets (Lexon (UK) Ltd)	Diclofenac sodium/Misoprostol
589	Voltarol 50mg dispersible tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
49788	Voltarol 1.16% Emulgel (DE Pharmaceuticals)	Diclofenac diethylammonium
42905	Diclofenac 75mg Modified-release tablet (Actavis UK Ltd)	Diclofenac sodium

64303	Diclofenac sodium 25mg gastro-resistant tablets (DE Pharmaceuticals)	Diclofenac sodium
15732	Diclovol 50mg gastro-resistant tablets (Arun Pharmaceuticals Ltd)	Diclofenac sodium
24122	Diclofenac sodium 50mg gastro-resistant tablets (Actavis UK Ltd)	Diclofenac sodium
46844	Dicloflex 75mg SR tablets (Actavis UK Ltd)	Diclofenac sodium
69584	Diclofenac sodium 100mg modified-release tablets (Sigma Pharmaceuticals Plc)	Diclofenac sodium
10917	Flamrase SR 100mg tablets (Teva UK Ltd)	Diclofenac sodium
35711	Dicloflex 25mg gastro-resistant tablets (Teva UK Ltd)	Diclofenac sodium
15201	Volraman 50mg gastro-resistant tablets (LPC Medical (UK) Ltd)	Diclofenac sodium
71088	Arthrotec 50 gastro-resistant tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac sodium/Misoprostol
9222	Dicloflex 75mg SR tablets (Dexcel-Pharma Ltd)	Diclofenac sodium
50785	Diclofenac sodium 50mg gastro-resistant tablets (Genesis Pharmaceuticals Ltd)	Diclofenac sodium
21610	Rhumalgan CR 100 tablets (Sandoz Ltd)	Diclofenac sodium
27677	Diclofenac 75mg/3ml Injection (Antigen Pharmaceuticals)	Diclofenac sodium
28764	Closteril 100mg Modified-release tablet (Pharmalife Healthcare Services Ltd)	Diclofenac sodium
24128	Diclofenac sodium 25mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium
29181	Dicloflex 75mg SR tablets (Almus Pharmaceuticals Ltd)	Diclofenac sodium
20105	Dicloflex 25mg Gastro-resistant tablet (Ratiopharm UK Ltd)	Diclofenac sodium
4713	Voltarol 75mg/3ml solution for injection ampoules (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
66123	Diclofenac sodium 100mg modified-release tablets (Ethigen Ltd)	Diclofenac sodium
59289	Diclofenac sodium 100mg modified-release tablets (AM Distributions (Yorkshire) Ltd)	Diclofenac sodium
1139	Voltarol 25mg Tablet (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
27362	Diclofenac 100mg Modified-release tablet (Actavis UK Ltd)	Diclofenac sodium
1446	Voltarol 50mg Tablet (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
16225	Dexomon retard 100mg Modified-release tablet (Hillcross Pharmaceuticals Ltd)	Diclofenac sodium
53164	Diclofenac sodium 25mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)	Diclofenac sodium
6435	Pennsaid 16mg/ml cutaneous solution (Movianto UK Ltd)	Diclofenac sodium
417	Diclofenac 50mg dispersible tablets sugar free	Diclofenac sodium
32536	Diclofenac 25mg Tablet (Berk Pharmaceuticals Ltd)	Diclofenac sodium
1075	Diclofenac sodium 50mg gastro-resistant tablets	Diclofenac Sodium
4880	Diclofenac sodium 75mg gastro-resistant / Misoprostol 200microgram tablets	Diclofenac sodium/Misoprostol
25329	Lofensaid 25mg gastro-resistant tablets (Opus Pharmaceuticals Ltd)	Diclofenac sodium
37763	Diclofenac 75mg/2ml solution for injection vials	Diclofenac sodium
34218	Diclofenac 25mg Gastro-resistant tablet (Pharmacia Ltd)	Diclofenac sodium
1692	Diclofenac sodium 50mg gastro-resistant / Misoprostol 200microgram tablets	Diclofenac sodium/Misoprostol
60368	Diclofenac 10mg/5ml oral solution	Diclofenac sodium
58842	Misofen 75mg/200microgram gastro-resistant tablets (Morningside Healthcare Ltd)	Diclofenac sodium/Misoprostol
4631	Voltarol 50mg gastro-resistant tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
39722	Voltarol Pain-eze 12.5mg tablets (Novartis Consumer Health UK Ltd)	Diclofenac potassium
4625	Voltarol 75mg SR tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
30790	Dicloflex sr 75mg Tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium

