

Article type : Original Research Article

Nonaspirin Nonsteroidal Antiinflammatory Drug Use in the Nordic Countries from a Cardiovascular Risk Perspective, 2000–2016: A Drug Utilization Study

Running title: NSAID use in Nordic countries

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/phar.2217

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Funding

No funding to report

Conflict of interests

The authors have no competing interests to declare.

Key words

NSAID; Drug utilization; Cardiac risk factors and prevention; Nordic countries

Abstract

Study Objective: Evidence on the cardiotoxicity of nonaspirin nonsteroidal antiinflammatory drugs (NSAIDs)—particularly diclofenac and the newer selective cyclooxygenase (COX)-2 inhibitors—has accumulated over the last decade. Our objective was to examine whether the use of NSAIDs in the Nordic countries changed with the emerging evidence, regulatory statements, and clinical guidelines advocating caution for use of specific NSAIDs.

Design: Drug utilization study.

Data Sources: Nationwide wholesale statistics and prescription registries in Denmark, Finland, Iceland, Norway, and Sweden (2000–2016).

Measurements and Main Results: Our main outcome measures were yearly total sales, expressed as number of sold defined daily doses (DDD)/1000 inhabitants/day, and yearly prevalence of prescription use, expressed as number of prescription users per 1000 inhabitants. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Total sales of NSAIDs

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increased in all countries and were highest in Iceland, with 74.3 DDDs/1000 inhabitants/day sold in 2016, followed by Finland (73.9), Sweden (54.4), Norway (43.8), and Denmark (31.8). Diclofenac use declined after 2008 in all countries but remained the most widely prescribed NSAID in Norway, with 63 prescription users/1000 inhabitants in 2016. Diclofenac sales also remained high in Iceland (12.7 DDD/1000 inhabitants/day), Norway (8.1), and Sweden (7.8). Since its introduction in 2003, the use of etoricoxib, a newer selective COX-2 inhibitor, increased in all countries except Denmark, with highest sales in Finland (6.7 DDD/1000 inhabitants/day in 2016).

Conclusion: Sales and prescription patterns of NSAIDs in the Nordic countries has changed along with the accumulating evidence for the cardiovascular risks of specific NSAIDs. However, given existing evidence on the cardiovascular risks associated with use of diclofenac and etoricoxib, the persistent high use of diclofenac in Iceland, Norway, and Sweden, the persistent over-the-counter availability of diclofenac in Norway and Sweden, and the increasing use of etoricoxib in most of the Nordic countries pose a cardiovascular health concern.

Nonaspirin nonsteroidal antiinflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide.¹ Although the associated gastrointestinal bleeding risk has been acknowledged for decades,² evidence of the adverse cardiovascular effects of NSAIDs is accumulating.³⁻⁵ Concerns regarding the cardiovascular safety of these agents were spurred by clinical trials reporting an increased risk of cardiovascular events in users of rofecoxib, a selective cyclooxygenase (COX)-2 inhibitor (coxib).⁶ As a result, rofecoxib was removed from the market worldwide in 2004, followed by valdecoxib in 2005.⁷ The European Medicines Agency (EMA) assessed the cardiovascular safety of traditional NSAIDs in 2006 and suggested that the cardiovascular risk of diclofenac could be of the same magnitude as the coxibs.⁸ In 2013, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the increased cardiovascular risk associated with diclofenac was comparable to the coxibs and that the precautions already in place for coxibs should be applied to diclofenac.⁹ As a result, the European Commission issued new safety advice for diclofenac in 2013 stating that diclofenac was contraindicated in patients with established ischemic heart disease and should be considered carefully in patients with risk factors for cardiovascular disease.¹⁰ In 2016, a position paper by the European Society of Cardiology stated that diclofenac should be avoided altogether and recommended that when NSAID use could not be avoided, low-dose ibuprofen ($\leq 1,200$ mg/day) or naproxen (≤ 500 mg/day) were recommended as the least

harmful alternatives in patients with or at high risk of cardiovascular disease.¹¹ The increased cardiovascular risk associated with diclofenac use has recently been confirmed for a range of cardiovascular outcomes and even for low doses and short-term treatment.¹²

Sales of NSAIDs are increasing worldwide, and diclofenac remains commonly used in both low- and high-income countries.^{1,13,14} The common use of NSAIDs and its impact on the cardiovascular disease burden pose a public health concern.¹¹ We therefore examined whether use of NSAIDs in the Nordic countries during 2000–2016 reflected the emerging evidence, regulatory statements, and clinical guidelines advocating caution for use of specific NSAIDs.

Methods

Study Design and Population

In this drug utilization study, we examined total sales and prescription use of NSAIDs during 2000–2016 in the Nordic countries of Denmark, Finland, Iceland, Norway, and Sweden. In all five countries, health care is offered primarily by publicly funded health care systems ensuring medical care for all inhabitants and partial reimbursement for most prescribed drugs. In total, the examined population consisted of 26.8 million inhabitants in 2016, with Denmark accounting for 5.7 million, Finland 5.5 million, Iceland 0.3 million, Norway 5.3 million, and Sweden 10 million inhabitants.¹⁵

Data Sources

Data sources and data availability are described in detail in Supplementary Table S1. Wholesale statistics covered all drug sales in Denmark, Finland, Norway, and Sweden during the entire study period (2000–2016) and during 2003–2016 in Iceland. We extracted data on sales by prescription (including packages to pharmacies and institutions) and over-the-counter (OTC) sales, and total sales (prescription and OTC sales).

