

ORIGINAL ARTICLE



## Utilization of etoricoxib in dental patients in the Nordic countries: a population-based register study

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### ABSTRACT

**Background:** Etoricoxib is a second-generation cyclooxygenase-2-inhibitor approved in 2012 for short-term treatment of pain associated with dental surgery.

**Objectives:** To evaluate etoricoxib utilization in dental patients in the Nordic countries, including its off-label use.

**Methods:** The entire populations of Denmark, Finland, Sweden and Norway with etoricoxib prescriptions written by dentists and dispensed in 2012–2014 were evaluated using national register data. Nationwide estimates of etoricoxib utilization were generated according to year, gender, age, dose and package size. Off-label use in paediatric patients, prescribed doses >90 mg/day or for dental contacts not associated with surgical procedures, and concomitant administration with anticoagulants were evaluated.

**Results:** Utilization of etoricoxib for dental pain was low (1615 prescriptions: Finland, 907; Sweden, 359; Norway, 337; Denmark, 12). Overall, 70% of the prescriptions were without an associated dental procedure. Moreover, 58%, 55%, 10% and 58% of the prescriptions in Denmark, Finland, Sweden and Norway, respectively, were for >90 mg/day doses. Few paediatric prescriptions were dispensed ( $n < 10$ ), and only a small overlap ( $n = 21$ ) was observed between etoricoxib and anticoagulant prescriptions.

**Conclusions:** Given the low overall number of prescriptions, it is unlikely that off-label use of etoricoxib within dentistry in the Nordic countries is an important public health concern.

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## Introduction

Etoricoxib (Anatomical Therapeutic Classification [ATC] code: M01AH05), is a second-generation selective cyclooxygenase (COX)-2 inhibitor (coxib) belonging to the non-steroidal anti-inflammatory group of drugs (NSAIDs). NSAIDs are commonly prescribed in dental practice for the management of pain and swelling [1]. COX-2 inhibitors represent an apt illustration of a new innovation rapidly gaining widespread acceptance in clinical practice following its launch (1998–1999) based on affirmative clinical trial data and the promise of improved safety (especially a lack of associated gastrointestinal side effects when compared with non-selective NSAIDs) [2,3]. However, after the market withdrawal of rofecoxib and valdecoxib (in 2004–2005) in the European Union (EU) as a result of concerns regarding increased risk of hypersensitivity reactions and cardiovascular toxicity, this pattern of rapid COX-2 inhibitor uptake and utilization is reported to have been altered, and supplementary contraindications and warnings issued for the coxibs that were allowed to remain

in the market [4,5]. Increased cardiovascular risk and gastrointestinal adverse outcomes of COX-2 inhibitors and non-selective NSAIDs have been demonstrated [6–8]. A systematic review of observational studies showed an overall increased risk of gastrointestinal adverse outcomes associated with COX-2 inhibitors versus non-exposed [9]. The highest gastrointestinal risk was seen for etoricoxib followed by rofecoxib and celecoxib. Currently, the product information of all NSAIDs (i.e. both non-selective NSAIDs and COX-2 inhibitors) include extensive information about cardiovascular risks [10].

Etoricoxib originally introduced in 2002 (for the symptomatic treatment of osteoarthritis and rheumatoid arthritis), continues to remain available for prescription in patients in the EU [11,12]. It was approved for short-term treatment of pain associated with dental surgery in 2012 [13]. Available as a prescription medication in the form of 30, 60, 90 and 120 mg tablets, the recommended dose for pain relief following dental procedures is 90 mg once daily for a maximum of three days [12]. The minimum package sizes of etoricoxib in the Nordic countries are 2, 5, 7 and 28 tablets in Denmark,

Finland, Norway and Sweden, respectively. Etoricoxib is contraindicated in children and adolescents under 16 years of age [12]. Therefore, potentially inappropriate use of etoricoxib in dental patients include off-label use in paediatric patients (<16 years of age), if doses >90 mg/day are prescribed, or if it is prescribed for more than 3 days. Moreover, close monitoring of patients is recommended if etoricoxib is co-administered with warfarin or other oral anticoagulants because of pharmacodynamic interactions resulting in prolongation of prothrombin time [12].

There is currently no published information on the prescription and utilization of etoricoxib for dental pain, nor its off-label use in dentistry. Moreover, no specific published data are available on its use in the Nordic countries. Such insight can be gained by combining detailed individual-level information on dental procedures and dispensed prescriptions written by dentists available in the national prescription, patient, and health services registers in the Nordic countries. The Nordic countries have population-based registers with information on hospital contacts, primary health care contacts, and prescription redemptions [14–16]. Such information would allow an understanding of the prevalence of etoricoxib prescribing and use in the general population and assessment of prescribing variations among the countries. Moreover, it could create a mechanism for facilitating safe and effective use of the medication by revealing potential inappropriate usage and comparing prescribing patterns with current recommendations and guidelines in order to identify areas for improving prescribing practices [17].