17124	Dicloflex sr 100mg Tablet (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
58572	Diclofenac potassium 25mg tablets (A A H Pharmaceuticals Ltd)	Diclofenac potassium
14085	Diclovol Retard 100mg tablets (Arun Pharmaceuticals Ltd)	Diclofenac sodium
59595	Diclofenac 50mg dispersible tablets sugar free (Sigma Pharmaceuticals Plc)	Diclofenac sodium
6208	Voltarol 1.16% Emulgel P (GlaxoSmithKline Consumer Healthcare)	Diclofenac diethylammonium
3852	Diclomax 100mg Modified-release capsule (Provalis Healthcare Ltd)	Diclofenac sodium
71364	Voltarol 1.16% Emulgel P (Sigma Pharmaceuticals Plc)	Diclofenac diethylammonium
21387	Diclofenac sodium 50mg gastro-resistant tablets (Mylan)	Diclofenac sodium
827	Voltarol 1.16% Emulgel (GlaxoSmithKline Consumer Healthcare)	Diclofenac diethylammonium
447	Diclofenac sodium 75mg modified-release capsules	Diclofenac sodium
58415	Diclofenac sodium 50mg gastro-resistant / Misoprostol 200microgram tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium/Misoprostol
56071	Voltarol Active 4% spray (Novartis Consumer Health UK Ltd)	Diclofenac sodium
56558	Voltarol 12 Hour Emulgel P 2.32% gel (GlaxoSmithKline Consumer Healthcare)	Diclofenac diethylammonium
32108	Diclofenac sodium 25mg gastro-resistant tablets (Teva UK Ltd)	Diclofenac sodium
17525	Fenactol Retard 100mg tablets (Discovery Pharmaceuticals)	Diclofenac sodium
57162	Diclofenac 50mg dispersible tablets sugar free (DE Pharmaceuticals)	Diclofenac sodium
38881	Diclomax SR 75mg capsules (Galen Ltd)	Diclofenac sodium
20621	Dicloflex 75mg SR tablets (Kent Pharmaceuticals Ltd)	Diclofenac sodium
65528	Arthrotec 75 gastro-resistant tablets (Lexon (UK) Ltd)	Diclofenac sodium/Misoprostol
917	Diclofenac sodium 50mg tablets	Diclofenac Sodium
14672	Defanac 75mg SR tablets (Ranbaxy (UK) Ltd)	Diclofenac sodium
628	Diclofenac potassium 25mg tablets	Diclofenac potassium
28256	Diclofenac 50mg Tablet (Berk Pharmaceuticals Ltd)	Diclofenac sodium
156	Diclofenac 1.16% gel	Diclofenac diethylammonium
58048	Diclofenac sodium 50mg gastro-resistant tablets (Waymade Healthcare Plc)	Diclofenac sodium
39264	Dicloflex Retard 100mg tablets (Dexcel-Pharma Ltd)	Diclofenac sodium
69582	Voltarol 100mg suppositories (Lexon (UK) Ltd)	Diclofenac sodium
68849	Diclofenac 12.5mg/5ml oral suspension	Diclofenac sodium
49862	Voltarol 1.16% Emulgel (Lexon (UK) Ltd)	Diclofenac diethylammonium
1766	Voltarol sr 75mg Modified-release tablet (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
649	Diclofenac sodium 25mg gastro-resistant tablets	Diclofenac sodium
74211	Diclofenac sodium 50mg gastro-resistant tablets (DE Pharmaceuticals)	Diclofenac sodium
2904	Diclofenac sodium 75mg gastro-resistant modified-release capsules	Diclofenac sodium
32916	Diclofenac 75mg Modified-release capsule (Sandoz Ltd)	Diclofenac sodium
34091	Diclofenac sodium 25mg gastro-resistant tablets (Sandoz Ltd)	Diclofenac sodium
30806	Rhumalgan 50mg Tablet (Lagap)	Diclofenac sodium
33457	Isclofen 50mg Gastro-resistant tablet (Isis Products Ltd)	Diclofenac sodium
70145	Voltarol Rapid 50mg tablets (Stephar (U.K.) Ltd)	Diclofenac potassium
40	Diclofenac sodium 50mg gastro-resistant tablets	Diclofenac sodium