The nationwide prescription registries covered, on individual level, all dispensed drugs by prescription at community pharmacies. Prescription registry data were available from 2000–2016 for Denmark¹⁶ and Finland,¹⁷ 2004–2016 for Norway,¹⁸ and 2006–2016 for Sweden.¹⁹ Prescription data from Iceland were

not available. In Finland, the prescription registry included only reimbursed drug purchases. Until 2005, Finnish patients paid a fixed deductible at each purchase, and purchases below this sum were not recorded. The deductible was removed in 2006, resulting in increased coverage in the Finnish prescription registry.²⁰

NSAIDs

We identified nonaspirin NSAIDs by Anatomical Therapeutic Chemical (ATC) codes, version 2016, and included drugs classified in group M01A.²¹ Accordingly, acetylsalicylic acid (aspirin) and topical NSAIDs were not included. We excluded glucosamine (ATC code M01AX05) and chondroitin sulfate (ATC code M01AX25) due to their unrelated pharmacologic properties. We presented sale and prescription data for all NSAIDs in group M01A combined (excluding glucosamine and chondroitin sulfate) as well as for all individual NSAIDs. Our main focus was NSAIDs of a priori interest (ibuprofen, naproxen, diclofenac, coxibs) and/or drugs in the drug utilization 90% segment in 2015—that is, the NSAIDs that accounted for at least 90% of total sales in 2015.²² A timeline of the numerous regulatory changes regarding the use of diclofenac and the coxibs in the Nordic countries that occurred during the study period is shown in Figure 1.

The variety of NSAIDs available for OTC purchase differed between the Nordic countries (Table 1). However, ibuprofen was available OTC in all countries. A range of regulation changes occurred during the study period including restrictions in pack sizes and age restrictions. OTC sales of NSAIDs were allowed from outlets other than pharmacies (e.g., grocery stores) in Denmark from 2002 and onward, in Norway from 2004 and onward, and in Sweden from 2009 and onward.

Outcome Measures and Statistical Analysis

We retrieved total sales as number of sold defined daily doses (DDDs)/1000 inhabitants/day from the public authorities in each country. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. As a fixed unit of measurement independent of price, currencies, package size, and strength, it is used to describe trends in drug consumption and to perform comparisons between population groups.²¹

We presented yearly prevalence of prescription use as number of users per 1000 inhabitants. We calculated the prevalence of use as the number of patients filling an NSAID prescription in a given year (using the prescription registries) relative to the total number of inhabitants in each country on January 1 of the same year or December 31 the preceding year (using data from the statistical agencies of each country). These figures were calculated for all patients and stratified by sex and age (0–19, 20–39, 40–59, 60–69, 70–79, and ≥ 80 years). A patient filling a prescription for more than one NSAID was counted only once in the numerator for each NSAID with a prescription fill and only once in the numerator for the all NSAIDs category. For Sweden, we slightly underestimated prescription use for the category all NSAIDs as prescription users of NSAIDs were not included if they also received a prescription for chondroitin sulfate or glucosamine. The yearly prevalence of prescription use of glucosamine or chondroitin sulfate in Sweden was 1.3% in 2006 and 0.2% in 2016.

Some NSAIDs were sold as combination products (diclofenac, ibuprofen, indomethacin, and naproxen). As the DDDs for combination products are equal to the DDDs of the corresponding individual NSAIDs,²¹ we simply combined the sales of combination products and the active NSAID. In Finland, the DDDs for some diclofenac combination products differed from the World Health Organization ATC/DDD index.²³ However, as diclofenac combinations constituted a small part of total diclofenac sales, this had limited influence on the results (e.g., in 2016, sales of diclofenac were 4.2 DDD/1000 inhabitants/day, and sales of diclofenac combinations were 0.09 DDD/1000 inhabitants/day). We were not able to collapse prescription use of combination products and the corresponding NSAID in an analogous way; thus, these figures were presented separately.

Results

NSAIDs Overall

Total NSAID sales increased in all countries during the study period (Figure 2, Supplementary Table S2). During 2000–2016 (2003–2016 for Iceland), sales rose by 48% in Sweden, 30% in Norway, 24% in Finland, 7% in Iceland, and 2% in Denmark. In 2016, total sales were highest in Iceland at 74.3 DDD/1000 inhabitants/day followed by Finland (73.9), Sweden (54.4), Norway (43.8), and Denmark (31.8). Despite the increasing NSAID sales, variability in the number of agents used decreased. In 2000,

6–7 agents accounted for at least 90% of total NSAID sales while this number declined to 3–4 in 2015 (Table 2).