Therefore, following a request by the European Medicines and Healthcare products Regulatory Agency (MHRA), this total population study on etoricoxib utilization was performed in four Nordic countries, namely, Denmark, Finland, Sweden and Norway. The objectives were to quantify and evaluate the patterns of utilization of etoricoxib in dental patients, including its off-label use (e.g. in paediatric patients or prescriptions of >90 mg/day doses) and co-administration with anticoagulants.

## Methods

### *Study design, population and setting*

This was a nationwide register-based study that included all individuals in Denmark, Finland, Sweden, and Norway with data on dispensed etoricoxib prescriptions written by dentists in the period from 1 January 2012 to 31 December 2014.

### *Data sources and variables*

Data for Denmark, Finland and Sweden were obtained from the respective national prescription, health services, patient and civil registration registers. For Norway, only data from the Norwegian prescription register could be obtained due to data access restrictions. Register-based research in the Nordic countries with individual-level linkage between registers is possible due to the unique personal identity code assigned to all residents at birth or immigration. The

registers have many similarities, including data structure and population coverage [16].

The civil registration systems were established in the Nordic countries in 1964–1968 [14,18,19]. Variables extracted from the civil registration systems include information on the unique personal identity code, gender, dates of birth, migration and death [18,20].

The prescription registers were established in 1994 and 1995 in Finland and Denmark, and in 2004 and 2005 in Norway and Sweden. The prescription registers include information on the date of prescription redemption, information on the provider and the purchaser, and the drug redeemed (e.g. ATC code, number of pills, daily dose, pack size and number of packs purchased) [14,16,21]. The validity and completeness of the prescription registers are in general considered high [14,16,21,22]. The prescription registers do not include information about the diagnosis for treatment. For the present study, etoricoxib prescription redemptions (ATC: M01AH05) were extracted from the national prescription registers. Information about the profession of the prescriber (i.e. dentist) was used to extract only etoricoxib prescription redemptions written by dentists [14]. Prescription redemptions of anticoagulant therapy (ATC: B01A) were also extracted from the prescription registers. Variables extracted from the prescription registers included the unique personal identity code, ATC codes for etoricoxib and anticoagulants, profession of the provider, date, dose, package size, number of prescriptions and quantity of tablets/packages dispensed for the prescriptions.

The national health services registers (i.e. primary healthcare visits) were established in 1990 (Denmark), 2001 (Sweden), 2006 (Norway) and 2011 (Finland), respectively. The health services registers contain information about primary care contacts including profession of the care providers, date of consultation and service provided (i.e. dental procedures in case of dentists). Information in the health services registers is used for reimbursement and the coverage is assumed to be good [23]. Variables extracted for the study included the unique personal identity code and types and dates of dental procedures.

The national patient registers with inpatient contacts were established in 1977 (Denmark), 1967 (Finland), 2008 (Norway) and 1987 (Sweden), respectively. Outpatient contacts were included in 1995 (Denmark), 1998 (Finland), 2008 (Norway) and 2001 (Sweden), respectively. Inpatient and outpatient contacts are included in the registers with administrative and clinical data. Information in the patient registers is used for reimbursement and the coverage is assumed to be high. Validity of the diagnoses and procedures performed is assumed to be good but varies depending on the specific diagnosis and procedure [24]. Variables extracted for the present study included the unique personal identity code, and date and types of dental procedures performed.

### *Data management and analysis*

After acquisition, validation and quality control of the data in each country, the datasets from Finland, Norway and Sweden were transferred to Statistics Denmark for all subsequent data handling and analyses. The national datasets were combined

to establish one joint Nordic dataset for the analysis. National estimates of the numbers and percentages of prescriptions of etoricoxib written by dentists and dispensed by pharmacies and drug outlets during 2012 to 2014 were generated, which were further stratified with regard to country, year, gender, age group, dose and number of tablets dispensed.

The number of individuals with at least one etoricoxib prescription redemption in the general population was extracted from national websites with information about users of particular drugs:

- Denmark: <http://medstat.dk>
- Finland: [http://raportit.kela.fi/ibi\\_apps/WFServlet?IBIF\\_ex=NIT137AL&YKIELI=E](http://raportit.kela.fi/ibi_apps/WFServlet?IBIF_ex=NIT137AL&YKIELI=E)
- Norway: <http://norpd.no/Prevalens.aspx>
- Sweden: <http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel>

To calculate the incidence rate of etoricoxib prescription redemption prescribed by a dentist, the population size in the four countries was extracted from the NORDCAN project [25].