52338	Diclofenac potassium 50mg tablets (Focus Pharmaceuticals Ltd)	Diclofenac potassium
16221	Diclozip 25mg gastro-resistant tablets (Ashbourne Pharmaceuticals Ltd)	Diclofenac sodium
65877	Diclofenac sodium 75mg modified-release tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac sodium
38992	Flamrase 75mg SR tablets (Teva UK Ltd)	Diclofenac sodium
29455	Flexotard MR 100mg tablets (Pfizer Ltd)	Diclofenac sodium
60786	Voltarol 50mg dispersible tablets (Sigma Pharmaceuticals Plc)	Diclofenac sodium
71307	Diclofenac sodium 100mg modified-release capsules (DE Pharmaceuticals)	Diclofenac sodium
54463	Diclofenac 50mg Tablet (Approved Prescription Services Ltd)	Diclofenac sodium
16222	Diclozip 50mg gastro-resistant tablets (Ashbourne Pharmaceuticals Ltd)	Diclofenac sodium
9688	Diclovol 75mg SR tablets (Mylan)	Diclofenac sodium
71362	Diclomax Retard 100mg capsules (Waymade Healthcare Plc)	Diclofenac sodium
26165	Diclofenac sodium 50mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium
3958	Diclofenac 25mg suppositories	Diclofenac sodium
54075	Voltarol 50mg dispersible tablets (Stephar (U.K.) Ltd)	Diclofenac sodium
20805	Dicloflex 75mg SR tablets (Teva UK Ltd)	Diclofenac sodium

Table A2. List of alternative analgesic drugs used to identify switching during the study period.

Drug name	ATC code
Other NSAIDs	
Naproxen	*M01AE02*
Ibuprofen	*M01AE01*
Fenoprofen	*M01AE04*
Flurbiprofen	*M01AE09*
Ketoprofen	*M01AE03*
Tiaprofenic acid	*M01AE11*
Dexibuprofen	*M01AE14*
Dexketoprofen	*M01AE17*
Celecoxib	*M01AH01*
Etoricoxib	*M01AH05*
Parecoxib	*M01AH04*
Indometacin	*M01AB01*
Aceclofenac	*M01AB16*
Acemetacin	*M01AB11*
Etodolac	*M01AB08*
Ketorolac trometamol	*M01AB15*
Sulindac	*M01AB02*
Mefenamic acid	*M01AG01*

Meloxicam	*M01AC06*
Piroxicam	*M01AC01*
Tenoxicam	*M01AC02*
Nabumetone	*M01AX01*
Aspirin	*N02BA01*
Opioids	
Codeine	*R05DA04*
Buprenorphine	*N02AE01*
Dihydrocodeine tartrate	*N02AA08*
Morphine	*N02AA01*
Oxycodone	*N02AA05*
Meptazinol	*N02AX05*
Tapentadol	*N02AX06*
Tramadol	*N02AX02*
Pentazocine	*N02AD01*
Pethidine	*N02AB02*
Fentanyl	*N02AB03*
Diamorphine (subcutaneous)	*N07BC06*
Other analgesic	
Paracetamol	*N02BE01*

Table A3. List of co-medication use, their drug class, and ATC codes.

Drug therapy	Drug Class	ATC code
Anti-hypertensive drugs	*Beta-blockers, diuretics, renin-angiotensin-aldosterone system (RAAS) inhibitors, and calcium channel blockers*	*C03A, C03B, C03D, C03E, C07, C08, C09A, C09C, C09D, C09BA, C07FB02*
Anti-hyperlipidaemic drugs	*Statins*	*C10*
Anti-diabetic drugs	*Insulin and oral diabetic drugs*	*A10*

