PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLE

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

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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 the 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 (DDDs)/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 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 the use of diclofenac and etoricoxib, the persistent high use of diclofenac in Iceland, Norway, and Sweden, the persistent over-the-counter

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availability of diclofenac in Norway and Sweden, and the increasing use of etoricoxib in most of the Nordic countries pose a cardiovascular health concern.

KEY WORDS NSAID, drug utilization, cardiac risk factors and prevention, Nordic countries.
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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 with 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 (1200 mg/day or less) or naproxen (500 mg/day or less) was 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 was recently 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 the 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 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 an individual level, all dispensed drugs by prescription at community pharmacies. Prescription registry data were available from 2000–2016 for Denmark[16] 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] Figure 1 shows 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.

The variety of NSAIDs available for OTC purchase differed among 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. The 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 of 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 yrs and older). A patient filling a prescription for more than one NSAID

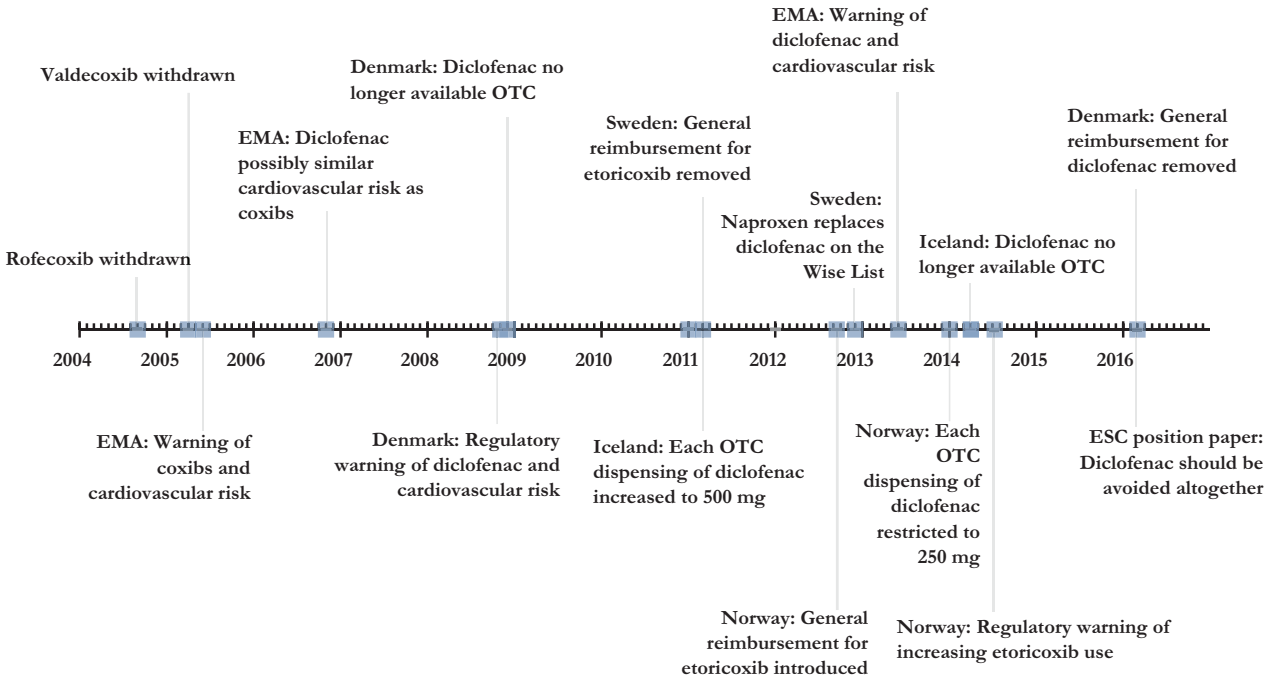

Figure 1. Timeline of important regulatory actions regarding diclofenac and cyclooxygenase (COX)-2 inhibitors (coxibs) in the Nordic countries. EMA = European Medicines Agency; ESC = European Society of Cardiology; OTC = over the counter.

