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ORIGINAL ARTICLE
Acute Coronary Syndromes

Cardiovascular risks of continuing vs. initiating NSAIDs after first-time myocardial infarction or heart failure: a nationwide cohort study

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Aims It is unknown whether the cardiovascular risks associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) shortly after first-time myocardial infarction (MI) or heart failure (HF) differ between patients continuing and initiating use.

Methods and results Using nationwide health registries, we conducted a cohort study of all patients with first-time MI or HF during 1996–2018 ($n = 273\,682$). NSAID users ($n = 97\,966$) were categorized as continuing (17%) and initiating (83%) users according to prescription fillings < 60 days before index diagnosis. The primary outcome was a composite of new MI, HF admission, and all-cause death. Follow-up started 30 days after the index discharge date. We used Cox regression to compute hazard ratios (HRs) with 95% confidence intervals (CIs) comparing NSAID users vs. non-users. The most commonly filled NSAIDs were ibuprofen (50%), diclofenac (20%), etodolac (8.5%), and naproxen (4.3%). The composite outcome HR of 1.25 (CI: 1.23–1.27) was driven by initiators (HR = 1.39, 1.36–1.41) and not continuing users (HR = 1.03, 1.00–1.07). The lack of association among continuing users was also observed for individual NSAIDs (ibuprofen and naproxen), except diclofenac (HR = 1.11, 95% CI: 1.05–1.18). Among initiators, the HR was 1.63 (CI: 1.57–1.69) for diclofenac, 1.31 (CI: 1.27–1.35) for ibuprofen, and 1.19 (CI: 1.08–1.31) for naproxen. The results were consistent for both MI and HF patients, the individual components of the composite outcome, and various sensitivity analyses.

Conclusion NSAID initiators were more susceptible to adverse cardiovascular outcomes after first-time MI or HF than continuing users.

Keywords Cardiovascular diseases • Epidemiology • NSAIDs • Trends

Introduction

Following several risk assessments by the European Medicines Agency and US Food and Drug Administration,[1,2] international risk minimization measures have been implemented, including box warning labelling, on the potential cardiovascular risks of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs). In accordance, the position of the European Society of Cardiology is to avoid the use of NSAIDs in patients with cardiovascular disease.[3]

In contrast to these recommendations, patients with myocardial infarction (MI) or heart failure (HF) are frequently prescribed NSAIDs.[4] It is unknown whether the associated risks of prescribing NSAIDs to patients with MI or HF depend on whether the patients are exposed to NSAIDs on their index event. We, therefore, examined whether the risks of NSAID use after first-time MI and HF differed between patients continuing and initiating NSAIDs.

Methods

Setting

The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals, and partial reimbursement for prescribed medications, including NSAIDs.[5] 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.[6]

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Over-the-counter (OTC) use of NSAIDs in Denmark is far less common than in many other countries. Thus, all NSAIDs are available by prescription, except for low-dose ibuprofen (200 mg tablets) and diclofenac (only between 16 July 2007 and 14 December 2008).[7] Moreover, OTC sales of ibuprofen have been restricted to age groups ≥18 years, to one package per person per dispensing since 2011 and to pack sizes containing a maximum of 20 tablets since 2013.[7] Regular users of NSAIDs have an economic incentive to obtain the drugs by prescription to receive reimbursement.[5] The potential for identifying NSAID use from Danish National Prescription Registry is therefore high.[8]

Data sources

We used Danish National Patient Registry to identify the study cohorts, non-fatal outcomes, and comorbidities.[9] We used the Danish National Prescription Registry to identify all prescription fillings since 1995.[10] We obtained information on all-cause mortality and migration status from the Danish Civil Registration System.[6]

Study cohort

The study cohorts comprised individuals with first-time MI and HF who survived until 30 days after discharge and were identified from the Patient Registry between 1 January 1996 and 31 December 2018.[9] Applying validated algorithms,[11] we used primary and secondary inpatient diagnoses to identify the index diagnoses of MI and HF. Emergency department diagnoses were not considered. First-time (incident) disease was identified by excluding patients with inpatient or outpatient diagnoses of MI or HF before our study period (i.e. from 1977 through 1995). To ensure complete medical history, we also excluded individuals who immigrated or emigrated before 1996. The index admission included consecutive hospital admissions ≤1 day between discharge and admission dates to account for transfer to other hospitals. The first and last dates in these consecutive hospital admissions defined the index admission date and index discharge date, respectively.

