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ORIGINAL ARTICLE
Prevention and epidemiology

Prescriber responsibility, predictors for initiation, and 20-year trends in use of non-aspirin non-steroidal anti-inflammatory drugs in patients with cardiovascular contraindications: a nationwide cohort study

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Aims To examine whether prescription patterns complied with recommendations not to use non-steroidal anti-inflammatory drugs (NSAIDs) in patients with cardiovascular contraindications. Moreover, we examined predictors for initiation and prescriber responsibility.

Methods and results We used Danish medical databases to identify all patients with first-time cardiovascular disease during 1996–2017 (n = 628 834). We assessed standardized prevalence proportions, predictors from logistic regression, and prescriber identifiers. One-year prevalence of NSAID initiation increased 3.4% from 1996 (19.4%) to 2001 (22.7%) and declined by 2.7% thereafter until 2017 (13.5%). Trends were independent of age, sex, and disease subtype, although larger annual declines occurred for heart failure (3.9%) and ischaemic heart disease (3.5%) since 2002. One-year prevalence remained highest among patients with venous thromboembolism (16.6%) and angina (13.8%), and lowest for ST-segment elevation myocardial infarction (7.0%) and heart failure (8.8%). Initiators were predominantly prescribed ibuprofen (59%), diclofenac (23%), and etodolac (6%). Diclofenac and coxib use declined, while ibuprofen and naproxen use increased. Median prescribed pill dose of ibuprofen declined after 2008 from moderate/high (600 mg) to low (400 mg). Treatment duration declined for all NSAIDs, except celecoxib. Rheumatic, obesity, and pain-related conditions predicted NSAID initiation. General practitioners issued 86–91% of all NSAID prescriptions, followed by hospital prescribers (7.3–12%).

Conclusions Initiation of NSAIDs in patients with cardiovascular disease declined since 2002. Shorter treatment duration, declining COX-2 inhibition, and increasing use of naproxen and low-dose ibuprofen suggest adherence to guidelines when NSAIDs cannot be avoided. Still, NSAID use remained prevalent despite cardiovascular contraindications, warranting awareness of appropriateness of use among general practitioners in particular.

Keywords Cardiovascular diseases • Epidemiology • NSAIDs • Trends

Introduction

Non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs worldwide for the treatment of pain, fever, and inflammation. All NSAIDs increase the risk of elevated blood pressure and congestive heart failure.[1] The risk of thromboembolic events varies with the type of drug but has been shown increased for several newer COX-2 inhibitors (coxibs), older

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COX-2 inhibitors (in particular diclofenac), and non-selective NSAID (in particular high-dose ibuprofen).[1]

Following several risk assessments by the Food and Drug Administration (FDA)[2,3] and the European Medicines Agency (EMA),[4–7] international risk minimization measures have been implemented including box warning labelling on the potential cardiovascular risks and general recommendations to avoid use of NSAIDs in patients with cardiovascular disease. These recommendations also reflect the position from the European Society of Cardiology.[1]

While general population trends show declining use of diclofenac and coxibs in Denmark, their use is persistently high in other Nordic countries such as Norway, Iceland, and Sweden.[8] These trends highlight a varying impact of international recommendations between countries, and likely also patient groups. Patients with existing cardiovascular disease are of key importance because NSAID use in this group is both common (due to age-related musculoskeletal comorbidity) and associated with higher absolute thromboembolic risk increase (due to higher baseline risk). Recent data indicate a persistent high prevalence of diclofenac use in patients with cardiovascular disease.[9] It remains unknown to what extent guidelines and regulatory actions have influenced use of NSAIDs in different cardiovascular subgroups.

We therefore studied temporal trends in NSAID use after first-time diagnosed cardiovascular diseases, and identified predictors for initiation as well as prescriber responsibility.

Methods

Setting

The Danish National Health Service (NHS) provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including NSAIDs.[10] Accurate linkage of all registries at the individual level is possible in Denmark using the unique Central Personal Register number assigned to each Danish citizen at birth and to residents upon immigration.[11]

Over-the-counter (OTC) use of NSAIDs in Denmark is far less common than in many other countries.[12] Thus, all NSAIDs are available by prescription only, except for low-dose ibuprofen (200 mg pills) and diclofenac (between 16 July 2007 and 14 December 2008).[12]Over-the-counter sales of ibuprofen have moreover been restricted to age groups ≥18 years and one package per person per day since 2011, and pack sizes containing a maximum of 20 tablets since 2013.[12] Finally, regular users of NSAIDs that are available OTC have an economic incentive to obtain the drugs by prescription to receive reimbursement.[10] The potential for identifying NSAID use from Danish prescription registries is therefore high with proportions of total sales captured of 66–70% during 2000–2013, increasing to 85% in 2018, for ibuprofen and virtually complete capture for all other non-aspirin NSAIDs.[12]

Data sources

We used the Danish National Patient Registry to identify the study cohorts, non-fatal outcomes, and comorbidities.[13] We used the Danish National Prescription Registry to identify all prescription fillings since 1995.[14] We obtained information on all-cause mortality and migration status from the Danish Civil Registration System.[11]

Cardiovascular disease cohorts

The study cohorts were identified from the Patient Registry between 1 January 1996 and 31 December 2017, with follow-up data through 2018. Applying validated algorithms,[13,15] we used inpatient diagnoses to identify stable angina pectoris, myocardial infarction [MI, including ST-segment elevation (STEMI) and non(N)STEMI], and ischaemic stroke; and in- and outpatient diagnoses to identify atrial fibrillation/flutter, heart failure, venous thromboembolism, valvular heart disease, and infective endocarditis. Both primary and secondary diagnoses were used.[15] For infective endocarditis, we further restricted to patients with admission length ≥2 weeks.[16]

Each of the cohorts was sampled separately (i.e. a patient may be included in more than one cohort). We restricted to first-time (incident) cardiovascular disease cohorts by excluding patients with inpatient or outpatient diagnoses of the index disease prior to our study period (i.e. from 1977 through 1995). Follow-up started at the date of the first-time diagnosis (index date).

Non-steroidal anti-inflammatory drug use

Information on usage of NSAID in the study period was obtained by identifying all filled prescriptions for NSAIDs (excluding glucosamine). The most frequently used individual NSAIDs were examined according to COX-selectivity as non-selective NSAIDs (ibuprofen and naproxen), older COX-2 inhibitors (diclofenac, meloxicam, and etodolac), and coxibs (celecoxib, etoricoxib, and rofecoxib).