Following linking of the dispensing and dental procedure data, redeemed dental prescriptions of etoricoxib without a contemporaneous link to a dental procedure was inferred and the aforementioned calculations were also performed separately for those with and without such a contemporaneous link. A prescription with a contemporaneous link to a dental procedure was defined as an etoricoxib prescription dispensed within two weeks prior to one week after a registered dental procedure.

A sensitivity analysis on the selected timeframe for a contemporaneous dental procedure was performed by modifying the timeframe to include an etoricoxib prescription dispensed within four weeks prior to two weeks after a registered dental procedure. Furthermore, similar analyses as those stated above were performed separately on those redeeming prescriptions written by dentists for >90 mg etoricoxib tablets. Due to data access restrictions, data on dental procedures were not available for the study from Norway. Therefore, all the aforementioned analyses were carried out only for Denmark, Finland, and Sweden. Data from Norway regarding etoricoxib prescription redemptions (with no information about concomitant dental procedures) were reported separately.

Additionally, to describe the concurrent administration of etoricoxib and anticoagulant therapy, frequency distributions were used to analyse the distribution of individuals with overlapping prescription redemptions of etoricoxib and anticoagulants. Varying periods of prescription overlap based on the date of prescription redemption of the anticoagulants prior to an etoricoxib prescription redemption were considered, namely, 0–14, 15–29, 30–59 and 60–90 days. Data on dispensed anticoagulant prescriptions could not be collected from Finland. Therefore, the analysis of concurrent administration of etoricoxib and anticoagulant therapy was limited to Denmark and Sweden. No hypothesis testing was performed in this study. All analyses are presented based on frequency distributions.

All calculations were performed using SAS, version 9.3 (Statistical Analysis Software, SAS Institute, Cary, NC, USA).

### Ethics approval

According to the law in Denmark, Finland, Norway and Sweden, scientific studies of significant public health importance can be carried out using register data without obtaining informed consent from individual subjects. Approvals for this study were obtained from the respective national data protection agencies prior to data collection, management and analyses. The four national statistical bureaus have different regulations regarding publication of tables with cells containing a small number of observations. In order to adhere to these assorted regulations, numbers of observations in categories with one to nine prescriptions were changed to 1–9.

### Results

In the four Nordic countries, from 2012 to 2014, a total of 1615 prescriptions of etoricoxib written by dentists were redeemed by adults and adolescents  $\geq 16$  years of age (Figure 1). Of these, the fewest redemptions were in Denmark ( $n = 12$ ), while the highest occurred in Finland ( $n = 907$ ). The number of redemptions in Sweden and Norway were 359 and 337, respectively.

The incidence rate of prescription redemption of etoricoxib in the period 2012–2014, independently of the profession of the provider, was on average 121 per 10,000 person-years in the four countries. However, great variation was seen with 1.9–2.3 per 10,000 person-years in Denmark and 343–350 per 10,000 person-years in Finland (Table 1). The incidence rate of prescription redemption of etoricoxib prescribed by a dentist in the period 2012–2014 was 0.15 per 10,000 person-years in the four countries. This rate was 0.007, 0.06, 0.15 and 0.46 per 10,000 person-years in Denmark, Sweden, Norway and Finland, respectively.

Overall, women redeemed more prescriptions than men (57% in Denmark, Finland, and Sweden; 63% in Norway) (Table 2). The number of prescriptions dispensed was roughly similar across the three study years in Denmark, Finland and Sweden. In Denmark, Finland and Sweden, 24% of the prescriptions were dispensed with packages containing  $\geq 30$  tablets. In Norway, only 2% of the prescriptions were dispensed for  $\geq 30$  tablets, the rest being for packages containing 7 to 28 tablets.

In Denmark, Finland and Sweden, 100%, 76% and 43% of the dispensed prescriptions (66.6% overall) were for individuals undergoing one or more dental procedures during the three-year study period. However, only 30% ( $n = 382$ ) of the prescriptions written by dentists were associated with a concurrent registered dental procedure ( $n = 460$ ). Thus, 33% of all etoricoxib prescriptions written by dentists and dispensed during the study period were not associated with any dental procedure, while 37% were dispensed to individuals undergoing dental procedures outside the timeframe for a contemporaneous procedure (Table 2). The