NSAID use

Information on NSAID use in the study period was obtained by retrieving all filled NSAID prescriptions. NSAID use before the index admission date (pre-index use) defined continuing and initiating use (with or without ≥1 prescription filling ≤60 days before the admission date, respectively). When examining continuing NSAID use, we allowed the re-prescribed NSAID to be different from pre-index NSAID use.

Outcomes

The primary outcome was a composite of new MI, HF admission, and all-cause mortality. The MI and HF outcomes were defined from primary inpatient diagnoses in the Patient Registry during follow-up.[9] Thus for the HF cohort, these included a first-time hospitalization for MI or rehospitalization for HF after the index discharge date and vice versa for the MI cohort. All-cause mortality was identified by the Danish Civil Registration System.[6] Secondary outcomes included the composite components.

Covariates

We identified comorbidities within 10 years before the index admission date based on primary and secondary inpatient and outpatient diagnoses in the Patient Registry.[9] To increase the completeness of diagnoses of diabetes and chronic obstructive pulmonary disease, we also identified any previous dispensing of antidiabetic and respiratory medication. Moreover, we defined hypertension as either a hospital diagnosis, redemption of antihypertensive combination tablets, or redemption of at least two antihypertensive drugs within 90 days before the index admission date.

We 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).[10] Finally, using the DANish Comorbidity Index for Acute Myocardial Infarction (DANCAMI), we categorized the total burden of comorbidity as none (score = 0), low (score = 1–3), moderate (score = 4–5), and severe (score ≥ 6).[12]

Statistical analyses

First, we characterized the cohort according to demographics, comorbidity, and comedication use.

Second, we characterized NSAID users by their number of prescriptions, used tablet strength, and treatment intensity (median number of redeemed prescriptions within 1 year among users). *Third*, we used the Kaplan–Meier method to describe the distribution of time from index discharge date to NSAID filling. *Fourth*, as a measure of prescriber responsibility, we assessed the proportion of NSAID prescriptions issued by general practitioners, private practicing specialists, hospital prescribers, and other prescribers (e.g. dentists) through 2019.[13] We used the first NSAID filling after the index admission of each individual in this calculation.

Fifth, for the time-to-event analyses, we considered patients formally unexposed until they filled their first NSAID prescription during follow-up to avoid immortal time bias. In a time-varying manner, we used Cox proportional-hazards regression to estimate the hazard ratio (HR) with a 95% confidence interval (CI) comparing outcome hazards between NSAID users and non-users. To avoid inclusion of hospitalizations that reflected manifestation of the index admission, we began follow-up for outcomes 30 days after the index discharge date (i.e. restricted to 30-day survivors) and continued until censoring from an outcome, emigration, or end of follow-up (31 December 2018), whichever came first. The longest follow-up was 23 years (median 3, interquartile range [IQR]: 1–7). Persons who filled or discontinued NSAIDs during follow-up were reclassified accordingly during follow-up as NSAID users or non-users. Each NSAID filling defined 60 days of exposure before being unexposed again unless filling a new prescription. If patients filled a prescription (e.g. 15 days) between their index discharge date and 30 days after, they were considered exposed in the remaining (e.g. 45 days) from the start of follow-up. We adjusted for age, sex, calendar period, comorbidity burden (using DANCAMI categories), and comedications as listed in *Table 1*. Age and calendar period were included in the regression as time-varying covariables. We repeated the analyses for NSAID subtypes and the components of the composite outcome. To examine whether the effect estimates varied among continuing users and initiators, we stratified the analyses according to pre-index use.

Sixth, we performed five sensitivity analyses: (1) We changed the definition of pre-index use from filling within 60 days to filling within 30 days, 90, and 120 days; (2) We capped the time-to-event analyses to a maximum of 5 years of follow-up; (3) We started follow-up at index discharge date instead of 30 days after; (4) We stratified by calendar period (1996–2005 and 2006–2018) to examine the impact of changing definitions of MI and HF over time; and (5) We adjusted for the individual comorbidities in *Table 1* instead of overall comorbidity burden (using DANCAMI).[14] All analyses were conducted in STATA software v17.0 (STATA, College Station, Texas, USA) and registry codes are provided in Supplementary material online, e*Table 1*.