Statistical analyses

First, we examined NSAID use after first-time cardiovascular diagnosis. We computed the 1- and 5-year prevalence of NSAID use. We standardized to the age distribution of the index cohort in 2000. We stratified by sex, age (at diagnosis), MI subtype, comorbidity burden (Charlson Comorbidity Index), and NSAID subtypes. We further described the prescribing characteristics of individual NSAIDs, including the proportion of NSAIDs prescribed, the median prescribed pill strength, 1-year accumulated dose distribution [light <15 daily defined dose (DDD), medium 15–50 DDD, and heavy >50 DDD], and number of prescription redemptions among initiators (within 1 year from initiation).

Second, we characterized NSAID initiators and non-initiators (within 1 year after index date) according to demographics, comorbidity, and comedication use, both overall and according to accumulated dose. Comorbidity was based on the complete inpatient and outpatient medical history available in the Patient Registry (both primary or secondary diagnoses) of the comorbidities listed in *Table 1*.[13] To increase the completeness of diagnoses of diabetes and chronic obstructive pulmonary disease, we also identified any previous dispensing of antidiabetic and respiratory medication.[14] We also used the Prescription Registry to obtain information on comedication use defined by prescription fills within 90 days before enrolment (as chronic medication use is usually prescribed for 3 months at a time).[14]

Third, we determined the degree to which age, calendar period, comorbidities, and comedication use predicted NSAID initiation in patients with cardiovascular disease. As prior NSAID use is likely a strong predictor for future use, we restricted these analyses to patients without NSAID redemptions within 90 days before their cardiovascular diagnosis. We used multivariate logistic regression analysis to identify patient covariates predicting NSAID use within 1 year. The model included all covariates in *Table 1*.

Fourth and last, we assessed the proportion of NSAID prescriptions issued by general practitioners, private practicing specialists, hospital prescribers and other prescribers (e.g. dentists).[17] All registry codes are

Table 1 Mean annual change in 1-year prevalence of NSAID use after first-time cardiovascular disease

	1-year prevalence						5-year prevalence					
	Prevalence (%)			Mean annual change (%)			Prevalence (%)			Mean annual change (%)		
	1996	2002	2017	1996–2001	2002–2017	1996–2017	1996	2002	2013	1996–2001	2002–2013	1996–2013
Overall	19.4	22.7	13.5	3.4%	-2.7%	-1.5%	39.9	44.0	34.4	2.1%	-2.0%	-0.8%
Ischaemic heart disease	17.4	20.9	9.9	4.1%	-3.5%	-2.0%	36.4	40.9	31.7	2.4%	-2.0%	-0.8%
Angina pectoris	22.1	24.7	13.8	2.3%	-2.9%	-1.8%	44.6	47.6	36.6	1.3%	-2.1%	-1.1%
Myocardial infarction	14.8	18.0	8.7	4.3%	-3.5%	-2.0%	33.4	38.0	30.5	2.8%	-1.8%	-0.5%
NSTEMI	18.1	20.3	9.6	2.4%	-3.5%	-2.2%	41.9	41.5	33.0	-0.2%	-1.9%	-1.2%
STEMI	12.7	16.3	7.0	5.6%	-3.8%	-2.1%	27.4	36.6	28.8	6.7%	-1.9%	0.3%
Atrial fibrillation/flutter	18.2	20.4	10.9	2.5%	-3.1%	-1.9%	37.5	39.3	28.8	0.9%	-2.4%	-1.4%
Heart failure	17.3	21.0	8.8	4.2%	-3.9%	-2.4%	32.4	37.6	25.5	3.2%	-2.9%	-1.3%
Venous thromboembolism	20.8	24.1	16.6	3.2%	-2.1%	-1.0%	43.1	46.6	37.9	1.6%	-1.7%	-0.7%
Ischaemic stroke	16.9	20.6	10.4	4.4%	-3.3%	-1.8%	34.6	38.8	29.4	2.5%	-2.2%	-0.9%
Valvular heart disease	18.9	22.5	15.3	3.8%	-2.1%	-0.9%	37.8	43.2	34.9	2.9%	-1.8%	-0.5%
Infective endocarditis	13.8	18.6	11.8	7.0%	-2.5%	-0.7%	30.2	33.6	28.2	2.2%	-1.4%	-0.4%

NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

provided in Supplementary material online, *eTable 1*. All analyses were conducted in STATA software V.16.1 (STATA, College Station, TX, USA).

Results

Trends in overall non-steroidal anti-inflammatory drug use

Overall, the use of NSAIDs in patients with cardiovascular disease showed a slight decline throughout the study period (*Figure 1* and *Table 1*). The overall 1-year prevalence initially increased from 1996 (19.4%) to 2002 (22.7%) after which it declined by an average of 2.9% annually to reach 13.5% in 2017 (mean annual decline 1996–2017 was 1.5%). Although higher, the 5-year prevalence followed a similar trajectory, from 40% in 1996, over 44% in 2002 (average annual increase of 2.1%) to 34% in 2013 (average annual decline of 2.0%). Temporal trends in prevalence of use was not influenced substantially by age-standardization and was independent of sex, age, and comorbidity burden (Supplementary material online, *eFigures 1* and *2*).

Similar patterns in trends for 1- and 5-year prevalence were also observed for all individual cardiovascular diseases (*Figure 2*), including MI subtypes (Supplementary material online, *eFigure 3*). However, although similar relative trends were observed, the absolute changes in NSAID initiation differed substantially according to the underlying cardiovascular disease. The mean annual decrease in 1-year prevalence since 2002 was highest for patients with heart failure (3.9%), ischaemic heart disease overall (3.5%), ischaemic stroke (3.3%), atrial fibrillation/flutter (3.1%), infective endocarditis (2.5%), valvular heart disease (2.1%), and venous thromboembolism (2.1%). Accordingly, contraindicated NSAID initiation within 1 year following diagnosis remained in 2017 highest for patients with venous thromboembolism (16.6%), valvular heart disease (15.3%), and angina pectoris (13.8%) and lowest for STEMI (7.0%) and heart failure (8.8%). Similarly, the 5-year prevalence of NSAID use for patients diagnosed in 2013 remained highest for patients with venous thromboembolism (37.9%), angina pectoris (36.6%), and valvular heart disease (34.9%) and lowest for heart failure (25.5%) and infective endocarditis (28.2%).