The yearly prevalence of prescription use of all NSAIDs increased from 174 users/1000 inhabitants in 2000 to 213 users/1000 inhabitants in 2016 in Finland, remained stable at around 140/1000 inhabitants in Denmark, and declined in Norway (from 179 users/1000 inhabitants in 2004 to 155 users/1000 inhabitants in 2016) and Sweden (from 123 users/1000 inhabitants in 2006 to 102 users/1000 inhabitants in 2016) (Supplementary Table S3). Prescription use of NSAIDs was most prevalent in patients aged 40–59, 60–69, and 70–79 years (Supplementary Figure S1).

Ibuprofen

Ibuprofen was the most commonly sold NSAID in all countries throughout the study period (Figure 2, Supplementary Table S2). OTC sales of ibuprofen were considerable in all countries and highest in Iceland, with 33.5 DDD/1000 inhabitants/day sold in 2016 corresponding to 82% of the total ibuprofen sales in Iceland (Supplementary Table S4). Corresponding numbers were 23.8 (86%) in Sweden, 23.3 (46%) in Finland, 9.3 (55%) in Norway, and 5.4 (21%) in Denmark.

Ibuprofen was the most commonly prescribed NSAID in Denmark and Finland throughout the study period, and the prevalence of use increased during this period. The prevalence of prescription use of ibuprofen in 2016 was 142 users/1000 inhabitants in Finland and 118 users/1000 inhabitants in Denmark (Figure 3, Supplementary Table S3). Prescription use of ibuprofen was rather constant in Norway and Sweden, with a prevalence of around 40 users/1000 inhabitants and 20 users/1000 inhabitants, respectively.

Naproxen

Naproxen sales were highest in Norway with 12.4 DDD/1000 inhabitants/day sold in 2016 followed by Sweden (12.3), Iceland (8.4), Finland (7.8), and Denmark (2.2) (Figure 2, Supplementary Table S2).

In Sweden, naproxen was the most commonly prescribed NSAID in 2016, with a prevalence of 44 users/1000 inhabitants (Figure 3, Supplementary Table S3). Prescription use of naproxen in Norway in

2016 was similar to that of Sweden, with a yearly prevalence of use of 20 users/1000 inhabitants for naproxen and 24 users/1000 inhabitants for naproxen combined with esomeprazole.

Diclofenac

Diclofenac sales were highest in Iceland, with 12.7 DDD/1000 inhabitants/day (only by prescription) in 2016 followed by Norway with 8.1 (9% sold OTC), Sweden 7.8 (33% sold OTC), Finland 4.3 (only by prescription), and Denmark 2.4 (only by prescription) (Figure 2, Supplementary Tables S2 and S4). From 2000–2016 (2003–2016 for Iceland), diclofenac sales decreased by 64% in Denmark, 26% in Iceland, 20% in Finland, and 16% in Sweden. In Norway, however, sales increased by 16% from 2000–2016.

Diclofenac was the most commonly prescribed NSAID in Norway during the entire study period, peaking in 2008 with a prevalence of 100 users/1000 inhabitants after which the prevalence of use declined to 63 users/1000 inhabitants in 2016 (Figure 3, Supplementary Table S3). In Sweden, diclofenac was, by far, the most widely prescribed NSAID in 2006, with a prevalence of 75 users/1000 inhabitants. Use declined markedly from 2012 onward resulting in a prevalence of 31 users/1000 inhabitants in 2016. The proportion of older patients with at least one prescription for diclofenac was considerable (Figure 4). In 2016, the prevalence of diclofenac use among patients aged 60–69 years was 80 users/1000 inhabitants in Norway, 49 users/1000 inhabitants in Sweden, 39 users/1000 inhabitants in Finland, and 17 users/1000 inhabitants in Denmark. For patients aged 70–79 years, the prevalence was slightly lower, and for patients aged 80 years or older, it was remarkably lower, ranging from 11 users/1000 inhabitants in Denmark to 26 users/1000 inhabitants in Norway.

Newer Selective COX–2 inhibitors

Since the introduction in 2000, sales of celecoxib increased rapidly to peak in 2003–2004 (Figure 2, Supplementary Table S2). In 2005–2006, sales declined sharply. The use of celecoxib remained limited after 2006 (<1 DDD/1000 inhabitants/day) except in Iceland, where sales began to increase again from 2005 onward resulting in 7.0 DDD/1000 inhabitants/day sold in 2016. Sales of etoricoxib increased in all countries except Denmark—for example, in Finland, sales rose from 3.1 DDD/1000 inhabitants/day in 2005 to 6.7 DDD/1000 inhabitants/day in 2016 (Figure 2, Supplementary Table S2). In Finland and

Norway, etoricoxib was the third and fourth, respectively, most sold NSAID in 2015 (Table 2). Other coxibs available during the study period had negligible market shares. Trends in prescription use of coxibs followed wholesale statistics, as coxibs were available by prescription only.