Results

Patient characteristics

Among all patients with first-time MI or HF during 1996–2018 (n = 273 682), 36% (97 966) filled NSAIDs during follow-up. Among NSAID users, 17% (n = 16 896) were continuing users, and 83% (n = 81 070) were initiators (*Table 1*). Compared with initiators, continuing users were more often women (48% vs. 39%), were older (median age 72 vs. 67 years), and had a more severe comorbidity burden (20% vs. 13%). The higher comorbidity burden reflected a higher prevalence of rheumatoid arthritis (4.1% vs. 1.5%), systemic connective tissue disease (2.8% vs. 1.8%), osteoarthritis (22% vs. 12%),

Table 1 Characteristics of patients with first-time myocardial infarction or heart failure (1996–2018), overall and according to continuing and initiating NSAID use*

		NSAID users		
	Total cohort	Overall use	Continuing use	Initiating use
Total	273 682 (100%)	97 966 (100%)	16 896 (100%)	81 070 (100%)
Sex (male)	157 639 (58%)	58 204 (59%)	8751 (52%)	49 453 (61%)
Age, median (IQR)	72 (61–81)	68 (58–78)	72 (61–80)	67 (57–77)
<50 years	21 985 (8.0%)	10 423 (11%)	1150 (6.8%)	9273 (11%)
50–59 years	33 590 (12%)	15 826 (16%)	2257 (13%)	13 569 (17%)
60–69 years	52 252 (19%)	21 494 (22%)	3294 (19%)	18 200 (22%)
70–79 years	67 201 (25%)	22 931 (23%)	4269 (25%)	18 662 (23%)
80 years or more	79 629 (29%)	20 331 (21%)	4689 (28%)	15 642 (19%)
Calendar year				
1996–2000	63 886 (23%)	28 205 (29%)	4872 (29%)	23 333 (29%)
2001–2005	68 109 (25%)	30 229 (31%)	5760 (34%)	24 469 (30%)
2006–2010	57 046 (21%)	21 414 (22%)	3380 (20%)	18 034 (22%)
2011–2015	53 968 (20%)	14 591 (15%)	2223 (13%)	12 368 (15%)
2016–2018	30 673 (11%)	3527 (3.6%)	661 (3.9%)	2866 (3.5%)
Comorbidities				
Diabetes	39 384 (14%)	12 201 (12%)	2610 (15%)	9591 (12%)
Hypertension	102 878 (38%)	32 854 (34%)	6731 (40%)	26 123 (32%)
Obesity	9864 (3.6%)	3827 (3.9%)	959 (5.7%)	2868 (3.5%)
COPD	79 868 (29%)	27 862 (28%)	5796 (34%)	22 066 (27%)
Sleep apnoea	3154 (1.2%)	1202 (1.2%)	248 (1.5%)	954 (1.2%)
Hyperthyroidism	4554 (1.7%)	1412 (1.4%)	262 (1.6%)	1150 (1.4%)
Osteoporosis	11 832 (4.3%)	2961 (3.0%)	763 (4.5%)	2198 (2.7%)
Rheumatoid arthritis	4685 (1.7%)	1881 (1.9%)	699 (4.1%)	1182 (1.5%)
SCTD	5800 (2.1%)	1892 (1.9%)	466 (2.8%)	1426 (1.8%)
Osteoarthritis	36 524 (13%)	13 814 (14%)	3799 (22%)	10 015 (12%)
Comorbidity burden†				
None	93 629 (34%)	39 177 (40%)	5011 (30%)	34 166 (42%)
Low	97 251 (36%)	35 243 (36%)	6513 (39%)	28 730 (35%)
Moderate	30 768 (11%)	9486 (9.7%)	2035 (12%)	7451 (9.2%)
Severe	52 034 (19%)	14 060 (14%)	3337 (20%)	10 723 (13%)
Medication use‡				
Antiplatelet drugs	60 499 (22%)	19 192 (20%)	4033 (24%)	15 159 (19%)
Anticoagulant drugs	20 404 (7.5%)	4499 (4.6%)	719 (4.3%)	3780 (4.7%)
Statins	35 253 (13%)	11 124 (11%)	2032 (12%)	9092 (11%)
ACE inhibitors	33 511 (12%)	10 871 (11%)	2225 (13%)	8646 (11%)
ARBs	16 083 (5.9%)	5130 (5.2%)	1066 (6.3%)	4064 (5.0%)
Beta-blockers	45 351 (17%)	14 592 (15%)	2770 (16%)	11 822 (15%)
CCBs	44 122 (16%)	14 488 (15%)	2976 (18%)	11 512 (14%)
Diuretics	87 593 (32%)	27 045 (28%)	6511 (39%)	20 534 (25%)
SSRI	19 351 (7.1%)	6070 (6.2%)	1557 (9.2%)	4513 (5.6%)
Antipsychotic drugs	9810 (3.6%)	3246 (3.3%)	926 (5.5%)	2320 (2.9%)
Anti-ulcer drugs	41 572 (15%)	13 447 (14%)	3402 (20%)	10 045 (12%)
Gout agents	7347 (2.7%)	2499 (2.6%)	809 (4.8%)	1690 (2.1%)
Glucocorticoids	20 368 (7.4%)	6688 (6.8%)	1754 (10%)	4934 (6.1%)
Methotrexate	1182 (0.4%)	531 (0.5%)	168 (1.0%)	363 (0.4%)
Paracetamol	52 127 (19%)	16 052 (16%)	5443 (32%)	10 609 (13%)
Opioids	37 787 (14%)	12 740 (13%)	4562 (27%)	8178 (10%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor antagonists; CCBs, calcium channel blockers; DANCAMI, DANish Comorbidity Index for Acute Myocardial Infarction; DDD, daily defined dose; Glucocorticoids, systemic glucocorticoids; NSAID, non-steroidal anti-inflammatory drug; SCTD, systemic connective tissue disease; SSRI, selective serotonin reuptake inhibitors.