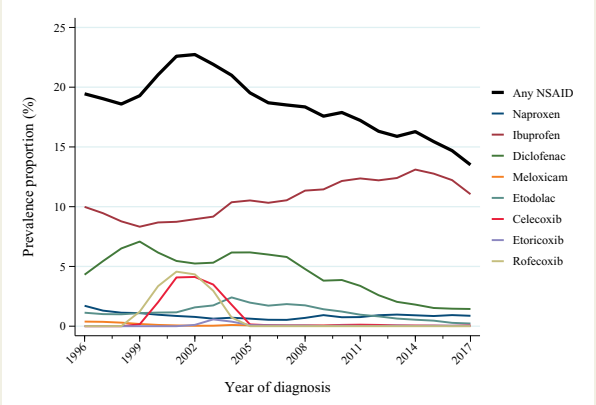

Figure 1 Temporal trends in 1-year prevalence of non-aspirin non-steroidal anti-inflammatory drug use after first-time cardiovascular disease in Denmark (1996–2017).

Trends in individual non-steroidal anti-inflammatory drug use

The majority of NSAID initiators were prescribed ibuprofen (59%), followed by diclofenac (23%) and etodolac (6.3%) (*Table 2*). Correspondingly, the proportion of filled prescriptions was highest for ibuprofen (48%), followed by diclofenac (21%) and etodolac (7.4%). Over time, the use of ibuprofen and naproxen increased alongside a

Figure 2 Temporal trends in 1-year prevalence of non-aspirin non-steroidal anti-inflammatory drug use after first-time diagnosis of individual cardiovascular diseases in Denmark (1996–2017).

decline in the use of diclofenac, meloxicam, etodolac, and a marked drop in use of coxibs (*Figure 1* and Supplementary material online, *eTable 2*).

These trends were generally found to be consistent when assessing individual cardiovascular diseases (*Table 1* and *Figure 2*). As exceptions, the prevalence of ibuprofen initiation 1 year after first-time heart failure diagnosis remained stable with a recent tendency to decline. A similar tendency for declining prevalence in ibuprofen initiation since 2014 was also apparent for the other cardiovascular diseases.

Table 2 Trends in prescribing characteristics of individual NSAIDs after first-time cardiovascular disease in Denmark according to dose and treatment duration

NSAID type	People treated, *n* (%)	Filled prescriptions, *n* (%)	Prescribed pill dose (mg), median (IQR)				Number of prescription redemptions among initiators within 1 year, median (IQR)			
			1996	2002	2017	1996–2017	1996	2002	2017	1996–2017
Any NSAID	116 167 (100)	303 759 (100)	—	—	—	—	5 (2–8)	5 (2–8)	3 (1–5)	4 (2–7)
Naproxen	5541 (4.8)	11 499 (3.8)	500 (250–500)	500 (250–500)	500 (500–500)	500 (250–500)	4 (2–7)	3 (2–7)	3 (1–6)	4 (2–7)
Ibuprofen	68 117 (59)	146 987 (48)	400 (400–600)	600 (400–600)	400 (400–600)	400 (400–600)	4 (2–7)	4 (2–7)	2 (1–5)	3 (2–7)
Diclofenac	27 215 (23)	63 180 (21)	50 (50–75)	50 (50–75)	50 (50–75)	50 (50–75)	4 (2–8)	5 (2–8)	3 (2–6)	4 (2–7)
Meloxicam	542 (0.47)	1395 (0.46)	7.5 (7.5–15)	7.5 (7.5–15)	15 (7.5–15)	7.5 (7.5–15)	5 (2–7)	5 (2–7)	4 (4–9)	5 (3–8)
Etodolac	7335 (6.3)	22 508 (7.4)	300 (200–300)	300 (200–300)	300 (200–300)	300 (200–300)	6 (3–9)	7 (3–10)	5 (2–8)	6 (3–10)
Celecoxib	4887 (4.2)	13 607 (4.5)	—	200 (200–200)	200 (100–200)	200 (200–200)	—	6 (3–8)	6 (3–13)	6 (3–9)
Etoricoxib	488 (0.42)	1041 (0.34)	—	120 (90–120)	120 (120–120)	90 (90–120)	—	6 (2–11)	4 (1.5–10)	5 (2–8)
Rofecoxib	4963 (4.3)	14 985 (4.9)	—	25 (12.5–25)	—	25 (12.5–25)	—	6 (3–9)	—	6 (3–9)

IQR, interquartile range.

Trends in dose and treatment duration

Temporal prescribing characteristics of individual NSAIDs (*Table 2* and Supplementary material online, *eTables 3 and 4*) revealed that the median prescribed pill dose (mg) was stable over time at 500 [interquartile range (IQR) 250–500] for naproxen, 50 (50–75) for diclofenac, 300 (200–300) for etodolac, 200 (200–200) for celecoxib, 90 (90–120) for etoricoxib, and 25 (12.5–25) for rofecoxib. There was a tendency for an increase in the median prescribed pill dose of meloxicam over time [overall median 7.5 (IQR 7.5–15) and in 2017 median 15 (IQR 7.5–15)]. The median prescribed pill dose for ibuprofen increased from 400 mg during 1996–2001 to predominantly 600 mg between 2002 and 2008, but then dropped again to 400 mg during 2009–2017.

Among those initiating NSAIDs, the median number (IQR) of prescription redemptions per patient within 1 year was overall 4 (2–7), which reflected a reduction from 5 (2–8) in 1996 to 3 (1–5) in 2017. The median number of prescription redemptions per patient overall varied according to NSAID type, from 3 for ibuprofen to 6 for etodolac, celecoxib, and rofecoxib. However, the number of consecutive prescriptions per patient declined over time for naproxen (from 4 to 3), ibuprofen (from 4 to 2), diclofenac (from 4 to 3), meloxicam (from 5 to 4), etodolac (from 6 to 5), and etoricoxib (from 6 to 4), but not celecoxib (6) (*Table 2*).

Patient characteristics

Overall, the prevalence of NSAID use increased with age up to 80 years after which it decreased for most NSAIDs except celecoxib and rofecoxib (Supplementary material online, *eTables 2 and 5*). Naproxen, ibuprofen, and diclofenac were used in all age groups, whereas meloxicam, etodolac, and coxibs were rarely prescribed in individuals below 50 years of age. The prevalence of individual comorbidities was generally similar across initiators of individual NSAIDs. However, meloxicam, etodolac, and coxibs were more frequently prescribed to individuals with rheumatic diseases or drug use suggestive of rheumatic disease (glucocorticoids and methotrexate) or pain syndromes (paracetamol and opioids). Coxibs were more often prescribed to individuals prescribed anti-ulcer drugs.