Discussion

Use of nonaspirin NSAIDs in the Nordic countries changed during 2000–2016, in parallel with accumulating evidence on the cardiovascular risks of NSAIDs. Total sales of ibuprofen and naproxen increased while diclofenac sales decreased. However, diclofenac remains commonly used in Iceland, Norway, and Sweden, and use of etoricoxib has increased in all Nordic countries except Denmark.

The cardiovascular risks of diclofenac are well documented.^{3–5,12} Thus, its high use is a cause of concern. Diclofenac is used mainly for short durations. However, even short-term use of diclofenac is associated with increased cardiovascular risk—not only compared with no NSAID use and acetaminophen but also compared with ibuprofen use (incidence rate ratio [IRR] 1.2, 95% confidence interval [CI] 1.1–1.3) and naproxen use (IRR 1.3, 95% CI 1.1–1.5).¹² The increased risk was present for all doses of diclofenac. In absolute terms, the risk increase corresponded to four additional major adverse cardiovascular events per 1000 diclofenac initiators compared with nonusers in low-risk patients, increasing to 40 additional events in high-risk individuals.¹² The high absolute risk of cardiovascular events among patients at risk for or with manifest cardiovascular disease is due to the high baseline cardiovascular risk in these patients. However, the relative risk increase associated with diclofenac is the same for high- and low-risk individuals.^{3,12} Thus, even on a population level, where most users are at low risk but the prevalence of diclofenac use is high, the use of diclofenac has potentially major public health implications. Further, given the fact that safer alternative NSAIDs with similar effectiveness exist, a high prevalent use of diclofenac is of concern despite being prescribed in low doses and short durations and to patients at low cardiovascular risk.¹¹

The marked variation in diclofenac use between the Nordic countries may indicate nonadherence to guidelines regarding NSAID use. Health and medicine agencies in the Nordic countries reacted differently as evidence for the cardiovascular risks associated with diclofenac came forth. In Denmark, prescription use of diclofenac declined markedly from 2008 to 2009. In 2008, a Danish observational

Accepted Article

study reported a hazard ratio for death or myocardial infarction of 1.6 (95% CI 1.5–1.8) for diclofenac use compared with no NSAID use.²⁴ This study was widely reported in the Danish media,²⁵ and the Danish Medicines Agency subsequently withdrew the authorization to sell diclofenac OTC²⁶ and issued a warning to health care professionals on the cardiovascular risks associated with diclofenac.²⁷ In Sweden in 2012, diclofenac was replaced by naproxen on the Wise list—a list for recommended essential medicines for common diseases in patients in Stockholm County Council²⁸—which was followed by increasing prescription use of naproxen and declining use of diclofenac in Sweden. We observed a similar trend of increasing naproxen use and decreasing diclofenac use in Norway. To our knowledge, the national medicine agencies, except for the Danish Medicines Agency, did not issue warnings regarding diclofenac use until 2013 when the results of the PRAC review were published.^{29–32}

The increasing use of etoricoxib in all countries except Denmark also raises concern. The use of etoricoxib rose after results from the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme was published in 2006.³³ The MEDAL programme showed that etoricoxib was comparable to diclofenac with regard to cardiovascular safety (hazard ratio for thrombotic cardiovascular events 0.9, 95% CI 0.7–1.1).³³ The choice of diclofenac as comparator was unfortunate, as diclofenac is associated with higher cardiovascular risk than low-dose ibuprofen and naproxen.³ Indeed, with naproxen as comparator instead of diclofenac, a hazard ratio of 2.5 (95% CI 1.2–5.2) for major vascular events with etoricoxib treatment was reported in a meta-analysis of clinical trial data.³ Correspondingly, etoricoxib was rejected entry into the United States market by the U.S. Food and Drug Administration in 2007 due to concerns regarding its cardiovascular risk.³⁴

To our knowledge, the present study is the first to examine NSAID utilization across all five Nordic countries. The main strengths of this study included the use of high-quality prescription registries and wholesale data. Further, by examining the differences among the Nordic countries, we were able to distinguish whether changes in NSAID use reflected international trends or, more importantly, variation among countries due to other factors such as nonadherence to clinical guidelines. Such marked cross-national differences among the Nordic countries has been shown for trends in acetaminophen use as well.³⁵