Table 1. Regulation of OTC Sales of NSAIDs

	Marketed OTC drugs	Period of OTC availability	Changes in regulations
Denmark	Diclofenac 12.5 mg	July 2007–December 2008	March 2011: NSAID sales restricted to persons aged ≥ 18 yrs
	Ibuprofen 200 mg	March 1989–present	October 2012: Sales of NSAIDs allowed from outlets other than pharmacies
			September 2013: Each sale of ibuprofen restricted to 4000 mg
Finland	Dexibuprofen 300 mg	1998–2008	1995: Each sale of ketoprofen decreased to 375 mg
	Ibuprofen 400 mg	1989–present	(from 750 mg)
	Ketoprofen 25 mg	1992–present	2008: Each sale of ibuprofen increased to 12,000 mg
	Ketoprofen 50 mg	1992–1995	(from 4000 mg)
	Naproxen 250 mg	December 2015–present	
Iceland	Diclofenac 12.5 mg	NA[a]–April 2014	2011: Each sale of diclofenac increased to
	Ibuprofen 200 mg	NA[a]–present	500 mg (from 250 mg)
	Ibuprofen 400 mg	NA[a]–present	November 2012: Each sale of ibuprofen increased to
	Naproxen 250 mg	1991–present	20,000 mg (from 12,000 mg)
Norway	Diclofenac 12.5 mg	2001–present	2003: Sales of NSAIDs allowed from outlets other than
	Diclofenac 25 mg	2012–present	pharmacies to persons aged ≥ 18 yrs
	Ibuprofen 200 mg	1989–present	2014: Each sale of diclofenac restricted to 250 mg
	Ibuprofen 400 mg	2004–present	
	Naproxen 250 mg	1997–present	
Sweden	Diclofenac 12.5 mg	2005–present	2009: Sales of NSAIDs (excluding diclofenac) allowed from
	Diclofenac 25 mg	2004–present	outlets other than pharmacies to persons aged ≥ 18 yrs
	Diclofenac 50 mg	2004–present	
	Ibuprofen 100 mg	2015–present	
	Ibuprofen 200 mg	1982–present	
	Ibuprofen 400 mg	1982–present	
	Naproxen 250 mg	1991–present	

NA = no data available; NSAIDs = nonsteroidal antiinflammatory drugs; OTC = over the counter.
[a]The OTC market entry occurred before 2003, but the exact dates were not available from the national medicine agencies.

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 because 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). Because 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, because 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, 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, six to seven agents accounted for at least 90% of total NSAID sales; this number declined to three to four 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