Appendix B

The following are the codes that were used in R studio to obtain the figures and the ITS analysis results. The R codes were very similar for all outcome rates and when stratified by covariates, hence, the R codes for the incidence rate was shown as an example.

```
> #### Incidence - overall
> # Fitting linear regression / OLS regression
> # In this model we have a separate covariate “postintervention” that
> # starts counting from intervention
> regincall <- lm(rate ~ t + intervention + postintervention, data = dincal
l)

> # now we want to test whether this is significant:
> summary(regincall)
> # 95% confidence interval
> confint(regincall)
> # we also want to check whether there is autocorrelation
> library(car)
> durbinWatsonTest(regincall)

> #### Plot Incidence overall
> # now we see how they look like in the graph
> # if don't want the connector but have 2 separate trend lines.
> # Then indicate break, read into dataset
> Break <- 19
> dincall$grp <- dincall$t < Break
> # addition of the grp variable makes this a bit easier to read
> mincall <- lm(rate ~ t*grp + intervention + postintervention, data = dinc
all)
> dincall$pred <- predict(mincall)
> # the same as predict.lm(regincall)
> # but wouldn't use summary of mincall for results

> opar = par(oma = c(2,0,0,0))
> plot(dincall$t,dincall$rate,
+      ylim = c(0,3),
+      xaxt="n",
+      #bty = "l",
+      main = "Diclofenac Incidence rate, 2009-2019
+      Overall",
+      cex.main=1.1,
+      xlab = "Year",
+      ylab = "Incidence per 100 persons")
> axis(1, at=0:11*4, labels = F)
> axis(1, at=0:10*4+2, tick=F, labels=2009:2019)
> with(subset(dincall, t < Break), lines(t, pred, col='red', lwd=2))
> with(subset(dincall, t >= Break), lines(t, pred, col='red', lwd=2))
> #line when intervention implemented
> abline(v=18, lty=1, lwd=1)
> par(opar) # Reset par
> #Now set the margins to zero and set the overplot.
> opar =par(oma = c(0,0,0,0), mar = c(0,0,0,0), new = TRUE)
> legend('bottom',
+        legend = c("Observed", "Fitted"),
+        horiz = TRUE,
+        lty=c(NA,1),
+        lwd = c(NA,2),
+        pch = c(1,NA),
+        col = c('black','red'),
+        bty = "n",
+        inset = -0.12,
+        cex = 0.9,
+        pt.lwd = 1,
+        pt.cex = 1,
+        text.width = c(4,5),
+        x.intersp = 0.25,
+        xpd = TRUE)
> par(opar) # reset par

> #### Incidence - men
> regincmen <- lm(rate ~ t + intervention + postintervention, data = dincme
n)
> summary(regincmen)
> confint(regincmen)
> durbinWatsonTest(regincmen)
```

```
> #### Incidence - women
> regincwom <- lm(rate ~ t + intervention + postintervention, data = dincwo
m)
> summary(regincwom)
> confint(regincwom)
> durbinWatsonTest(regincwom)

> dincmen$grp <- dincmen$t < Break
> mincmen <- lm(rate ~ t*grp + intervention + postintervention, data = dinc
men)
> dincmen$pred <- predict(mincmen)
> dincwom$grp <- dincwom$t < Break
> mincwom <- lm(rate ~ t*grp + intervention + postintervention, data = dinc
wom)
> dincwom$pred <- predict(mincwom)

> #### Plot Incidence gender
> opar = par(oma = c(2,0,0,0))
> plot(dincmen$t,dincmen$rate,
+      ylim=c(0,3),
+      col=2,
+      pch=1,
+      main = "Diclofenac Incidence rate
+      By gender",
+      cex.main=1.1,
+      xlab = "Year",
+      ylab = "Incidence per 100 persons",
+      xaxt="n")
> #bty = "l")
> axis(1, at=0:11*4, labels = F)
> axis(1, at=0:10*4+2, tick=F, labels=2009:2019)
> points(dincwom$t, dincwom$rate, pch=1, col=4)
> with(subset(dincmen, t < Break), lines(t, pred, col='red', lwd=2))
> with(subset(dincmen, t >= Break), lines(t, pred, col='red', lwd=2))
> with(subset(dincwom, t < Break), lines(t, pred, col='blue', lwd=2))