We focused on diclofenac and the coxibs because they increase cardiovascular risk the most; however, it must be noted that all NSAIDs potentially have a negative cardiovascular influence, dependent on dose and duration.¹¹ For example, high-dose ibuprofen (≥ 2400 mg/day) increases cardiovascular risk to a similar extent as diclofenac.³ We did not examine the prevalence of cardiovascular risk factors in NSAID users or evaluate the dose or duration of use. Thus, future studies should investigate how the differences in NSAID utilization among the Nordic countries affected the cardiovascular disease burden.^{11,12} Nonetheless, this study provides evidence that policy interventions aimed at further reducing the use of diclofenac and reversing the trend of increasing etoricoxib use is needed in most Nordic countries. Such interventions include education and active dissemination of guidelines, a reimbursement system that promotes rational NSAID use, and stricter regulation of OTC sales. In a Swedish setting, such policy interventions have been shown to impact use of the direct oral anticoagulants when they were introduced.³⁶ An initial step to promote safer use of NSAIDs could be to restrict the OTC availability of diclofenac in Norway and Sweden. In contrast to the other Nordic countries, diclofenac was still, as of 2018, available OTC in Norway and Sweden, with OTC sales constituting 33% and 9% of the total diclofenac sales in 2016 in Sweden and Norway, respectively. Safer use of NSAIDs could also be promoted by a reimbursement system that provided incentives to follow guidelines for rational prescribing of NSAIDs. For example, the general reimbursement for diclofenac was removed in February 2016 in Denmark to promote prescribing of safer alternatives.³⁷ Similarly, reimbursement for etoricoxib was restricted to select patients with high bleeding risk in February 2011 in Sweden.³⁸ On the contrary, general reimbursement for etoricoxib was introduced in Norway in September 2012.³⁹ This resulted in increasing use to an extent where the Norwegian Medicines Agency warned against the high uptake of etoricoxib in 2014.⁴⁰ Implementation of guidelines or recommendations seems to have the greatest effect when they are actively implemented by education, active dissemination, and feedback to physicians on prescribing patterns.⁴¹ An example of this include the Wise list, which is actively disseminated to physicians and patients in Stockholm County, Sweden.⁴²

Choosing among different NSAIDs involves balancing cardiovascular and gastrointestinal risks. Ibuprofen and naproxen are associated with augmented gastrointestinal risk; however, coxibs and diclofenac also increase risk of upper gastrointestinal complications compared with placebo (relative risk

[RR] 1.8, 95% CI 1.2–2.8 for coxibs; RR 1.9, 95% CI 1.2–3.1 for diclofenac; RR 4.0, 95% CI 2.2–7.1 for ibuprofen; and RR 4.2, 95% CI 2.7–6.6 for naproxen).³ Some data even suggest that diclofenac initiation is associated with a higher risk of gastrointestinal bleeding than ibuprofen and a risk similar to that of naproxen.¹² The need for concomitant proton pump inhibitor therapy should be considered in patients at increased risk of gastrointestinal events.⁴³

Conclusion

NSAID sales and prescription patterns in the Nordic countries has changed along with the accumulating evidence for the cardiovascular risks of specific NSAIDs. However, the high prevalent use of diclofenac in Iceland, Norway, and Sweden, the persistent OTC availability of diclofenac in Norway and Sweden, and the increasing use of etoricoxib in most Nordic countries should raise concerns among Nordic national medicines authorities.

REFERENCES

1. McGettigan P, Henry D. Use of Non-Steroidal Anti-Inflammatory Drugs That Elevate Cardiovascular Risk: An Examination of Sales and Essential Medicines Lists in Low-, Middle-, and High-Income Countries. Turnbull FM, editor. *PLoS Med.* 2013 Feb 12;10(2):e1001388.
2. Castellsague J, Riera-Guardia N, Calingaert B, Varas-Lorenzo C, Fourrier-Reglat A, Nicotra F, et al. Individual NSAIDs and Upper Gastrointestinal Complications: A Systematic Review and Meta-Analysis of Observational Studies (the SOS Project). *Drug Saf.* 2012 Dec;35(12):1127–46.
3. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *The Lancet.* 2013 Aug;382(9894):769–79.
4. McGettigan P, Henry D. Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. Strom BL, editor. *PLoS Med.* 2011 Sep 27;8(9):e1001098.
5. Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *BMJ.* 2017 May 9;j1909.
6. Baron JA, Sandler RS, Bresalier RS, Lanos A, Morton DG, Riddell R, et al. Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. *The Lancet.* 2008 Nov;372(9651):1756–64.

- Accepted Article
7. Food and Drug Administration. Public Health Advisory: FDA Announces Series of Changes to the Class of Marketed Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [Internet]. 2005. Available from: <http://wayback.archive-it.org/7993/20161024015705/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108427.htm>
 8. European Medicines Agency. Public CHMP assesment report for medicinal products containing non-selective non steroidal antiinflammatory drugs (NSAIDs) [Internet]. European Medicines Agency; 2006. Available from: https://www.ema.europa.eu/documents/report/public-chmp-assessment-report-medicinal-products-containing-non-selective-non-steroidal-anti_en.pdf
 9. European Medicines Agency. Assessment report for diclofenac containing medicinal products (systemic formulations) [Internet]. European Medicines Agency; 2013. Available from: https://www.ema.europa.eu/documents/referral/diclofenac-article-31-referral-prac-assessment-report_en.pdf
 10. European Medicines Agency. New safety advice for diclofenac – CMDh endorses PRAC recommendation [Internet]. European Medicines Agency; 2013. Available from: https://www.ema.europa.eu/documents/press-release/new-safety-advice-diclofenac-cmdh-endorses-prac-recommendation_en.pdf
 11. Schmidt M, Lamberts M, Olsen A-MS, Fosbøll E, Niessner A, Tamargo J, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J*. 2016 Apr 1;37(13):1015–23.
 12. Schmidt, M, Sørensen, HT, Pedersen, L. Diclofenac use and cardiovascular risks: series of nationwide cohort studies. *BMJ*. 2018;362:k3426.
 13. Inotai A, Hankó B, Mészáros Á. Trends in the non-steroidal anti-inflammatory drug market in six Central-Eastern European countries based on retail information. *Pharmacoepidemiol Drug Saf*. 2010 Feb;19(2):183–90.
 14. Barozzi N, Sketris I, Cooke C, Tett S. Comparison of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 (COX-2) inhibitors use in Australia and Nova Scotia (Canada). *Br J Clin Pharmacol*. 2009 Jul;68(1):106–15.
 15. Haagensen KM, Agerskov U, editors. *Nordic Statistics 2017* [Internet]. Copenhagen: Nordic Council of Ministers; 2017. Available from: <http://dx.doi.org/10.6027/ANP2017-748>
 16. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2017 Jun 1;46(3):798–798f.
 17. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic Countries as a Cohort for Pharmacoepidemiological Research. *Basic Clin Pharmacol Toxicol*. 2010 Feb;106(2):86–94.
 18. Furu K. Drug utilisation in a public health perspective: Establishing a national prescription register in Norway. *Nor Epidemiol* [Internet]. 2009 Nov 6;11(1). Available from: <http://www.ntnu.no/ojs/index.php/norepid/article/view/534>
 19. Wettermark B, Hammar N, MichaelFored C, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007 Jul;16(7):726–35.