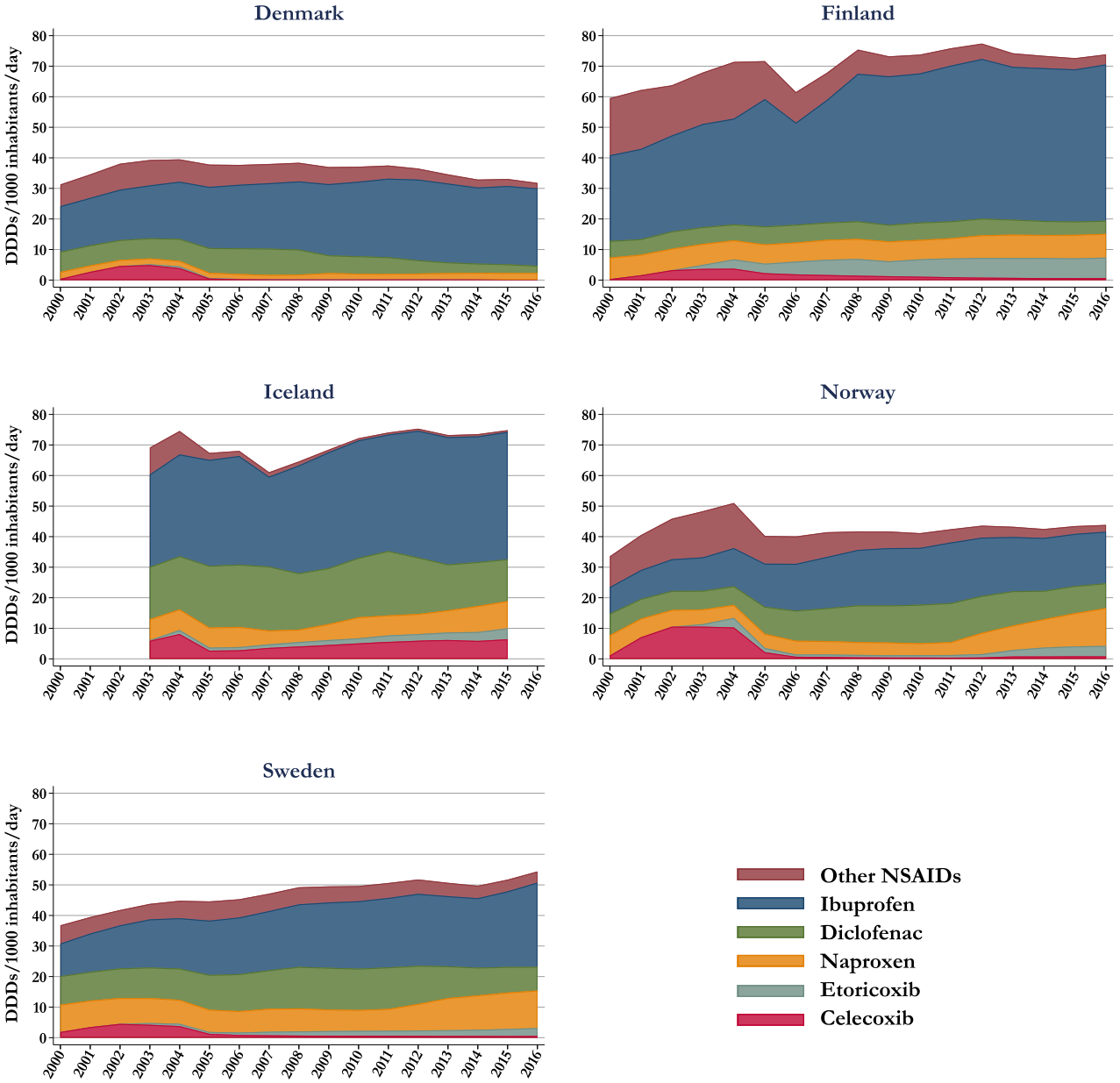

Figure 2. Yearly total sales of nonsteroidal antiinflammatory drugs (NSAIDs) in the Nordic countries from 2000–2016. DDDs = defined daily doses.

Finland, remained stable at ~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) (Table S3). Prescription use of NSAIDs was most prevalent in patients aged 40–59, 60–69, and 70–79 years (Figure S1).

Ibuprofen

Ibuprofen was the most commonly sold NSAID in all countries throughout the study period (Figure 2, Table S2). The 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 (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 the prescription use of ibuprofen in 2016 was 142 users/1000

Table 2. Total Sales and Proportion of Total Sales[a]

	Total sales in 2000[b]	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			

NA = no data available; NSAIDs = nonsteroidal antiinflammatory drugs.
[a]In 2000, 2005, and 2015 for NSAIDs that accounted for at least 90% of total sales.
[b]Total 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.

inhabitants in Finland and 118 users/1000 inhabitants in Denmark (Figure 3, Table S3). Prescription use of ibuprofen was rather constant in Norway and Sweden, with a prevalence of ~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, Table S2).