> with(subset(dincwom, t >= Break), lines(t, pred, col='blue', lwd=2))
> abline(v=18, lty=1, lwd=1)
> par(opar) # Reset par
> opar =par(oma = c(0,0,0,0), mar = c(0,0,0,0), new = TRUE)
> legend("bottom",
+        legend = c("Gender","Men","Women"),
+        pch=c(NA,1,1),
+        lty = c(NA,1,1),
+        col =c(NA,2,4),
+        bty = "n",
+        horiz = TRUE,
+        inset = -0.12,
+        cex = 1,
+        pt.lwd = 1,
+        pt.cex = 1,
+        text.width = c(3.5,2,2),
+        x.intersp = 0.5,
+        xpd = TRUE)
> par(opar) # reset par

> #### Incidence - age 18-39
> regincage1839 <- lm(rate ~ t + intervention + postintervention, data = di
ncage1839)
> summary(regincage1839)
> confint(regincage1839)
> durbinWatsonTest(regincage1839)

> #### Incidence - age 40-49
> regincage4049 <- lm(rate ~ t + intervention + postintervention, data = di
ncage4049)
> summary(regincage4049)
> confint(regincage4049)
> durbinWatsonTest(regincage4049)

> #### Incidence - age 50-69
```

```
> regincage5069 <- lm(rate ~ t + intervention + postintervention, data = di
ncage5069)
> summary(regincage5069)
> confint(regincage5069)
> durbinWatsonTest(regincage5069)

> #### Incidence - age 70+
> regincage70 <- lm(rate ~ t + intervention + postintervention, data = dinc
age70)
> summary(regincage70)
> confint(regincage70)
> durbinWatsonTest(regincage70)

> #### Plot Incidence age
> dincage1839$grp <- dincage1839$t < Break
> mincage1839 <- lm(rate ~ t*grp + intervention + postintervention, data =
dincage1839)
> dincage1839$pred <- predict(mincage1839)
> dincage4049$grp <- dincage4049$t < Break
> mincage4049 <- lm(rate ~ t*grp + intervention + postintervention, data =
dincage4049)
> dincage4049$pred <- predict(mincage4049)
> dincage5069$grp <- dincage5069$t < Break
> mincage5069 <- lm(rate ~ t*grp + intervention + postintervention, data =
dincage5069)
> dincage5069$pred <- predict(mincage5069)
> dincage70$grp <- dincage70$t < Break
> mincage70 <- lm(rate ~ t*grp + intervention + postintervention, data = di
ncage70)
> dincage70$pred <- predict(mincage70)

> opar = par(oma = c(2,0,0,0))
> plot(dincage1839$t,dincage1839$rate,
+      ylim=c(0,3),
+      col=2,
+      pch=1,
+      main = "Diclofenac Incidence rate
+      By age",
+      cex.main=1.1,
+      xlab = "Year",
+      ylab = "Incidence per 100 persons",
+      xaxt="n")
> #bty = "l")
> axis(1, at=0:11*4, labels = F)
> axis(1, at=0:10*4+2, tick=F, labels=2009:2019)
> points(dincage4049$t, dincage4049$rate, pch=1, col=3)
> points(dincage5069$t, dincage5069$rate, pch=1, col=4)
> points(dincage70$t, dincage70$rate, pch=1, col=6)
> with(subset(dincage1839, t < Break), lines(t, pred, col=2, lwd=1))
> with(subset(dincage1839, t >= Break), lines(t, pred, col=2, lwd=1))
> with(subset(dincage4049, t < Break), lines(t, pred, col=3, lwd=1))
> with(subset(dincage4049, t >= Break), lines(t, pred, col=3, lwd=1))
> with(subset(dincage5069, t < Break), lines(t, pred, col=4, lwd=1))
> with(subset(dincage5069, t >= Break), lines(t, pred, col=4, lwd=1))
> with(subset(dincage70, t < Break), lines(t, pred, col=6, lwd=1))
> with(subset(dincage70, t >= Break), lines(t, pred, col=6, lwd=1))
> abline(v=18, lty=1, lwd=1)
> par(opar) # Reset par
> #Now set the margins to zero and set the overplot.
> opar =par(oma = c(0,0,0,0), mar = c(0,0,0,0), new = TRUE)
> legend("bottom",
+        legend = c("Age group","18-39","40-49","50-69","70+"),
+        pch=c(NA,1,1,1,1),
+        lty = c(NA,1,1,1,1),
+        col =c(NA,2,3,4,6),
+        bty = "n",
+        horiz = TRUE,
+        inset = -0.12,
+        cex = 0.9,
+        pt.lwd = 1,
+        pt.cex = 1,
+        text.width = c(3,2,2,2,2),
```

```
+         x.intersp = 0.5,
+         xpd = TRUE)
> par(opar) # reset par
```