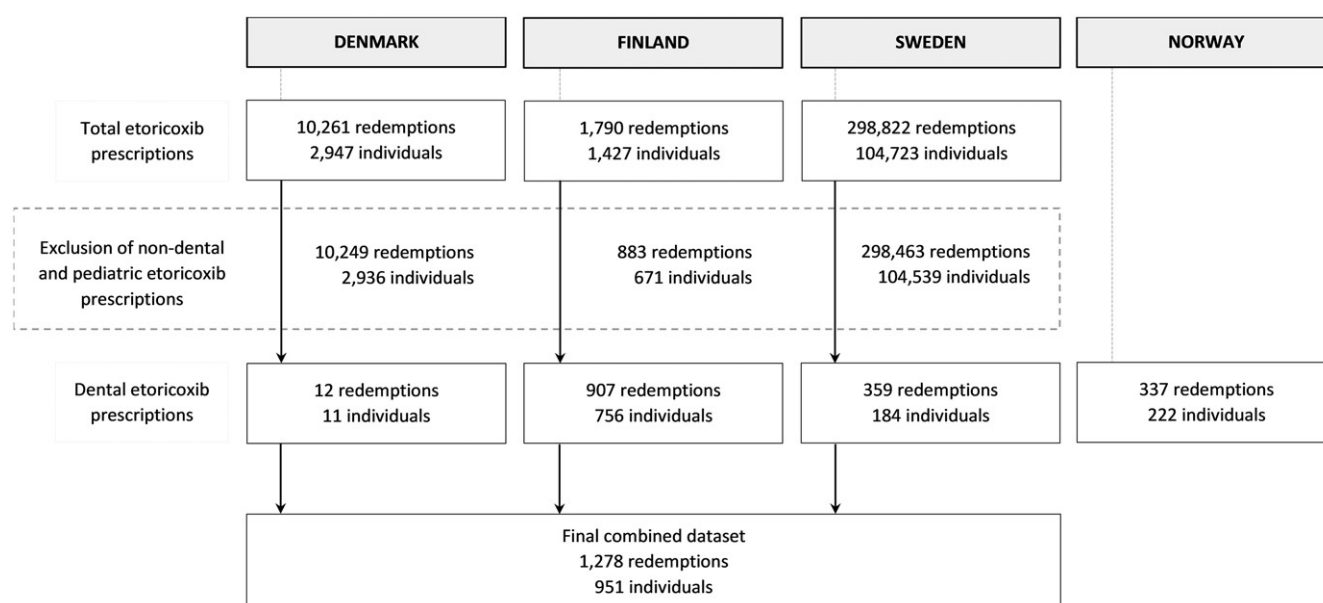


Figure 1. Study flow diagram.

**Table 1.** Incidence rate (IR) of prescription redemptions of etoricoxib per 10,000 person-years (PY) in the general population (all prescribers) and in the study population prescribed by a dentist in Denmark, Finland Norway and Sweden in 2012–2014.

| Country | Etoricoxib prescription redemptions                            |       |       |                                                         |                  |
|---------|----------------------------------------------------------------|-------|-------|---------------------------------------------------------|------------------|
|         | IR in the general population<br>per 10,000 PY, all prescribers |       |       | Study population, prescribed by a<br>dentist, 2012–2014 |                  |
|         | 2012                                                           | 2013  | 2014  | N <sub>Individuals</sub>                                | IR per 10,000 PY |
| Denmark | 2.3                                                            | 1.9   | 1.9   | 11                                                      | 0.007            |
| Finland | 343.2                                                          | 350.3 | 346.1 | 756                                                     | 0.46             |
| Norway  | 67.8                                                           | 112.7 | 151.5 | 222                                                     | 0.15             |
| Sweden  | 74.6                                                           | 67.8  | 61.7  | 184                                                     | 0.06             |
| Total   | 114.8                                                          | 121.9 | 125.9 | 1,173                                                   | 0.15             |

contemporaneous procedures for which etoricoxib was prescribed were mostly tooth extraction (including surgical removal of teeth) (66%) followed by dental cavity fillings without pulp communication (10%) (Table 3). The prescriptions associated with contemporaneous dental procedures were primarily for 7 etoricoxib tablets, while only 6% were for packages containing  $\geq 30$  tablets (Table 2). Sensitivity analyses with an extended timeframe for qualifying as a contemporaneous dental procedure resulted in only a few additional prescriptions dispensed in connection with a dental procedure ( $n=23$ ; the numerical value changing from 382 [30%] to 405 [32%]).

Regarding off-label use, in all four countries combined, there were less than 10 prescriptions dispensed for paediatric patients. Due to the low number, no further analyses of these prescriptions were undertaken. Altogether, of all the prescriptions with a contemporaneous link to a dental procedure, a majority (242/382 or 63%) were for the 120 mg tablets, that is, the etoricoxib dose prescribed was higher than the recommended daily dose of 90 mg (Table 2). However, only 10% ( $n=36$ ) of the prescriptions dispensed in Sweden were for the 120 mg tablets compared to 55% to 58% of the prescriptions in the other countries. Furthermore, women were less likely (35%) to be prescribed higher than recommended doses ( $>90$  mg tablets) than men (52%) as

were individuals in the older age groups (Table 4). Ninety per cent (90%) of the prescriptions for the 120 mg tablets were for a total of 7 tablets only, while 18% and 12% were for 28 and  $\geq 30$  tablets, respectively. Prescriptions associated with tooth extractions and other surgical procedures such as dental implant treatment were most likely to be for  $>90$  mg/day doses (Table 5).