In Sweden, naproxen was the most commonly prescribed NSAID in 2016, with a prevalence of 44 users/1000 inhabitants (Figure 3, 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, 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%

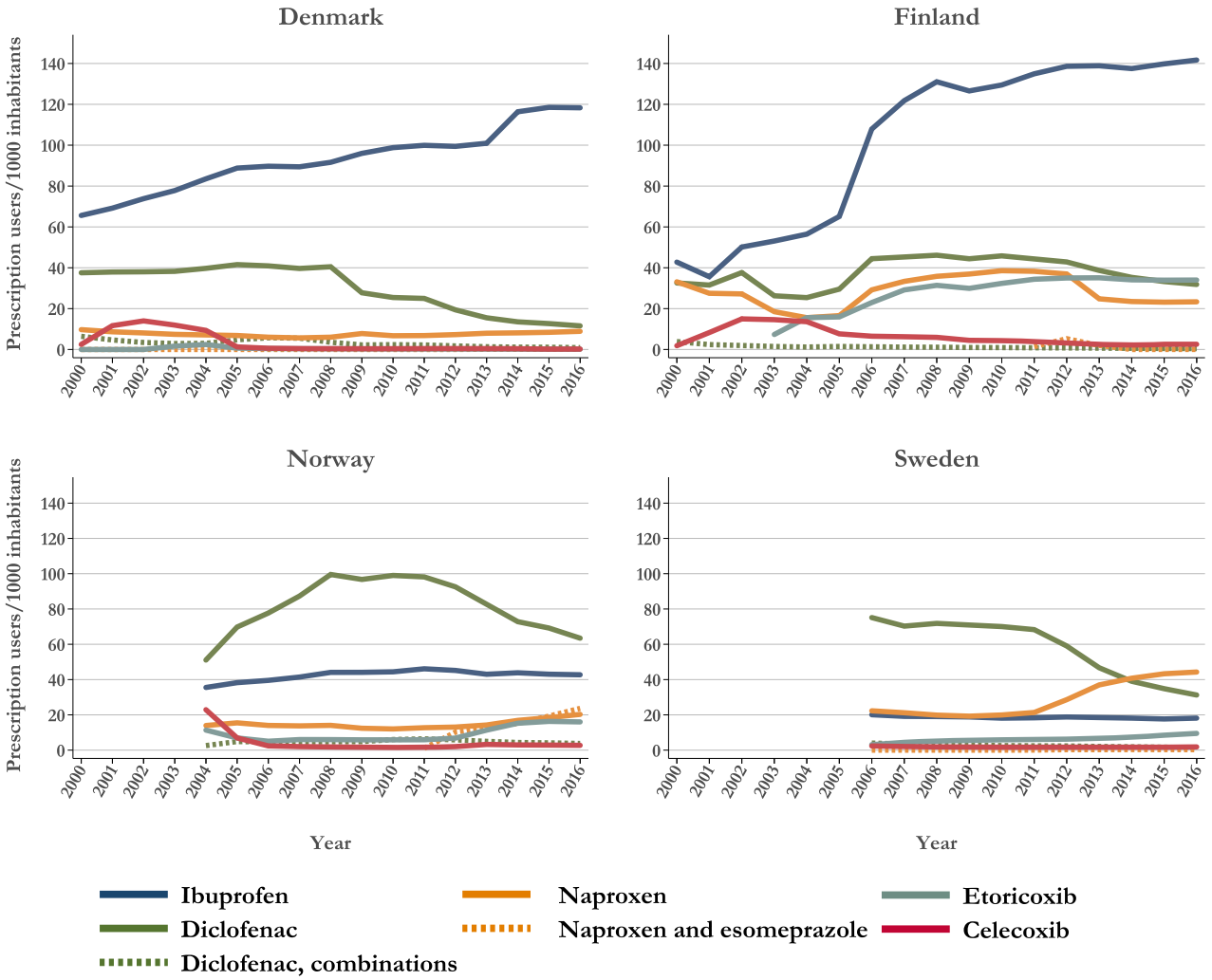

Figure 3. Use of nonsteroidal antiinflammatory drugs by prescription in the Nordic countries from 2000–2016.