Predictors for non-steroidal anti-inflammatory drug initiation

Whereas use of non-selective NSAIDs was independent of sex, female gender was associated with use of both older and newer COX-2 inhibitors (*Table 3*). Age below 50 years predicted initiation of naproxen, ibuprofen, and diclofenac. There was no strong association between age and meloxicam and etodolac. Older age strongly predicted initiation of coxibs. Calendar periods after 2006 predicted ibuprofen initiation. In contrast, recent calendar periods were increasingly inversely associated with initiation of diclofenac, meloxicam, etodolac, celecoxib, etoricoxib, and rofecoxib.

Comorbidity burden was overall also inversely related to NSAID initiation. Among individual comorbidities, the strongest predictors for NSAID initiation were osteoarthritis [odds ratio = 1.53, 95% confidence interval (CI) 1.49–1.56], rheumatoid arthritis (1.48, 95% CI 1.40–1.56), sleep apnoea (1.37, 95% CI 1.29–1.46), obesity (1.32, 95% CI 1.27–1.37), and chronic obstructive pulmonary disease (1.24, 95% CI 1.22–1.26).

Table 3 Associations between patient characteristics and NSAID initiation within 1 year after first-time cardiovascular disease[a]

	Adjusted odds ratio (95% confidence interval)[b]								
	Overall	Non-selective NSAIDs		Older COX-2 inhibitors			Newer COX-2 inhibitors (coxibs)		
		Naproxen	Ibuprofen	Diclofenac	Meloxicam	Etodolac	Celecoxib	Etoricoxib	Rofecoxib
Sex									
Male	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Female	1.07 (1.05–1.08)	0.92 (0.86–0.99)	1.02 (1.00–1.04)	1.07 (1.04–1.11)	1.42 (1.12–1.81)	1.30 (1.22–1.39)	1.49 (1.37–1.61)	1.30 (1.22–1.39)	1.07 (1.04–1.11)
Age									
<50 years	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
50–59 years	0.89 (0.86–0.91)	0.88 (0.78–0.98)	0.85 (0.82–0.88)	0.91 (0.86–0.96)	1.29 (0.80–2.07)	1.15 (1.01–1.32)	1.23 (1.03–1.47)	1.15 (1.01–1.32)	0.91 (0.86–0.96)
60–69 years	0.73 (0.71–0.75)	0.70 (0.63–0.78)	0.67 (0.65–0.69)	0.80 (0.76–0.84)	0.93 (0.58–1.49)	1.14 (1.01–1.29)	1.26 (1.07–1.49)	1.14 (1.01–1.29)	0.80 (0.76–0.84)
70–79 years	0.61 (0.59–0.62)	0.61 (0.55–0.69)	0.53 (0.51–0.54)	0.65 (0.61–0.68)	1.24 (0.80–1.93)	1.07 (0.95–1.21)	1.50 (1.28–1.77)	1.07 (0.95–1.21)	0.65 (0.61–0.68)
80 years or more	0.47 (0.45–0.48)	0.47 (0.42–0.54)	0.37 (0.36–0.39)	0.52 (0.49–0.55)	1.03 (0.65–1.63)	1.00 (0.88–1.13)	1.39 (1.18–1.64)	1.00 (0.88–1.13)	0.52 (0.49–0.55)
Calendar year									
1996–2000	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
2001–2005	1.07 (1.05–1.10)	0.62 (0.56–0.68)	1.12 (1.09–1.16)	0.87 (0.83–0.90)	0.19 (0.14–0.27)	1.52 (1.40–1.66)	4.69 (4.23–5.21)	1.52 (1.40–1.66)	0.87 (0.83–0.90)
2006–2010	0.85 (0.84–0.88)	0.56 (0.50–0.62)	1.31 (1.27–1.35)	0.69 (0.66–0.72)	0.11 (0.07–0.17)	1.09 (0.99–1.19)	0.11 (0.08–0.15)	1.09 (0.99–1.19)	0.69 (0.66–0.72)
2011–2015	0.73 (0.71–0.75)	0.67 (0.61–0.74)	1.43 (1.39–1.47)	0.30 (0.28–0.31)	0.08 (0.05–0.12)	0.39 (0.35–0.44)	0.11 (0.08–0.14)	0.39 (0.35–0.44)	0.30 (0.28–0.31)
2016–2017	0.61 (0.59–0.63)	0.67 (0.59–0.76)	1.29 (1.24–1.34)	0.18 (0.17–0.20)	0.03 (0.01–0.09)	0.16 (0.13–0.20)	0.07 (0.04–0.11)	0.16 (0.13–0.20)	0.18 (0.17–0.20)
Comorbidities									
Diabetes	1.06 (1.03–1.09)	1.12 (1.00–1.26)	1.06 (1.02–1.09)	1.07 (1.01–1.13)	1.24 (0.82–1.88)	1.15 (1.03–1.28)	1.08 (0.94–1.24)	1.15 (1.03–1.28)	1.07 (1.01–1.13)
Hypertension	1.03 (1.00–1.05)	1.16 (1.06–1.28)	1.04 (1.01–1.07)	1.01 (0.96–1.06)	0.74 (0.50–1.11)	1.04 (0.95–1.14)	0.98 (0.88–1.10)	1.04 (0.95–1.14)	1.01 (0.96–1.06)
Obesity	1.32 (1.27–1.37)	1.14 (0.97–1.34)	1.29 (1.23–1.35)	1.36 (1.26–1.46)	1.14 (0.59–2.20)	1.30 (1.12–1.51)	1.25 (1.02–1.54)	1.30 (1.12–1.51)	1.36 (1.26–1.46)
COPD	1.24 (1.22–1.26)	1.25 (1.16–1.35)	1.22 (1.19–1.24)	1.26 (1.22–1.31)	1.11 (0.85–1.45)	1.26 (1.17–1.35)	1.21 (1.11–1.32)	1.26 (1.17–1.35)	1.26 (1.22–1.31)
Sleep apnoea	1.37 (1.29–1.46)	1.35 (1.05–1.72)	1.37 (1.28–1.46)	1.20 (1.04–1.38)	0.74 (0.10–5.32)	1.14 (0.83–1.55)	1.14 (0.67–1.95)	1.14 (0.83–1.55)	1.20 (1.04–1.38)
Hyperthyroidism	0.97 (0.92–1.02)	0.88 (0.69–1.12)	0.98 (0.92–1.05)	0.99 (0.89–1.09)	0.85 (0.38–1.92)	0.89 (0.72–1.10)	0.95 (0.75–1.20)	0.89 (0.72–1.10)	0.99 (0.89–1.09)
Osteoporosis	0.90 (0.87–0.94)	0.89 (0.75–1.06)	0.93 (0.89–0.97)	0.89 (0.82–0.97)	1.59 (0.97–2.62)	0.97 (0.84–1.12)	0.86 (0.72–1.04)	0.97 (0.84–1.12)	0.89 (0.82–0.97)
Rheumatoid arthritis	1.48 (1.40–1.56)	1.74 (1.41–2.15)	1.28 (1.19–1.37)	1.27 (1.13–1.42)	1.76 (0.93–3.33)	1.47 (1.21–1.78)	1.59 (1.27–1.99)	1.47 (1.21–1.78)	1.27 (1.13–1.42)
SCTD	1.08 (1.03–1.13)	1.18 (0.97–1.43)	1.08 (1.01–1.14)	1.08 (0.98–1.18)	1.12 (0.61–2.05)	0.92 (0.77–1.11)	1.14 (0.93–1.40)	0.92 (0.77–1.11)	1.08 (0.98–1.18)
Osteoarthritis	1.53 (1.49–1.56)	1.33 (1.21–1.46)	1.46 (1.42–1.50)	1.41 (1.36–1.47)	1.85 (1.38–2.48)	1.73 (1.60–1.87)	1.59 (1.44–1.75)	1.73 (1.60–1.87)	1.41 (1.36–1.47)
Comorbidity burden[c]									
None	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Low	0.96 (0.94–0.98)	0.95 (0.87–1.04)	0.97 (0.94–0.99)	0.96 (0.92–1.00)	0.89 (0.65–1.21)	0.94 (0.87–1.02)	1.03 (0.94–1.14)	0.94 (0.87–1.02)	0.96 (0.92–1.00)
Moderate	0.83 (0.80–0.86)	0.81 (0.69–0.96)	0.82 (0.78–0.86)	0.85 (0.79–0.92)	1.02 (0.61–1.72)	0.89 (0.78–1.03)	0.92 (0.78–1.09)	0.89 (0.78–1.03)	0.85 (0.79–0.92)
Severe	0.73 (0.70–0.76)	0.70 (0.58–0.83)	0.78 (0.75–0.82)	0.76 (0.70–0.82)	0.71 (0.36–1.42)	0.62 (0.52–0.74)	0.81 (0.67–0.99)	0.62 (0.52–0.74)	0.76 (0.70–0.82)
Medication use[d]									
Antiplatelet drugs	1.03 (1.01–1.05)	0.96 (0.87–1.05)	1.01 (0.98–1.04)	1.06 (1.01–1.10)	0.95 (0.68–1.32)	1.11 (1.02–1.21)	1.03 (0.94–1.14)	1.11 (1.02–1.21)	1.06 (1.01–1.10)
Anticoagulent drugs	0.77 (0.74–0.80)	0.84 (0.71–0.99)	0.75 (0.71–0.78)	0.77 (0.71–0.84)	0.90 (0.46–1.77)	0.80 (0.68–0.95)	0.97 (0.79–1.18)	0.80 (0.68–0.95)	0.77 (0.71–0.84)