*NSAID use defined by prescription filling ≤60 days before index date.

†Four categories of comorbidity burden were defined based on DANCAMI scores of 0 (none), 1–3 (low), 4–5 (moderate), and ≥6 (severe).

‡Prescription filling within 90 days before index disease.

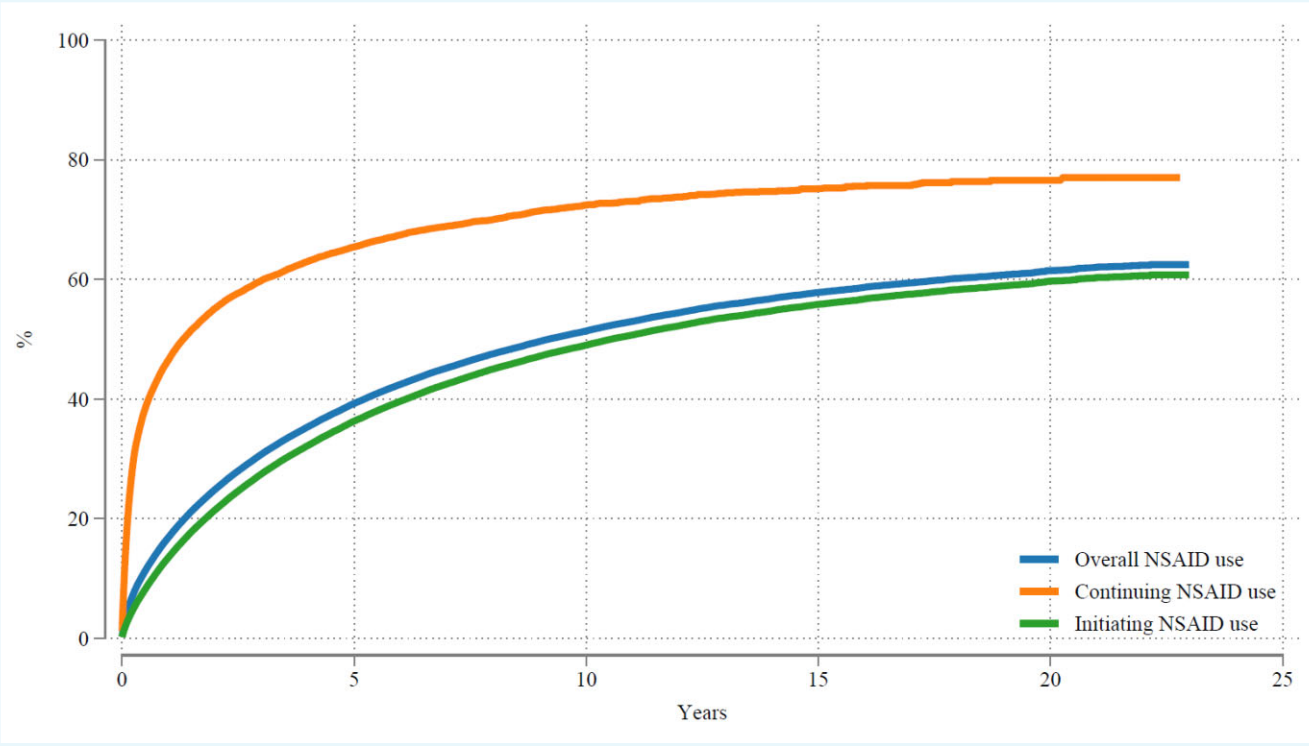

Figure 1 Cumulative rate of NSAID fillings after first-time myocardial infarction or heart failure among patients with continuing and initiating NSAID use.