As regards co-administration of etoricoxib and anticoagulant therapy, none of the 12 etoricoxib prescriptions dispensed in Denmark overlapped with a redeemed anticoagulant prescription. Only in Sweden, such an overlap was observed in 16 individuals who had been dispensed an anticoagulant prescription within 30 days of redeeming an etoricoxib prescription. When the time period for assessing concurrent administration of etoricoxib and anticoagulants was extended to 90 days, a further 1–9 individuals (exact number not given because of national statistical bureaus' regulations) were found with overlapping prescriptions.

## Discussion

This population-based study provides nationally representative data on the prevalence and pattern of etoricoxib use in dental patients in four Nordic countries, namely Denmark, Finland, Sweden and Norway. At the time, this study was

**Table 2.** Description of prescription redemptions of etoricoxib prescribed by a dentist in Denmark, Finland and Sweden in 2012–2014 with and without a contemporaneous dental procedure.

|                                                         | Total    | Prescription redemptions                           |                                                       |                            |
|---------------------------------------------------------|----------|----------------------------------------------------|-------------------------------------------------------|----------------------------|
|                                                         |          | With a dental procedure                            |                                                       | Without a dental procedure |
|                                                         |          | With a contemporaneous link to a dental procedure* | Without a contemporaneous link to a dental procedure* |                            |
|                                                         | N (100%) | N (row % of total)                                 | N (row % of total)                                    | N (row % of total)         |
| <b>Overall</b>                                          | 1278     | 382 (30%)                                          | 469 (37%)                                             | 427 (33%)                  |
| <b>Gender</b>                                           |          |                                                    |                                                       |                            |
| Female                                                  | 724      | 190 (26%)                                          | 272 (38%)                                             | 262 (36%)                  |
| Male                                                    | 554      | 192 (35%)                                          | 197 (36%)                                             | 165 (30%)                  |
| <b>Age group at prescription redemption<sup>†</sup></b> |          |                                                    |                                                       |                            |
| 16–25                                                   | 121      | 41 (34%)                                           | 17 (14%)                                              | 63 (52%)                   |
| 26–35                                                   | 181      | 81 (45%)                                           | 53 (29%)                                              | 47 (26%)                   |
| 36–45                                                   | 198      | 61 (31%)                                           | 71 (36%)                                              | 66 (33%)                   |
| 46–55                                                   | 277      | 69 (25%)                                           | 115 (42%)                                             | 93 (34%)                   |
| 56–65                                                   | 330      | 80 (24%)                                           | 134 (41%)                                             | 116 (35%)                  |
| ≥66                                                     | 171      | 50 (29%)                                           | 79 (46%)                                              | 42 (25%)                   |
| <b>Year at prescription redemption</b>                  |          |                                                    |                                                       |                            |
| 2012                                                    | 395      | 119 (30%)                                          | 143 (36%)                                             | 133 (34%)                  |
| 2013                                                    | 464      | 114 (25%)                                          | 181 (39%)                                             | 169 (36%)                  |
| 2014                                                    | 419      | 149 (30%)                                          | 145 (35%)                                             | 125 (30%)                  |
| <b>Dose (mg/tablet)</b>                                 |          |                                                    |                                                       |                            |
| 30                                                      | 103      | 25 (24%)                                           | 36 (35%)                                              | 42 (41%)                   |
| 60                                                      | 284      | 43 (15%)                                           | 121 (43%)                                             | 120 (42%)                  |
| 90                                                      | 350      | 72 (21%)                                           | 130 (37%)                                             | 148 (42%)                  |
| 120                                                     | 541      | 242 (45%)                                          | 182 (34%)                                             | 117 (22%)                  |
| <b>Number of tablets</b>                                |          |                                                    |                                                       |                            |
| 7                                                       | 403      | 215 (53%)                                          | 108 (27%)                                             | 80 (20%)                   |
| 14, 21                                                  | 62       | 11 (18%)                                           | 35 (57%)                                              | 16 (26%)                   |
| 28                                                      | 509      | 138 (27%)                                          | 222 (44%)                                             | 149 (29%)                  |
| ≥30                                                     | 304      | 18 (6%)                                            | 104 (34%)                                             | 182 (60%)                  |

<sup>a</sup>A prescription redemption with a contemporaneous link to a dental procedure is defined as an etoricoxib prescription redeemed within the timeframe of two weeks before to one week after a dental procedure. An etoricoxib prescription redemption without a contemporaneous link to a dental procedure is an etoricoxib prescription redemption occurring outside this timeframe.