Continued

Table 3 *Continued*

	Adjusted odds ratio (95% confidence interval)[b]								
	Overall	Non-selective NSAIDs		Older COX-2 inhibitors			Newer COX-2 inhibitors (coxibs)		
		Naproxen	Ibuprofen	Diclofenac	Meloxicam	Etodolac	Celecoxib	Etoricoxib	Rofecoxib
Statins	1.08 (1.05–1.11)	1.15 (1.02–1.29)	1.11 (1.08–1.15)	1.06 (1.00–1.12)	0.85 (0.46–1.57)	0.97 (0.86–1.09)	0.85 (0.71–1.01)	0.97 (0.86–1.09)	1.06 (1.00–1.12)
ACE inhibitors	1.01 (0.98–1.03)	1.04 (0.93–1.17)	1.01 (0.98–1.04)	0.98 (0.93–1.04)	1.01 (0.65–1.55)	0.95 (0.85–1.06)	0.93 (0.81–1.07)	0.95 (0.85–1.06)	0.98 (0.93–1.04)
ARBs	1.04 (1.00–1.07)	0.95 (0.81–1.11)	1.01 (0.97–1.06)	1.06 (0.99–1.14)	1.27 (0.70–2.31)	1.06 (0.92–1.22)	1.10 (0.92–1.31)	1.06 (0.92–1.22)	1.06 (0.99–1.14)
Beta-blockers	1.01 (0.99–1.03)	1.03 (0.93–1.14)	0.97 (0.94–1.00)	1.10 (1.05–1.15)	0.94 (0.64–1.38)	1.00 (0.91–1.10)	1.12 (1.00–1.25)	1.00 (0.91–1.10)	1.10 (1.05–1.15)
CCBs	1.01 (0.99–1.04)	0.96 (0.86–1.06)	1.01 (0.98–1.04)	0.96 (0.91–1.01)	1.22 (0.88–1.71)	1.13 (1.03–1.24)	1.04 (0.93–1.17)	1.13 (1.03–1.24)	0.96 (0.91–1.01)
Diuretics	0.99 (0.97–1.01)	1.01 (0.92–1.10)	0.97 (0.94–0.99)	0.97 (0.93–1.01)	0.91 (0.69–1.19)	1.04 (0.96–1.12)	1.06 (0.97–1.16)	1.04 (0.96–1.12)	0.97 (0.93–1.01)
SSRI	1.03 (1.00–1.06)	0.76 (0.64–0.89)	1.04 (1.00–1.08)	1.09 (1.02–1.16)	1.24 (0.79–1.94)	1.09 (0.96–1.23)	1.14 (0.99–1.30)	1.09 (0.96–1.23)	1.09 (1.02–1.16)
Antipsychotic drugs	0.94 (0.90–0.98)	0.84 (0.68–1.03)	0.99 (0.93–1.04)	0.92 (0.85–1.00)	1.12 (0.65–1.93)	0.82 (0.69–0.98)	0.91 (0.76–1.11)	0.82 (0.69–0.98)	0.92 (0.85–1.00)
Anti-ulcer drugs	0.98 (0.96–1.01)	0.99 (0.89–1.10)	0.88 (0.86–0.91)	1.10 (1.05–1.16)	1.28 (0.91–1.81)	1.19 (1.08–1.30)	1.35 (1.21–1.50)	1.19 (1.08–1.30)	1.10 (1.05–1.16)
Gout agents	1.38 (1.30–1.46)	1.84 (1.51–2.25)	1.30 (1.21–1.39)	1.40 (1.26–1.56)	0.83 (0.31–2.23)	1.08 (0.86–1.36)	0.94 (0.70–1.27)	1.08 (0.86–1.36)	1.40 (1.26–1.56)
Systemic glucocorticoids	1.01 (0.97–1.04)	0.98 (0.85–1.13)	0.95 (0.91–0.99)	0.99 (0.93–1.06)	1.49 (1.00–2.23)	1.17 (1.04–1.32)	1.23 (1.07–1.41)	1.17 (1.04–1.32)	0.99 (0.93–1.06)
Methotrexate	1.04 (0.92–1.17)	1.12 (0.71–1.77)	0.95 (0.82–1.11)	1.16 (0.92–1.47)	3.31 (1.21–9.05)	1.32 (0.89–1.96)	1.50 (0.95–2.37)	1.32 (0.89–1.96)	1.16 (0.92–1.47)
Paracetamol	1.11 (1.08–1.14)	1.14 (1.02–1.27)	1.12 (1.08–1.16)	1.01 (0.96–1.06)	0.92 (0.64–1.31)	1.21 (1.10–1.33)	1.29 (1.16–1.44)	1.21 (1.10–1.33)	1.01 (0.96–1.06)
Opiods	1.05 (1.02–1.07)	0.93 (0.83–1.05)	0.93 (0.90–0.97)	1.13 (1.07–1.19)	1.00 (0.69–1.45)	1.12 (1.02–1.24)	1.45 (1.31–1.62)	1.12 (1.02–1.24)	1.13 (1.07–1.19)

ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor antagonists; CCBs, calcium channel blockers; DDD, daily defined dose; Glucocorticoids, systemic glucocorticoids; SCTD, systemic connective tissue disease; SSRI, selective serotonin reuptake inhibitors.

[a]Restriction to those patients without ongoing NSAID treatment at time of their cardiovascular diagnosis.

[b]Adjusted for all the other variables.

[c]Four categories of comorbidity burden were defined based on Charlson Comorbidity Index scores of 0 (none), 1 (low), 2 (moderate), and 3 or more (severe).

[d]Prescription filling within 90 days before index disease.

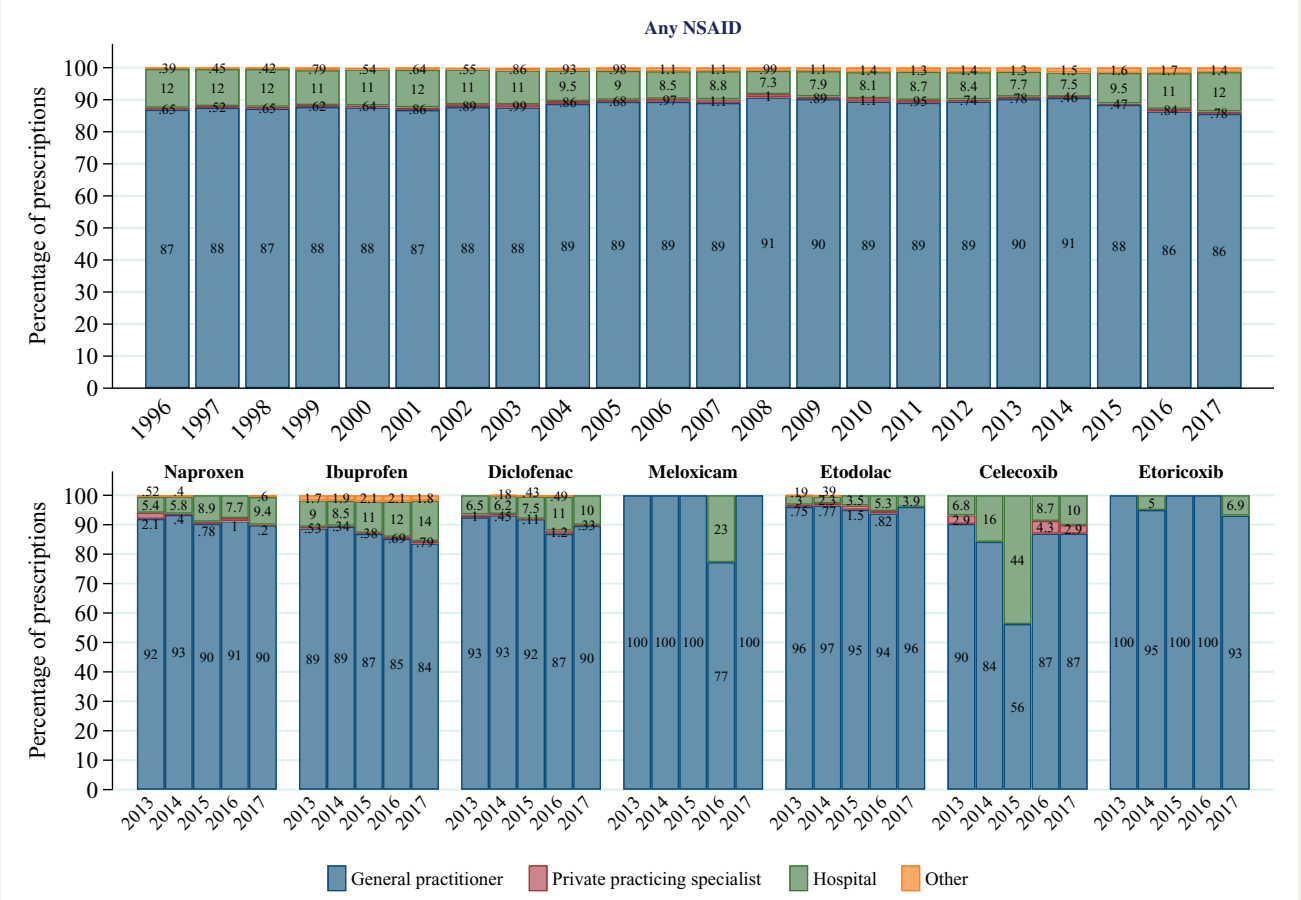

Figure 3 Prescriber responsibility for initiating non-aspirin non-steroidal anti-inflammatory drugs within 1 year after first-time cardiovascular disease (1996–2017).