20. Paakkari P, Voipio T, Saastamoinen L, Martikainen J. Medicines in 2016. In: Finnish Statistics on Medicines 2006. Helsinki: Finnish National Agency for Medicines and Finnish Social Insurance Institution; 2007. p. 21–8.
21. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. ATC/DDD Index [Internet]. Available from: <https://www.whocc.no>
22. Bergman U, Popa C, Tomson Y, Wettermark B, Einarson TR, Aberg H, et al. Drug utilization 90%-a simple method for assessing the quality of drug prescribing. *Eur J Clin Pharmacol*. 1998 Apr;54(2):113–8.
23. Classification of drugs (ATC) and defined daily doses (DDD) 2018 [Internet]. Helsinki, Finland: Finnish Medicines Agency; 2018. Available from: http://www.julkari.fi/bitstream/handle/10024/136204/ATC-kirja2018_netti.pdf?sequence=1&isAllowed=y
24. Fosbøl E, Gislason G, Jacobsen S, Folke F, Hansen M, Schramm T, et al. Risk of Myocardial Infarction and Death Associated With the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Among Healthy Individuals: A Nationwide Cohort Study. *Clin Pharmacol Ther*. 2009 Feb;85(2):190–7.
25. Andersen, Morten Garly, Vasconcellos, Bianca Z. Farlig medicin fjernes fra håndkøb (Dangerous drug no longer available over-the-counter). *Politiken* [Internet]. 2008 Dec 6; Available from: <https://politiken.dk/indland/art5705346/Farlig-medicin-fjernes-fra-haendkoeb>
26. Danish Medicines Agency. Redegørelse vedrørende den kardiovaskulære risiko ved brug af non-selektive NSAID præparater (Briefing regarding cardiovascular risks of NSAIDs) [Internet]. Danish Health and Medicines Agency; 2008. Available from: <http://www.ft.dk/samling/20081/almdel/suu/bilag/265/645749.pdf>
27. Danish Medicines Agency. New information about cardiovascular adverse reactions from the use of NSAID [Internet]. Danish Medicines Agency; 2008. Available from: <http://www.sst.dk>
28. The Drug Therapeutic Committee and the Health and Medical Care Administration of the Stockholm County Council, Sweden. Viktiga förändringar i Kloka Listan nästa år (Important changes in the Wise List next year) [Internet]. 2011. Available from: <https://janusinfo.se/nyheter/nyheter/2011/viktigaforandringariklokalistannastaar.5.467926b615d084471acec57.html>
29. Finnish Medicines Agency. Terveystuotojen ammattilaisille - Diklofenaakki uusia vasta aiheita ja varoituksia Euroopassa toteutetun kardiovaskulaarista turvallisuutta koskeneen arvioinnin jälkeen (For health professionals: Diclofenac - New Contraindications and Warnings After Evaluating Cardiovascular Safety in Europe) [Internet]. Finnish Medicines Agency; 2013. Available from: http://www.fimea.fi/documents/160140/765540/23610_Systeemisesti_vaikuttavien_diklofenaakki_valmisteiden_DHPC_2013-07-10.pdf
30. Icelandic Medicines Agency. Nýjar leiðbeiningar varðandi notkun lyfja sem innihalda díklófenak (New instructions for the use of diclofenac containing drugs) [Internet]. Icelandic Medicines Agency; 2013. Available from: <https://www.lyfjastofnun.is/utgefid-efni/frettir/nr/2643>
31. Swedish Medical Products Agency. Samma försiktighetsåtgärder för att förhindra allvarliga hjärt-kärlbiverkningar rekommenderas för diklofenak som för selektiva COX-2-hämmare (The same precautions to prevent serious cardiovascular adverse events are recommended for diclofenac as for selective COX-2 inhibitors) [Internet]. Swedish Medical Products Agency; 2013. Available from: <https://lakemedelsverket.se/Alla-nyheter/Nyheter-2013/Samma-forsiktighetsatgarder-for-att>

forhindra-allvarliga-hjart-karlbiverkningar-rekommenderas-for-diklofenak-som-for-selektiva-COX-2-hammare/