<sup>b</sup>According to the regulations of the national statistical bureaus, it is not allowed to present results if there are less than 10 individuals in a group. Therefore, the age group 0–15 was not included in the table.

**Table 3.** Types of dental procedures associated with a contemporaneous link<sup>a</sup> to prescription redemptions of etoricoxib prescribed by a dentist during the period 2012–2014.

| Type of dental procedure                          | Number and Percent of total dental procedures |
|---------------------------------------------------|-----------------------------------------------|
| Prescription redemptions, total                   | 382                                           |
| Procedures, total                                 | 460 (100%)                                    |
| Dental cavity fillings without pulp communication | 47 (10%)                                      |
| Pulp capping                                      | 1–9 (.) <sup>c</sup>                          |
| Coronal amputation of pulp                        | 1–9 (.) <sup>c</sup>                          |
| Opening to pulp and canal cleaning                | 35 (8%)                                       |
| Surgical apical amputation                        | 1–9 (.) <sup>c</sup>                          |
| Extraction of tooth                               | 146 (32%)                                     |
| Surgical removal of tooth                         | 156 (34%)                                     |
| Treatment of bleeding after extraction            | 0 (0%)                                        |
| Periodontal treatment                             | 32 (7%)                                       |
| Expanded periodontal treatment                    | 1–9 (.) <sup>c</sup>                          |
| Scaling of teeth <sup>b</sup>                     | 0 (0%)                                        |
| Scaling of root surfaces <sup>b</sup>             | 0 (0%)                                        |
| Surgical periodontal treatment                    | 0 (0%)                                        |
| Surgical measures - implant treatment etc.        | 34 (7%)                                       |
| Prosthetic measures                               | 1–9 (.) <sup>c</sup>                          |

<sup>a</sup>A prescription redemption with a contemporaneous link to a dental procedure is defined as an etoricoxib prescription redeemed within the timeframe of two weeks before to one week after a dental procedure.

<sup>b</sup>Often part of periodontal treatment.

<sup>c</sup>According to the regulations of the national statistical bureaus, it is not allowed to present results if there are less than 10 individuals in a group. So, in these cases, the exact data or percentages are not provided.

requested, these Nordic countries were the only ones in which nationwide data on dental procedures and dispensed etoricoxib prescriptions (written by dentists) were available.

Overall, the utilization of etoricoxib for dental pain in these Nordic countries was low and relatively constant over the study period (2012–2014). Yet, there was heterogeneity among the countries in terms of etoricoxib use. The highest utilization of etoricoxib was in Finland, which between 2012 and 2014, had 907 prescriptions dispensed compared to Denmark where only 12 prescriptions were redeemed. Unexpectedly, only approximately 30% of the prescriptions dispensed in Denmark, Finland and Sweden were contemporaneously associated with a dental procedure. Moreover, almost one-third were dispensed to individuals for whom there was no registry evidence that they underwent a dental procedure in the 3-year study period. In Sweden and Denmark, where concurrent administration of etoricoxib and oral anticoagulants was assessed, only a small overlap between etoricoxib and anticoagulant prescriptions was noted in Sweden; no such overlap was observed in Denmark. Reassuringly, over the 3-year study period, there were <10 prescriptions dispensed for paediatric patients (<16 years), in whom etoricoxib is contraindicated. Nonetheless, over 40% of the prescriptions in Denmark, Finland and Sweden and almost 60% of those in Norway were for etoricoxib doses higher than the recommended daily dose of 90 mg.

Several factors could influence variations in analgesic utilization across countries. These include factors driving prescriber behaviour such as knowledge about drugs, years in practice, practice type, size and patient mix, and patient-