Appendix C

The following are the results in the sensitivity analysis with a gap length of 30 days when constructing treatment episodes.

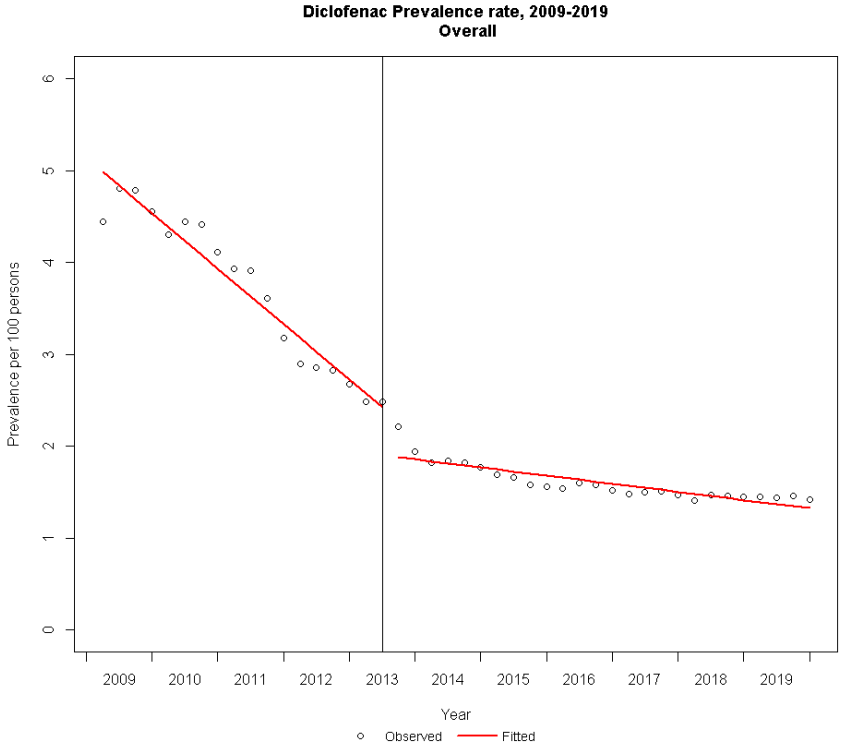

Figure C1. Sensitivity analysis with a gap length of 30 days. The overall prevalence rate of diclofenac use during the study period.

Table C1. Sensitivity analysis with gap length of 30 days. Trend and level change results of the ITS analysis in the prevalence of diclofenac use.

Usage patterns of prevalent users			
Variables	**Pre-intervention**	**Intervention**	**Post-intervention**
Overall	*-0.151 (-0.165, -0.136), P = <.001*	*-0.521 (-0.714, -0.327), P = <.001*	*0.129 (0.112, 0.145), P = <.001*
Gender			
Female	*-0.163 (-0.178, -0.149), P = <.001*	*-0.539 (-0.735, -0.342), P = <.001*	*0.142 (0.125, 0.159), P = <.001*
Male	*-0.138 (-0.152, -0.124), P = <.001*	*-0.502 (-0.694, -0.311), P = <.001*	*0.115 (-0.099, 0.132), P = <.001*
Age			
18-39 years	*-0.077 (-0.085, -0.069), P = <.001*	*-0.261 (-0.364, -0.159), P = <.001*	*0.067 (0.058, 0.075)), P = <.001*
40-49 years	*-0.141 (-0.156, -0.126), P = <.001*	*-0.591 (-0.793, -0.390), P = <.001*	*0.114 (0.096, 0.131), P = <.001*
50-69 years	*-0.230 (-0.252, -0.208), P = <.001*	*-0.858 (-1.15, -0.564), P = <.001*	*0.191 (0.165, 0.216), P = <.001*
≥70 years	*-0.185 (-0.204, -0.166), P = <.001*	*-0.377 (-0.631, -0.123), P = .005*	*0.168 (0.146, 0.190), P = <.001*

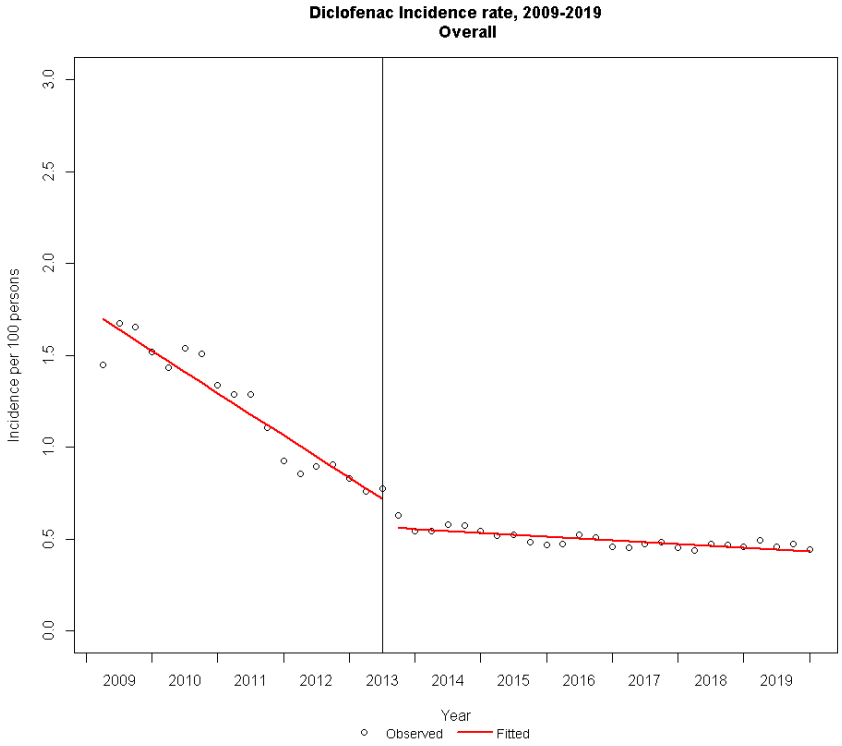

Figure C2. Sensitivity analysis with a gap length of 30 days. The overall incidence rate of diclofenac use during the study period.