32. The Norwegian Medicines Agency. Nye anbefalinger for diklofenak (New recommendations for use of diclofenac) [Internet]. The Norwegian Medicines Agency; 2013. Available from: <https://legemiddelverket.no/nyheter/nye-anbefalinger-for-diklofenak>
33. Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet Lond Engl.* 2006 Nov 18;368(9549):1771–81.
34. Harris, Gardiner. F.D.A. Rejects Merck's New Pain Medication. *The New York Times* [Internet]. 2007 Apr; Available from: <https://www.nytimes.com/2007/04/13/us/13vioxx.html>
35. Wastesson JW, Martikainen JE, Zoëga H, Schmidt M, Karlstad Ø, Pottegård A. Trends in Use of Paracetamol in the Nordic Countries. *Basic Clin Pharmacol Toxicol.* 2018 Sep;123(3):301–7.
36. Komen J, Forslund T, Hjemdahl P, Andersen M, Wettermark B. Effects of policy interventions on the introduction of novel oral anticoagulants in Stockholm: an interrupted time series analysis: NOAC introduction in Stockholm region. *Br J Clin Pharmacol.* 2017 Mar;83(3):642–52.
37. Danish Medicines Agency. Afgørelse om fremtidig tilskudsstatus for NSAID'er og lægemidler mod svage smerter (Decision regarding reimbursement status for NSAIDs and weak analgetics) [Internet]. Danish Medicines Agency; 2015. Available from: <https://laegemiddelstyrelsen.dk/da/nyheder/2015/~~/media/783466AECDF44173B2541D25C9966EEA.ashx>
38. Arcoxia ingår i högkostnadsskyddet med begränsning (Arcoxia is included for high-cost reimbursement with limitations) [Internet]. The Dental and Pharmaceutical Benefits Agency, Sweden; 2010. Available from: <https://www.tlv.se/download/18.467926b615d084471ac33454/1510316385284/bes101026-arcoxia.pdf>
39. The Norwegian Medicines Agency. Refusjonsrapport Etoricoksib (Arcoxia) til behandling av artrose, revmatoid artritt og ankyloserende spondylitt (Bekhterevs sykdom). Vurdering av søknad om forhåndsgodkjent refusjon §2 [Internet]. The Norwegian Medicines Agency; 2012. Available from: https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/A/Arcoxia_Artrose%2C%20RA%2C%20Bekhterev_2012.pdf
40. The Norwegian Medicines Agency. Bekymring for økt bruk av etorikoksib (Arcoxia) (Concerns regarding increasing use of etoricoxib (Arcoxia)) [Internet]. The Norwegian Medicines Agency; 2014. Available from: <https://legemiddelverket.no/nyheter/bekymring-for-okt-bruk-av-etorikoksib-arcoxia>
41. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *The Lancet.* 2003 Oct;362(9391):1225–30.
42. Eriksen J, Gustafsson LL, Ateva K, Bastholm-Rahmner P, Ovesjö M-L, Jirlow M, et al. High adherence to the 'Wise List' treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines. *BMJ Open.* 2017 Apr;7(4):e014345.
43. Lanza FL, Chan FKL, Quigley EMM. Guidelines for Prevention of NSAID-Related Ulcer Complications. *Am J Gastroenterol.* 2009 Mar;104(3):728–38.

Tables

Table 1. Regulation of OTC Sales of NSAIDs

	Marketed OTC drugs	Period of OTC availability	Changes in regulations
Denmark	Diclofenac 12.5 mg Ibuprofen 200 mg	July 2007 – Dec 2008 March 1989 – present	March 2011: NSAID sales restricted to persons aged \geq 18 years October 2012: Sales of NSAIDs allowed from outlets other than pharmacies September 2013: Each sale of ibuprofen restricted to 4,000 mg
Finland	Dexibuprofen 300 mg Ibuprofen 400 mg Ketoprofen 25 mg Ketoprofen 50 mg Naproxen 250 mg	1998 – 2008 1989 – present 1992 – present 1992 – 1995 December 2015 – present	1995: Each sale of ketoprofen decreased to 375 mg (from 750 mg) 2008: Each sale of ibuprofen increased to 12,000 mg (from 4,000 mg)
Iceland	Diclofenac 12.5 mg Ibuprofen 200 mg Ibuprofen 400 mg Naproxen 250 mg	NA ¹ – April 2014 NA ¹ – present NA ¹ – present 1991 – present	2011: Each sale of diclofenac increased to 500 mg (from 250 mg) November 2012: Each sale of ibuprofen increased to 20,000 mg (from 12,000 mg)
Norway	Diclofenac 12.5 mg Diclofenac 25 mg Ibuprofen 200 mg Ibuprofen 400 mg Naproxen 250 mg	2001 – present 2012 – present 1989 – present 2004 – present 1997 – present	2003: Sales of NSAIDs allowed from outlets other than pharmacies to persons aged \geq 18 years 2014: Each sale of diclofenac restricted to 250 mg
Sweden	Diclofenac 12.5 mg Diclofenac 25 mg Diclofenac 50 mg Ibuprofen 100 mg Ibuprofen 200 mg Ibuprofen 400 mg Naproxen 250 mg	2005 – present 2004 – present 2004 – present 2015 – present 1982 – present 1982 – present 1991 – present	2009: Sales of NSAIDs (excluding diclofenac) allowed from outlets other than pharmacies to persons aged \geq 18 years