**Table 4.** Description of utilization of etoricoxib >90 mg tablets prescribed by a dentist.

|                                                                                         | Total number of prescriptions redeemed | Number of prescriptions redeemed with a dose >90 mg per tablet<br>N (% of total prescription redemptions) |
|-----------------------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Overall                                                                                 | 1278                                   | 541 (42%)                                                                                                 |
| Gender                                                                                  |                                        |                                                                                                           |
| Female                                                                                  | 724                                    | 253 (35%)                                                                                                 |
| Male                                                                                    | 555                                    | 288 (52%)                                                                                                 |
| Age group at prescription redemption                                                    |                                        |                                                                                                           |
| 16–25                                                                                   | 121                                    | 57 (47%)                                                                                                  |
| 26–35                                                                                   | 181                                    | 106 (59%)                                                                                                 |
| 36–45                                                                                   | 198                                    | 101 (51%)                                                                                                 |
| 46–55                                                                                   | 277                                    | 128 (46%)                                                                                                 |
| 56–65                                                                                   | 330                                    | 98 (30%)                                                                                                  |
| ≥66                                                                                     | 171                                    | 51 (30%)                                                                                                  |
| Year at prescription redemption                                                         |                                        |                                                                                                           |
| 2012                                                                                    | 395                                    | 149 (38%)                                                                                                 |
| 2013                                                                                    | 464                                    | 149 (32%)                                                                                                 |
| 2014                                                                                    | 419                                    | 244 (58%)                                                                                                 |
| Number of tablets                                                                       |                                        |                                                                                                           |
| 7                                                                                       | 403                                    | 363 (90%)                                                                                                 |
| 14, 21                                                                                  | 62                                     | 51 (82%)                                                                                                  |
| 28                                                                                      | 509                                    | 92 (18%)                                                                                                  |
| ≥30                                                                                     | 304                                    | 35 (12%)                                                                                                  |
| Prescription redemptions with a contemporaneous link to a dental procedure <sup>a</sup> |                                        |                                                                                                           |
| Yes                                                                                     | 382                                    | 242 (63%)                                                                                                 |
| No                                                                                      | 896                                    | 299 (33%)                                                                                                 |

aA prescription redemption with a contemporaneous link to a dental procedure is defined as an etoricoxib prescription redeemed within the timeframe of two weeks before to one week after a dental procedure. An etoricoxib prescription redemption without a contemporaneous link to a dental procedure is an etoricoxib prescription redemption occurring outside this timeframe.

**Table 5.** Types of dental procedures associated with a contemporaneous link<sup>a</sup> to prescription redemptions of >90 mg etoricoxib tablets prescribed by a dentist during the period 2012–2014.

|                                                                                                   |                                                   |                      |
|---------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------|
| Type of procedures for prescription redemptions with a contemporaneous link to a dental procedure | Dental cavity fillings without pulp communication | 17 (36%)             |
|                                                                                                   | Pulp capping                                      | 1–9 (.) <sup>c</sup> |
|                                                                                                   | Coronal amputation of pulp                        | 0 (0%)               |
|                                                                                                   | Opening to pulp and canal cleaning                | 12 (34%)             |
|                                                                                                   | Surgical apical amputation                        | 1–9 (.) <sup>c</sup> |
|                                                                                                   | Extraction of tooth                               | 101 (70%)            |
|                                                                                                   | Surgical removal of tooth                         | 126 (81%)            |
|                                                                                                   | Treatment of bleeding after extraction            | 0 (0%)               |
|                                                                                                   | Periodontal treatment                             | 13 (41%)             |
|                                                                                                   | Expanded periodontal treatment                    | 0 (0%)               |
|                                                                                                   | Scaling of teeth <sup>b</sup>                     | 0 (0%)               |
|                                                                                                   | Scaling of root surfaces <sup>b</sup>             | 0 (0%)               |
|                                                                                                   | Surgical periodontal treatment                    | 0 (0%)               |
|                                                                                                   | Surgical measures - implant treatment etc.        | 25 (74%)             |
|                                                                                                   | Prosthetic measures                               | 1–9 (.) <sup>c</sup> |

aA prescription redemption with a contemporaneous link to a dental procedure is defined as an etoricoxib prescription redeemed within the timeframe of two weeks before to one week after a dental procedure.

bOften part of periodontal treatment.

cAccording to the regulations of the national statistical bureaus, it is not allowed to present results for less than 10 individuals. So, in these cases, the exact data or percentages are not provided.

related factors such as co-morbidities, socioeconomic position and ethnicity along with knowledge, beliefs, perceptions and attitudes to drugs [17]. In Finland, etoricoxib seems to be perceived as a good alternative analgesic to non-selective NSAIDs; therefore, it may have been prescribed more frequently for dental pain and often irrespective of an accompanying dental procedure. However, this pattern of use is not consistent with the approved etoricoxib labelling and instructions for use. The general lack of concordance with the etoricoxib treatment guidelines in this respect indicates that the Nordic dentists who are prescribing etoricoxib, may often be prescribing it off-label for dental pain that is not related to any specific dental procedure.