Table C2. Sensitivity analysis with a gap length of 30 days. Trend and level change results of the ITS analysis in the incidence of diclofenac use.

Usage patterns of incident users			
Variables	**Pre-intervention**	**Intervention**	**Post-intervention**
Overall	*-0.058 (-0.064, -0.051), P = <.001*	*-0.152 (-0.238, -0.066), P = <.001*	*0.053 (0.045, 0.060), P = <.001*
Gender			
Female	*-0.062 (-0.068, -0.055), P = <.001*	*-0.157 (-0.243, -0.071), P = <.001*	*0.057 (0.049, 0.064), P = <.001*
Male	*-0.058 (-0.064, -0.051), P = <.001*	*-0.152 (-0.237, -0.067), P = <.001*	*0.053 (-0.045, 0.060), P = <.001*
Age			
18-39 years	*-0.047 (-0.052, -0.042), P = <.001*	*-0.162 (-0.226, -0.097), P = <.001*	*0.042 (0.036, 0.048), P = <.001*
40-49 years	*-0.068 (-0.075, -0.060), P = <.001*	*-0.253 (-0.352, -0.153), P = <.001*	*0.060 (0.051, 0.069), P = <.001*
50-69 years	*-0.070 (-0.078, -0.062), P = <.001*	*-0.177 (-0.283, -0.070), P = .002*	*0.064 (0.055, 0.074), P = <.001*
≥70 years	*-0.046 (-0.054, -0.037), P = <.001*	*-0.038 (-0.078, 0.153), P = .512*	*0.043 (0.033, 0.053), P = <.001*

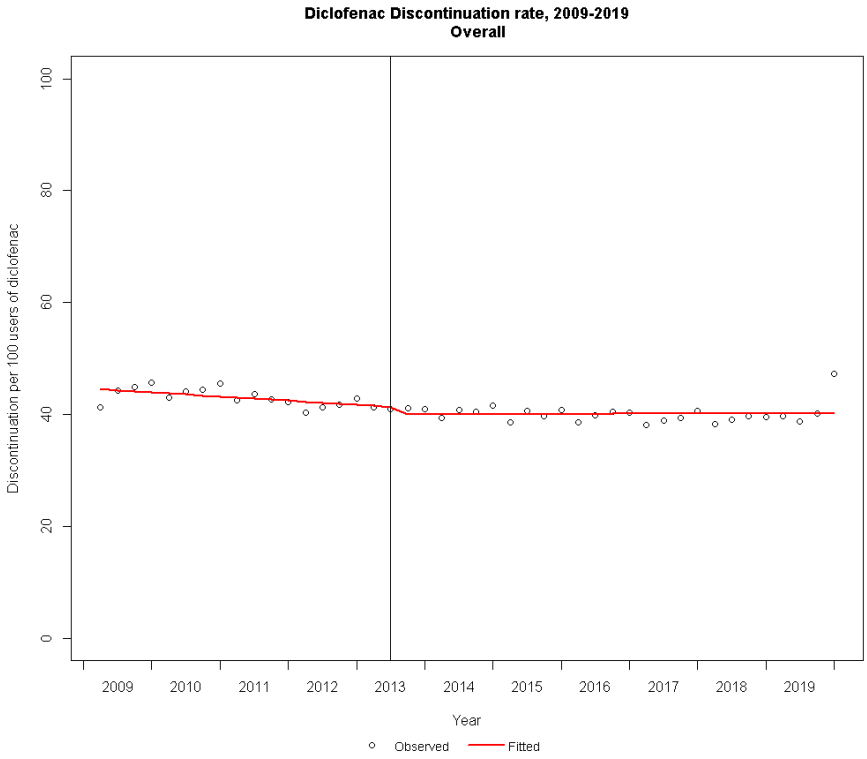

Figure C3. Sensitivity analysis with a gap length of 30 days. The overall discontinuation rate of diclofenac use during the study period.

Table C3. Sensitivity analysis with a gap length of 30 days. Trend and level change results of the ITS analysis in the discontinuation of diclofenac use.