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, 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, Table S2). In 2005–2006, sales declined sharply. The use of celecoxib remained limited after 2006 (less than 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

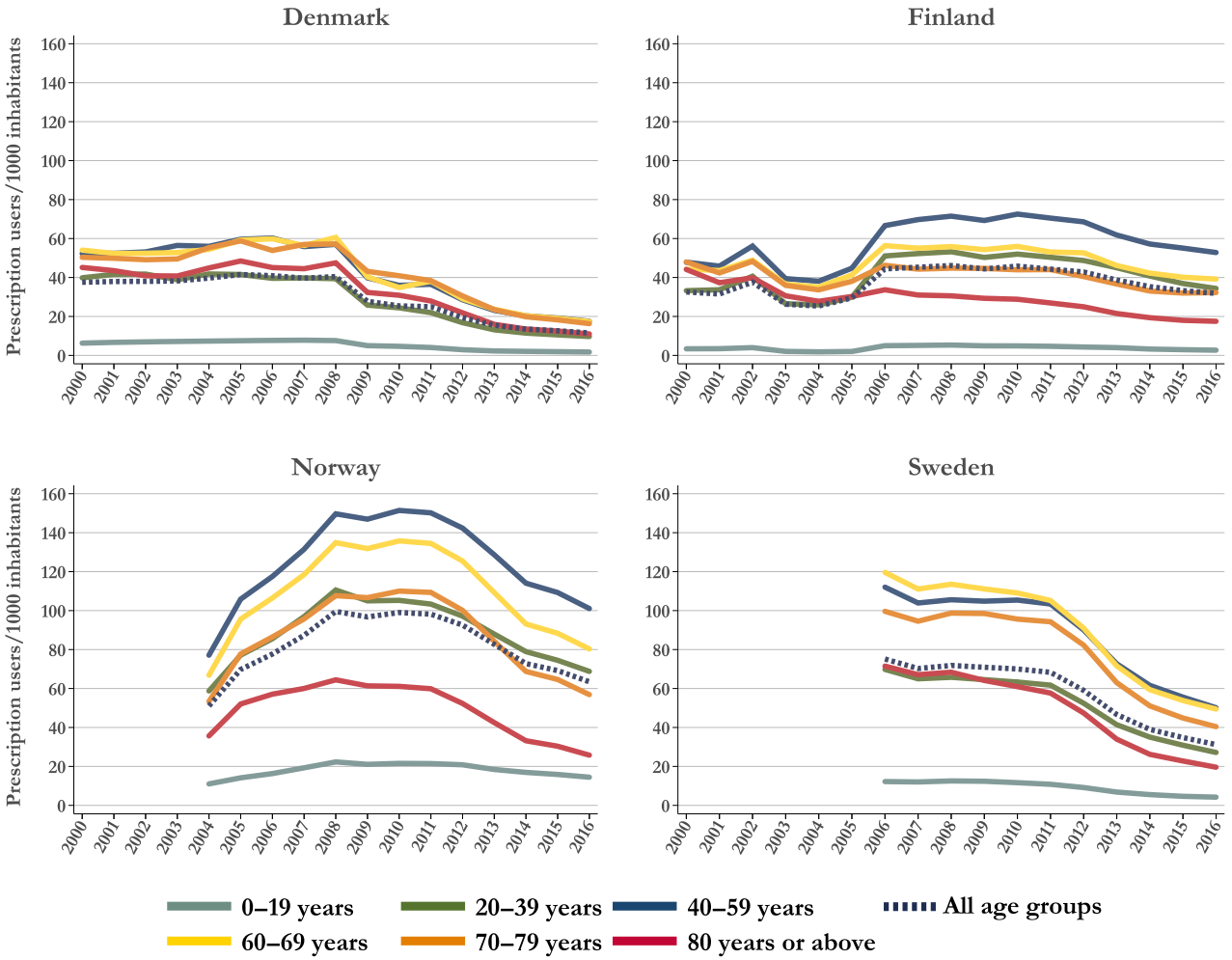

Figure 4. Use of diclofenac by prescription in the Nordic countries from 2000–2016 according to age.