It could be speculated that the low utilization of etoricoxib in Denmark may be due to the reluctance of clinicians to prescribe COX-2 inhibitors in general for pain relief, possibly due to potential perceived safety concerns reported with rofecoxib and valdecoxib as a class effect. Imperative among factors affecting analgesic utilization profiles in a country are medical society guidelines and recommendations and declarations made by the national health authority. The Danish Health Authority advocates using alternate classes of analgesics in preference to etoricoxib [26], and this may play a role in influencing etoricoxib utilization in the country. In fact, in the EU as a whole, following withdrawal of rofecoxib and valdecoxib, a number of strategies

were implemented in around 2005 to improve and optimize the prescription and utilization of analgesics [5]. After rofecoxib withdrawal, recommendations were issued in some countries to help clinicians switch their patients from coxibs to appropriate alternative therapies [4]. These factors may have culminated in a worldwide drop in COX-2 inhibitor prescribing. Nevertheless, nowadays, all NSAIDs (i.e. both non-selective and coxibs) contain contraindications and warnings in their labels about cardiovascular risks [10], and according to a Danish Health Authority report, there has been a general decrease in the number of NSAID users (both coxibs and non-selective NSAIDs) in the last decade (except for propionic acid derivatives such as ibuprofen, naproxen and dexibuprofen) [26].

Given that very few (1–9) etoricoxib prescriptions were dispensed for paediatric patients over the 3-year study period, off-label paediatric use of etoricoxib appears to be limited. However, the relatively high proportion of prescriptions for doses >90 mg/day (i.e. for the 120 mg tablets) is surprising, especially, since the national guidelines are consistent with etoricoxib labelling and instructions for use, which recommend a dose of 90 mg once daily for up to three days for pain associated with dental procedures [12]. It is possible that individual dentists have found higher doses of etoricoxib to be more effective and are using these doses for dental conditions associated with higher levels of pain such as temporomandibular joint pain, dental abscesses or implant procedures. A recent Cochrane systematic review (6 studies,  $n=1214$  participants) reported that etoricoxib administered at a dose of 120 mg provides four times higher post-operative analgesia than placebo [27]. However, in the individual studies, only orally administered single doses of etoricoxib were evaluated.

The fact that dentists appear to be prescribing etoricoxib for pain not exclusively associated with a dental procedure and that the minimum pack size includes more than three tablets, it cannot be ruled out that they may also instruct patients to take etoricoxib for more than three days or patients themselves consume more than three tablets. It is also possible that a larger number of tablets might be prescribed when it is anticipated that a patient will have additional procedures (e.g. patients who are having dental implants may have several dental procedures over multiple months).

## Limitations

With respect to prescriptions, prescribing restrictions in the Nordic countries preclude over-the-counter and pharmacist-prescribed etoricoxib dispensation; however, the potential issue of dentists distributing etoricoxib tablets directly to the patients exists, which is not measurable.

Missing information about prescriber information (including profession of the prescriber) in the prescription registers will cause an underestimation of the number of etoricoxib prescription redemptions. A Danish study evaluated the validity of the prescriber information of non-electronic prescriptions [28]. It was shown that 17.8% of non-electronic prescriptions were

incorrect regarding prescriber profession. Overall, correct classification of prescriber profession was estimated at 97.5% in 2015 with approximately 14% non-electronic prescriptions. It is unknown whether these figures apply for dentists and for the other Nordic countries. Applying the same proportion of completeness to the present study, a total of 32 more etoricoxib prescription redemptions could be expected.

Given that the minimum package sizes in the Nordic countries range from 2 to 28 tablet blister packs, it is not possible to ascertain exactly how much off-label use lasting for more than three days actually occurs. Thus, while the data quality and level of sophistication of record keeping of the Nordic registers are high, the information available from these registers to ascertain off-label drug use is limited for the present study. The register data used in this study also did not include direct information on the reasons for etoricoxib prescribing (e.g. dental diagnoses associated with the prescriptions). Consequently, the relationship between prescriptions and procedures within a particular time frame had to be inferred. Because of the data request process for the registers, the procedures of interest had to be pre-specified. It is possible that this pre-specified list is not exhaustive and certain practices among the dentists related to etoricoxib prescription may not have been accounted for. These methodological challenges could potentially result in overestimation of the off-label use [29].

No information was available regarding whether the patients were instructed to withhold their anticoagulant medications while taking etoricoxib. Prescription redemptions of anticoagulants in Finland and Norway were not available for the study. Moreover, given the observed heterogeneity in etoricoxib prescribing by dentists across the four countries, the generalizability of these study results is unknown.

## Conclusion

The overall utilization of etoricoxib for dental pain across Denmark, Finland, Sweden and Norway from 2012 to 2014 was quite low. Over the 3-year study period, a total of 1615 etoricoxib prescriptions written by dentists were dispensed in the Nordic countries. The prescription pattern varied across the countries. While some dentists appear to be prescribing etoricoxib not exclusively associated with a dental procedure, at higher than recommended doses, and potentially for longer than three days, given the low overall prescribing rate by dentists, it is unlikely that this infrequent off-label use within dentistry in the Nordic countries would be of significant public health concern.

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