Among individual drugs, gout agents most strongly predicted overall NSAID initiation (odds ratio = 1.38, 95% CI 1.30–1.46), primarily driven by use of naproxen (1.84, 95% CI 1.51–2.25), ibuprofen (1.30, 95% CI 1.21–1.39), and diclofenac (1.40, 95% CI 1.26–1.56). In contrast, paracetamol, opioids, antiulcer drugs, and systemic glucocorticoids were strongly associated with coxib initiation.

Prescriber responsibility

General practitioners issued 86–91% of the NSAID prescriptions to patients with first-time cardiovascular disease between 1996 and 2017, while hospital prescribers were responsible for 7.3–12% and private practicing specialists ≤1.1% of NSAID prescribing (*Figure 3*). The figures for general practice were driven by ibuprofen (84–89%), naproxen (90–93%), and diclofenac (87–93%), but even higher for meloxicam (77–100%), etodolac (94–97%), and etoricoxib (93–100%). An exception was celecoxib with a lower proportion prescribed in general practice (56–90%) and a higher proportion of hospital prescribers (6.8–44%).

Discussion

The prevalence of NSAID initiation after first-time cardiovascular disease has declined in Denmark by close to 3% annually since 2002. This trend was observed for all major cardiovascular diseases, but strongest for patients with heart failure and ischaemic heart disease. The overall trends, however, reflected large differences in the temporal use of individual NSAIDs. As recommended by clinical guidelines when NSAID use cannot be avoided, treatment duration was shortened, initiation of older and newer COX-2 inhibitors declined, and naproxen and low-dose ibuprofen use increased. Rheumatic, obesity, and pain-related comorbidity predicted NSAID initiation in general, whereas factors associated with gastrointestinal bleeding risk (older age, antiulcer drugs, systemic glucocorticoids, and severe comorbidity burden) predicted use of coxibs specifically. Despite declining overall trends, the prevalence of contraindicated NSAID initiation after newly diagnosed cardiovascular disease remained high, with general practice being the health care sector responsible for the vast majority of all NSAID prescriptions.

Previous literature

Drug utilization studies are fundamental to identify and improve potential irrational drug prescribing habits. Few studies have examined nationwide trends and predictors of NSAID use in patients with cardiovascular disease. The available evidence, as summarized below, all indicate high-prevalent use of NSAID in cardiovascular patients across Europe, USA, and Canada, with a concerning higher proportion of older and newer COX-2 inhibitors used in these countries compared with Denmark.

Following a 2005 FDA warning,[2] initial studies of the rate of potentially inappropriate medication prescriptions in the USA decreased from 46% in 2006–2007 to 41% in 2009–2010,[18] among which the prevalence of NSAID prescriptions showed the largest decline compared with other drug categories.[18] However, subsequent data from the US National Health and Nutrition Examination Survey 2009–2010 on self-reported NSAID use in patients with pre-existing cardiovascular disease showed higher prevalence of NSAID use among patients with vs. without cardiovascular disease (43% vs. 24%), consistent for both prescription (10% vs. 4%) and OTC use (38% vs. 22%). Fifty-four percent of cardiovascular patients reported prescribed NSAID use for 1 year or longer compared with 46% among those without cardiovascular disease.[19] When adjusting for age, sex, race, and education, the odds for NSAID use was overall 2.1-fold increased among individuals with vs. without cardiovascular disease, but with substantial variation within cardiovascular disease subtypes (1.6-fold for ischaemic heart disease and 0.8-fold for congestive heart failure).[19] Another US study showed that prescribed NSAID for musculoskeletal pain management in subsequent years (2010–2013) increased from 14% to 16% in patients with hypertension, heart failure, or chronic kidney disease.[20]

A Canadian cohort study during 2012–2016 of 814 049 elderly patients ≥65 years with a musculoskeletal disorder and hypertension, heart failure, or chronic kidney disease showed an overall declining trend in prescription NSAID use over time, with an absolute reduction of 2.1% from 2012 (10%) to 2016 (8.1%).[21] The prescribing rate decreased relatively by 2.0% per quarter during the period.[21] Almost one-fifth of all prescribed NSAID was coxibs (18%).[21]

An Italian study during 2008–2011 of 511 989 elderly patients ≥65 years with cerebro-cardiovascular disease showed a 21–48% prevalence of NSAID use across five different regions.[22] The prevalence of NSAID use decreased from 31% in 2008 to 23% in 2011 and was highest for nimesulide (9.6%) and diclofenac (7.5%), followed by ketoprofen (5.4%), ibuprofen (5.3%), coxibs (3.8%), ketorolac (2.4), piroxicam (1.9%), aceclofenac (1.3%), meloxicam (0.9%), and naproxen (0.7%). The highest proportion of new NSAID use was nimesulide (22% in 2011), diclofenac (21% in 2011), and coxibs (9% in 2011), which sum COX-2 selective agents to at least 30% of all NSAIDs in 2011.[22]

Most recent, a German study compared diclofenac use before and after implementation of European risk minimization measures in 2013.[9] The study focused on the prevalence of congestive heart failure, ischaemic heart disease, peripheral arterial disease, and cerebrovascular disease among diclofenac initiators and found, similar to our study, that although use of diclofenac declined, the prevalence of NSAID initiators with cardiovascular contraindications remained high (12% in 2014).[9] The study also reported on the diclofenac prescribers in general (not only for cardiovascular patients) and found 61% prescribed by general practitioners, 22% by orthopaedists, 6.8% by surgeons, and 9.1% by others.[9]

Interpretation of trends

While NSAIDs are generally now considered contraindicated in patients with cardiovascular disease (except pericarditis),[1] it was not the case through the entire study period. The declining trends in prevalence since 2002 therefore likely in part reflect temporal changes in clinical guidelines and regulatory actions.