to 6.7 DDD/1000 inhabitants/day in 2016 (Figure 2, 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 because 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 2008–2009. In 2008, a Danish observational study reported a hazard ratio (HR) 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 OTC[26] 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 the Stockholm County Council,[28] 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) program was published in 2006.[33] The MEDAL program showed that etoricoxib was comparable with diclofenac with regard to cardiovascular safety (HR for thrombotic cardiovascular events 0.9, 95% CI 0.7–1.1).[33] The choice of diclofenac as comparator was unfortunate because diclofenac is associated with higher cardiovascular risk than low-dose ibuprofen and naproxen.[3] Indeed, with naproxen as the comparator instead of diclofenac, an HR 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 U.S. market by the 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 were 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 or more) 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 use 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 were 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 would provide 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 a 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 that 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 includes the Wise List that 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 the 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 have 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. PLoS Med 2013;10(2):e1001388.
2. **Castellsague J, Riera-Guardia N, Calingaert B, et al.** Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). Drug Saf 2012;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. Lancet 2013;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. PLoS Med 2011;8(9):e1001098.
5. **Bally M, Dendukuri N, Rich B, et al.** Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909.
6. **Baron JA, Sandler RS, Bresalier RS, et al.** Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. Lancet 2008;372(9651):1756–64.
7. **Food and Drug Administration.** Public Health Advisory: FDA Announces Series of Changes to the Class of Marketed Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), 2005. Available from http://wayback.archive-it.org/7993/20170113092344/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108427.htm. Accessed November 30, 2018.
8. **European Medicines Agency.** Public CHMP assessment report for medicinal products containing non-selective non-steroidal antiinflammatory drugs (NSAIDs). 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. Accessed November 30, 2018.
9. **European Medicines Agency.** Assessment report for diclofenac containing medicinal products (systemic formulations). European Medicines Agency, 2013. Available from https://www.ema.europa.eu/documents/referral/diclofenac-article-31-referral-prac-assessment-report_en.pdf. Accessed November 30, 2018.
10. **European Medicines Agency.** New safety advice for diclofenac —CMDh endorses PRAC recommendation. European Medicines Agency, 2013. Available from https://www.ema.europa.eu/documents/press-release/new-safety-advice-diclofenac-cmdh-endorses-prac-recommendation_en.pdf. Accessed November 30, 2018.
11. **Schmidt M, Lamberts M, Olsen A-MS, 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;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;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 Novembera Scotia (Canada). Br J Clin Pharmacol 2009;68(1):106–15.
15. Haagensen KM, Agerskov U, eds. Nordic Statistics 2017. Copenhagen: Nordic Council of Ministers, 2017. Available from https://doi.org/10.6027/anp2017-748. Accessed November 30, 2018.
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;46(3):798–f.
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;106(2):86–94.
18. **Furu K.** Drug utilisation in a public health perspective: establishing a national prescription register in Norway. Nor Epidemiol 2009;11(1):55–60. Available from http://www.ntnu.no/ojs/index.php/norepid/article/view/534 Accessed November 30, 2018.
19. **Wettermark B, Hammar N, MichaelFored C, et al.** The new Swedish Prescribed Drug Register—opportunities for

pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16 (7):726–35.
20. **Paakkari P, Voipio T, Saastamoinen L, Martikainen J.** Medicines in 2016. In: Finnish Statistics on Medicines 2006. Helsinki, Finland: Finnish National Agency for Medicines and Finnish Social Insurance Institution, 2007:21–8.
21. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. ATC/DDD Index. Available from https://www.whocc.no. Accessed November 30, 2018.
22. **Bergman U, Popa C, Tomson Y, et al.** Drug utilization 90%—a simple method for assessing the quality of drug prescribing. Eur J Clin Pharmacol 1998;54(2):113–8.
23. Classification of drugs (ATC) and defined daily doses (DDD) 2018. Helsinki, Finland: Finnish Medicines Agency, 2018. Available from http://www.julkari.fi/bitstream/handle/10024/136204/ATC-kirja2018_netti.pdf?sequence=1&isAllowed=y. Accessed November 30, 2018.
24. **Fosbøl E, Gislason G, Jacobsen S, 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;85 (2):190–7.
25. **Andersen MG, Vasconcellos BZ.** Farlig medicin fjernes fra håndkøb (Dangerous drug no longer available over-the-counter). Politiken. Available from https://politiken.dk/indland/art5705346/Farlig-medicin-fjernes-fra-håndkøb. Accessed December 6, 2008.
26. **Danish Medicines Agency.** Redegørelse vedrørende den kardiovaskulære risiko ved brug af non-selektive NSAID præparater (Briefing regarding cardiovascular risks of NSAIDs). Danish Health and Medicines Agency, 2008. Available from http://www.ft.dk/samling/20081/almdel/suu/bilag/265/645749.pdf. Accessed November 30, 2018.
27. **Danish Medicines Agency.** New information about cardiovascular adverse reactions from the use of NSAID. Danish Medicines Agency, 2008. Available from http://www.sst.dk. Accessed November 30, 2018.
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), 2011. Available from https://janusinfo.se/nyheter/nyheter/2011/viktigaforandringarikl okalistannastaar.5.467926b615d084471acec57.html. Accessed November 30, 2018.
29. **Finnish Medicines Agency.** Terveydenhuollon 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). Finnish Medicines Agency, 2013. Available from http://www.fimea.fi/documents/160140/765540/23610_Systeemisesti_vaikuttavien_diklofenaakkivalmisteiden_DHPC_2013-07-10.pdf. Accessed November 30, 2018.
30. **Icelandic Medicines Agency.** Nýjar leiðbeiningar varðandi notkun lyfja sem innihalda díklófenak (New instructions for the use of diclofenac containing drugs). Icelandic Medicines Agency, 2013. Available from https://www.lyfjastofnun.is/utgefid-efni/frettir/nr/2643. Accessed November 30, 2018.
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). 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/. Accessed November 30, 2018.
32. **The Norwegian Medicines Agency.** Nye anbefalinger for diklofenak (New recommendations for use of diclofenac). The Norwegian Medicines Agency, 2013. Available from https://legemiddelverket.no/nyheter/nye-anbefalinger-for-diklofenak. Accessed November 30, 2018.
33. **Cannon CP, Curtis SP, FitzGerald GA, 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 2006;368 (9549):1771–81.
34. **Harris G.** F.D.A. Rejects Merck's New Pain Medication. The New York Times. Available from https://www.nytimes.com/2007/04/13/us/13vioxx.html. Accessed November 30, 2018.
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;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;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). Danish Medicines Agency, 2015. Available from https://laegemiddelstyrelsen.dk/da/nyheder/2015/~/media/783466AECDF44173B2541D25C9966EEA.ashx. Accessed November 30, 2018.
38. Arcoxia ingår i högkostnadsskyddet med begränsning (Arcoxia is included for high-cost reimbursement with limitations). The Dental and Pharmaceutical Benefits Agency, Sweden, 2010. Available from https://www.tlv.se/download/18.467926b615d084471ac33454/1510316385284/bes101026-arcoxia.pdf. Accessed November 30, 2018.
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. 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. Accessed November 30, 2018.
40. **The Norwegian Medicines Agency.** Bekymring for økt bruk av etorikoksib (Arcoxia) (Concerns regarding increasing use of etoricoxib [Arcoxia]). The Norwegian Medicines Agency, 2014. Available from https://legemiddelverket.no/nyheter/bekymring-for-okt-bruk-av-etorikoksib-arcoxia. Accessed November 30, 2018.
41. **Grol R, Grimshaw J.** From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362(9391):1225–30.
42. **Eriksen J, Gustafsson LL, Ateva K, 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;7(4): e014345.
43. **Lanza FL, Chan FKL, Quigley EMM.** Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009;104(3):728–38.

Supporting Information

The following supporting information is available in the online version of this paper:

Figure S1. Use of NSAIDs by prescription in the Nordic countries 2000–2016 according to age.

Table S1. Wholesale and prescription registries in the Nordic countries.

Table S2. Yearly total sales of NSAIDs (DDDs/1000 inhabitants/day) in the Nordic countries 2000–2016.

Table S3. Yearly prevalence of NSAID use by prescription in the Nordic countries 2000–2016.

Table S4. Yearly total over the counter (OTC) sales of NSAIDs (DDDs/1000 inhabitants/day) in the Nordic countries 2000–2016.