Usage patterns of discontinuers			
Variables	**Pre-intervention**	**Intervention**	**Post-intervention**
Overall	*-0.186 (-0.334, -0.038), P = .015*	*-1.376 (-3.347, 0.596), P = .166*	*0.193 (0.022, 0.363), P = .028*
Gender			
Female	*-0.196 (-0.342, -0.049), P = .010*	*-1.765 (-3.717, 0.187), P = .075*	*0.196 (0.028, 0.365), P = .024*
Male	*-0.171 (-0.325, -0.018), P = .030*	*-0.798 (-2.847, 1.251), P = .436*	*0.195 (0.019, 0.372), P = .032*
Age			
18-39 years	*-0.143 (-0.300, 0.015), P = .075*	*-1.849 (-3.953, 0.256), P = .083*	*0.099 (-0.083, 0.281), P = .279*
40-49 years	*-0.248 (-0.395, -0.101), P = .001*	*-2.266 (-4.229, -0.302), P = .025*	*0.280 (0.110, 0.450), P = .002*
50-69 years	*-0.119 (-0.254, 0.015), P = .081*	*-0.681 (-2.478, 1.115), P = .448*	*0.236 (0.081, 0.391), P = .004*
≥70 years	*-0.060 (-0.220, 0.100), P = .452*	*0.522 (-1.608, 2.652), P = .623*	*0.082 (-0.102, 0.266), P = .376*

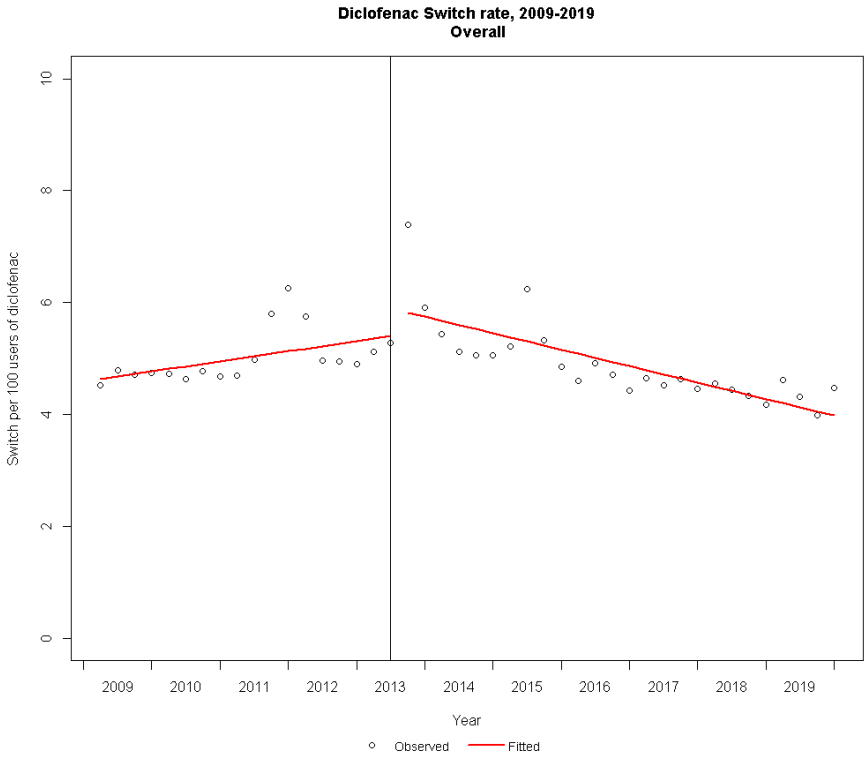

Figure C4. Sensitivity analysis with a gap length of 30 days. The overall switching to alternative analgesic drugs during the study period.

Table C4. Sensitivity analysis with a gap length of 30 days. Trend and level change results of the ITS analysis in switching to alternative analgesic drugs.

Usage patterns of switchers			
Variables	**Pre-intervention**	**Intervention**	**Post-intervention**
Overall	*0.045 (0.004, 0.085), P = .032*	*0.494 (-0.047, 1.036), P = .073*	*-0.115 (-0.162, -0.068), P = <.001*
Gender			
Female	*0.040 (-0.001, 0.080), P = .053*	*0.431 (-0.104, 0.967), P = .112*	*-0.110 (-0.156, -0.064), P = <.001*
Male	*0.050 (0.007, 0.093), P = .023*	*0.567 (-0.007, 1.141), P = .053*	*-0.122 (-0.172, -0.073), P = <.001*
Age			
18-39 years	*0.071 (0.031, 0.109), P = <.001*	*0.853 (0.334, 1.372), P = .002*	*-0.105 (-0.150, -0.060), P = <.001*
40-49 years	*0.055 (0.007, 0.103), P = .026*	*0.619 (-0.022, 1.261), P = .058*	*-0.112 (-0.167, -0.056), P = <.001*
50-69 years	*0.052 (-0.002, 0.106), P = .058*	*0.808 (0.089, 1.528), P = .029*	*-0.138 (-0.200, -0.075), P = <.001*
≥70 years	*0.017 (-0.020, 0.054), P = .368*	*0.021 (-0.472, 0.515), P = .930*	*-0.075 (-0.117, -0.032), P = .001*