The FDA requested in 2005 revised NSAID labelling to include a boxed warning about the potential increased risk of cardiovascular disease.[2] FDA warnings were further strengthened in 2015.[3] The EMA raised first concerns about the cardiovascular risks of coxibs as a class in 2005, and in 2006 also diclofenac (particularly at a high dose of 150 mg daily) and high-dose ibuprofen (2400 mg daily).[4] As smaller risks with use of other NSAIDs could not be excluded, the EMA recommended use of NSAIDs at the lowest effective dose for the shortest possible duration.[4] Updated risk assessments were carried out by the EMA in the following years: in 2012, previous conclusions were confirmed but also added that naproxen may be associated with lower thromboembolic risk than other NSAIDs although small risks cannot be excluded[5]; in 2013, a firm conclusion was drawn that diclofenac use was associated with an elevated risk of acute cardiovascular events[6]; and in 2015 that ibuprofen in high dose (≥2400 mg/day) increased cardiovascular risks to a degree similar to coxibs and diclofenac, that moderate dose (1200–2400 mg/day) likely increased risk in a dose-dependent manner, and that low dose (≤1200 mg/day) did not increase risk.[7] Dexibuprofen was expected to have similar cardiovascular risk as high-dose of ibuprofen when used at equipotent doses. The clinical impact of a potential reduced antiplatelet drug effect of acetylsalicylic acid when administered concomitantly with ibuprofen/dexibuprofen remains debated.[7] Latest the EMA called in 2017 again for another safety assessment of diclofenac.[23] As a result, data accumulate on the cardiotoxicity of diclofenac,[8,24] prompting recent withdrawal of OTC diclofenac also in Norway and Sweden,[25] although the final EMA report is yet to be made public.

The Danish Medicines Agency issued the first national warning about diclofenac in 2008 after which OTC diclofenac was prohibited.[12] Latest, the European Society of Cardiology stated in 2016 their position that NSAIDs should in general not be used in patients with established or at high risk of cardiovascular disease and when prescribing traditional NSAIDs, older selective COX-2 inhibitors such as diclofenac, should be avoided.[1] The Danish Society for Cardiology has adapted this position.[26]

The overall trends in NSAID use paralleled widely with trends for the whole Danish population[8,12] and were thus not specific or markedly better for patients with cardiovascular disease. Nonetheless, considering the changes to national and international recommendations above, our results are encouraging in showing a substantial and ongoing decline in NSAID use since 2002, with a particular decline in use of coxibs after 2004 and diclofenac after 2008, but also a beginning decline in ibuprofen use after 2014. Moreover, the general shift away from selective COX-2 inhibitors towards ibuprofen/naproxen supports adherence to guideline recommendations when NSAID cannot be avoided. Finally, the general reduction in treatment

duration and shift from predominantly moderate/high to low-dose ibuprofen supports the EMA recommendation of lowest effective dose for the shortest possible duration.[4,5]

The relatively short delay from guideline changes to clinical implications in Denmark, likely reflected a combination of supportive digital health solutions and a long tradition for and adherence to national guidelines.[10] Still, it should be noted that adherence to guidelines does not alone explain the trend in use as the decline started in 2002, that is, before the first FDA/EMA (2005)[2,4] and Danish (2008)[12] recommendations. The establishment of the Institute for Rational Pharmacotherapy in Denmark in 1999 with its impact on general practitioners' prescribing habits and enforcement of paracetamol as the first-line drug for pain management likely contributed to reduce NSAID use in the early period of the decline.[27]

Despite these positive trends, the recommendation from the European Society of Cardiology to consider NSAIDs contraindicated in patients with cardiovascular disease is clear.[1] A continuous 1-year prevalence of NSAID use in 2017 close to 15%, increasing to above 30% within 5 years, is therefore too high. Part of the explanation for this apparent high-prevalent contraindicated use is likely that NSAIDs previously was thought to be risk-neutral in low doses and short treatment periods. Both assumptions are incorrect as general rules. While ibuprofen in low doses (≤1200 mg/day) according to EMA recommendations are considered safe for low-risk populations,[7] it is not the case in the presence of cardiovascular disease.[1] The cardiovascular risks of older COX-2 inhibitors as diclofenac are clinical relevant even at low doses and also short treatment durations.[24] The adverse event rate thus increases at time of initiation and accumulate thereafter.

Strengths and limitations

The 22-year nationwide inclusion period provided high statistical precision and enabled subgroup analyses of individual cardiovascular diseases and NSAIDs. The population-based design in the setting of a tax supported, universal healthcare system largely removed selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups.[10] The prescription data, including prescriber information, are considered valid.[14,17] Moreover, NSAID use was not based on written prescriptions, but on actual dispensing at pharmacies.[14] Required copayments increased the likelihood of compliance, although any non-compliance would not influence the estimated proportion of patients prescribed NSAIDs. Any OTC use of ibuprofen or diclofenac would only underestimate results.[12]

The algorithms identifying the individual cardiovascular diseases have all been validated and found adequate with positive predictive values around 93% for angina pectoris,[15] 97% for MI (96% for STEMI and 92% for NSTEMI),[15] 95% for atrial fibrillation/flutter,[15] 76%–84% for heart failure,[15,28] 88% for venous thromboembolism,[15] 97% for ischaemic stroke,[13] 96% for valvular heart disease,[15] and 90% infective endocarditis.[16] The mortality and migration data were accurate and complete.[11]

Implications

The persistent high-prevalent contraindicated NSAID use in patients with newly diagnosed cardiovascular disease is a major public health concern that needs attention from health care authorities and relevant medical societies. A novel finding in our study was the assessment of prescriber responsibility, which documents the central role of general practice. Although general practitioners should be acknowledged for their contributions to overall declining and more differentiated NSAID use in patients with cardiovascular disease as described above, the burden of minimizing the remaining contraindicated NSAID use, however, also lies in general practice given that 9 out 10 such prescriptions are issued here.

Conclusions

Following regulatory actions and changes in clinical guidelines, initiation of NSAIDs after newly diagnosed cardiovascular disease has declined consistently in Denmark since 2002, and most for patients with heart failure or ischaemic heart disease. Temporal changes in prescribing behaviour towards shorter treatment periods, less use of COX-2 inhibitors—in particular diclofenac and coxibs—and more naproxen and low-dose ibuprofen, indicate adherence to clinical guidelines when NSAIDs cannot be avoided. Despite these overall encouraging utilization trends, contraindicated NSAID use remain too common, being initiated in more than one in 10 cardiac patients within a year after diagnosis, increasing to above three in 10 patients within 5 years. Safer alternatives to pain relief should always be sought out before initiating NSAIDs in the presence of cardiovascular disease. Interventions to promote appropriateness of use, in particular targeted at general practitioners, are warranted.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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Data permission

The study was approved by the Danish Data Protection Agency.

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Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics committee approval

No ethical committee approval was needed.

Data sharing

Data cannot be shared according to Danish law. Data can be obtained upon application to the Danish Health Data Authority. Cohort definition as well as statistical codes may be shared upon reasonable request.

Patient and public involvement

No patient involvement.

Conflict of interest: none declared.

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