OTC = over-the-counter; NSAIDs = nonsteroidal antiinflammatory drugs.

¹OTC market entry occurred before 2003, but the exact dates were not available from the national medicine agencies.

Table 2. Total Sales and Proportion of Total Sales in 2000, 2005, and 2015 for NSAIDs That Accounted for At Least 90% of Total Sales

	Total Sales in 2000 ^a	Proportion of Total Sales (%)		Total Sales in 2005 ^a	Proportion of Total Sales (%)		Total Sales in 2015 ^a	Proportion of Total Sales (%)
Denmark								
Ibuprofen	14.9	47.6	Ibuprofen	20.0	52.9	Ibuprofen	25.6	77.3
Diclofenac	6.6	21.1	Diclofenac	8.1	21.4	Diclofenac	2.9	8.8
Naproxen	2.3	7.3	Etodolac	3.8	10.1	Naproxen	2.2	6.6
Etodolac	1.4	4.5	Naproxen	1.7	4.5			
Rofecoxib	1.3	4.2	Ketoprofen	0.6	1.6			
Piroxicam	1.0	3.2						
Ketoprofen	0.8	2.6						
Finland								
Ibuprofen	28.0	47.1	Ibuprofen	41.7	58.1	Ibuprofen	49.8	68.5
Naproxen	7.1	11.9	Naproxen	6.3	8.8	Naproxen	7.7	10.6
Nimesulide	6.2	10.5	Diclofenac	5.9	8.2	Etoricoxib	6.5	8.9
Ketoprofen	6.1	10.3	Meloxicam	3.9	5.4	Diclofenac	4.4	6.0
Diclofenac	5.4	9.1	Ketoprofen	3.8	5.3			
Tolfenamic acid	1.3	2.1	Etoricoxib	3.1	4.3			
Iceland								
	NA	NA	Ibuprofen	34.7	51.4	Ibuprofen	41.7	55.6
			Diclofenac	20.2	30.0	Diclofenac	13.7	18.3
			Naproxen	6.6	9.7	Naproxen	8.9	11.9
						Celecoxib	6.4	8.6
Norway								
Ibuprofen	8.7	25.8	Ibuprofen	14.1	34.8	Ibuprofen	17.1	39.2
Diclofenac	7.0	20.9	Diclofenac	8.8	21.8	Naproxen	10.9	25.0
Naproxen	6.7	19.9	Naproxen	4.6	11.4	Diclofenac	8.9	20.4
Piroxicam	5.0	14.9	Piroxicam	4.5	11.2	Etoricoxib	3.3	7.5
Ketoprofen	1.7	5.0	Celecoxib	2.2	5.4			
Celecoxib	1.1	3.3	Meloxicam	1.8	4.4			
Nabumetone	0.9	2.6	Etoricoxib	1.4	3.5			
Sweden								
Ibuprofen	10.7	28.9	Ibuprofen	17.8	39.8	Ibuprofen	24.7	47.8
Diclofenac	9.3	25.4	Diclofenac	11.4	25.5	Naproxen	11.9	23.1
Naproxen	8.9	24.2	Naproxen	7.3	16.4	Diclofenac	8.4	16.2
Ketoprofen	3.2	8.8	Ketoprofen	3.4	7.5	Ketoprofen	2.8	5.4
Celecoxib	1.9	5.1	Celecoxib	1.3	2.8			

NSAIDs = nonsteroidal antiinflammatory drugs; NA = no data available.

^aTotal sales are expressed as defined daily doses sold/1000 inhabitants/day.

For each country, NSAIDs appear in descending order by proportion of their total sales each year.

Figure legends

Figure 1. Timeline of important regulatory actions regarding diclofenac and cyclooxygenase (COX)-2 inhibitors (coxibs) in the Nordic countries. EMA = European Medicines Agency; OTC = over the counter; ESC = European Society of Cardiology.

Figure 2. Yearly total sales of nonsteroidal antiinflammatory drugs (NSAIDs) in the Nordic countries from 2000–2016. DDDs = defined daily doses.

Figure 3. Use of nonsteroidal antiinflammatory drugs by prescription in the Nordic countries from 2000–2016.

Figure 4. Use of diclofenac by prescription in the Nordic countries from 2000–2016 according to age.