and use of anti-ulcer drugs (20% vs. 12%), gout agents (4.8% vs. 2.1%), glucocorticoids (10% vs. 6.1%), paracetamol (32% vs. 13%), and opioids (27% vs. 10%) (*Table 1*).

Filling characteristics

The 97 966 NSAID users filled a total of 657 469 NSAID prescriptions (Supplementary material online, e*Table 2*), among which most often ibuprofen (50%), diclofenac (20%), etodolac (8.5%), and naproxen (4.3%). The prescribed tablet strength was stable for most NSAIDs between 1996 and 2018, with a median of 500 mg (IQR: 250–500) for naproxen, 400 mg (IQR: 400–600) for ibuprofen, 50 mg (IQR: 50–75) for diclofenac, 15 mg (IQR: 7.5–15) for meloxicam, 300 mg (IQR: 200–300) for etodolac, 200 mg (IQR: 200–200) for celecoxib, and 120 mg (IQR: 90–120) for etoricoxib. Only etodolac and celecoxib had a median tablet strength that reduced over time to 200 mg for etodolac and 150 mg for celecoxib in 2018. The prescribed tablet strength dose did not vary according to pre-index NSAID use.

Treatment intensity declined during the study period from a median of 5 to 2 redeemed prescriptions (Supplementary material online, e*Table 2*). This decline reflected a decline from 4 to 2 for naproxen, 5 to 2 for ibuprofen, 4 to 1 for diclofenac, 3 to 0 for meloxicam, and 6 to 1 for etoricoxib. It increased for etodolac from 5 to 6 and for celecoxib from 6 to 7. Treatment intensity was overall stronger for continuing users than initiators with an overall median of 2 vs. 1 in 2018.

Filling rate

The cumulative proportion of NSAID fillings among users was 21% after 3 months, 31% after 6 months, 45%, after 12 months, 73% after 36 months, and 86% after 60 months. It, however, varied considerably between patients continuing and initiating use (Figure 1). Thus, among continuing users, the re-filling rate accumulated at 50% already after 3 months and increased to 75% after 12 months. In contrast, the filling rate among initiators was much lower (15% at 3 months and 38% at 12 months), although still numerically high. Filling rates were generally higher for patients with HF than MI.

Prescriber responsibility

The distribution of the entities responsible for prescribing NSAIDs to patients after first-time MI or HF remained stable between 1996 and 2019. As of 2019 (*Figure 2*), general practitioners accounted for around 80% of all NSAID prescriptions and hospital physicians around 15%. This distribution was similar for ibuprofen, whereas general practitioners prescribed closer to 95% of all naproxen prescriptions and 75% of all diclofenac prescriptions. General practitioners generally accounted for continuing use of ibuprofen (95%) and naproxen (100%), and to a lesser extent continuing diclofenac use (60%).

Continuing vs. Initiating NSAID use

We encountered a total of 189 807 outcomes during follow-up, including 27 190 MIs, 74 946 HF admissions, and 89 627 deaths. The rate per 1000 person-years for the main composite outcome was 148 overall, 172 for continuing users, and 145 for initiators. The adjusted HR associated with NSAID use vs. non-use was 1.25 (CI: 1.23–1.27) for the main composite outcome, 1.35 (CI: 1.30–1.41) for MI, 1.22 (CI: 1.19–1.25) for HF admission, and 1.25 (CI: 1.23–1.28) for all-cause death (*Table 2*). The increased HR of all outcomes varied considerably between continuing users (composite HR 1.03, CI: 1.00–1.07) and initiators (1.39, CI: 1.36–1.41).

Among all users of the individual NSAIDs (*Figure 3* and Supplementary material online, *eTable 4*), the adjusted HR for the composite outcome was 1.43 (CI: 1.39–1.48) for diclofenac, 1.20 (CI: 1.18–1.23)

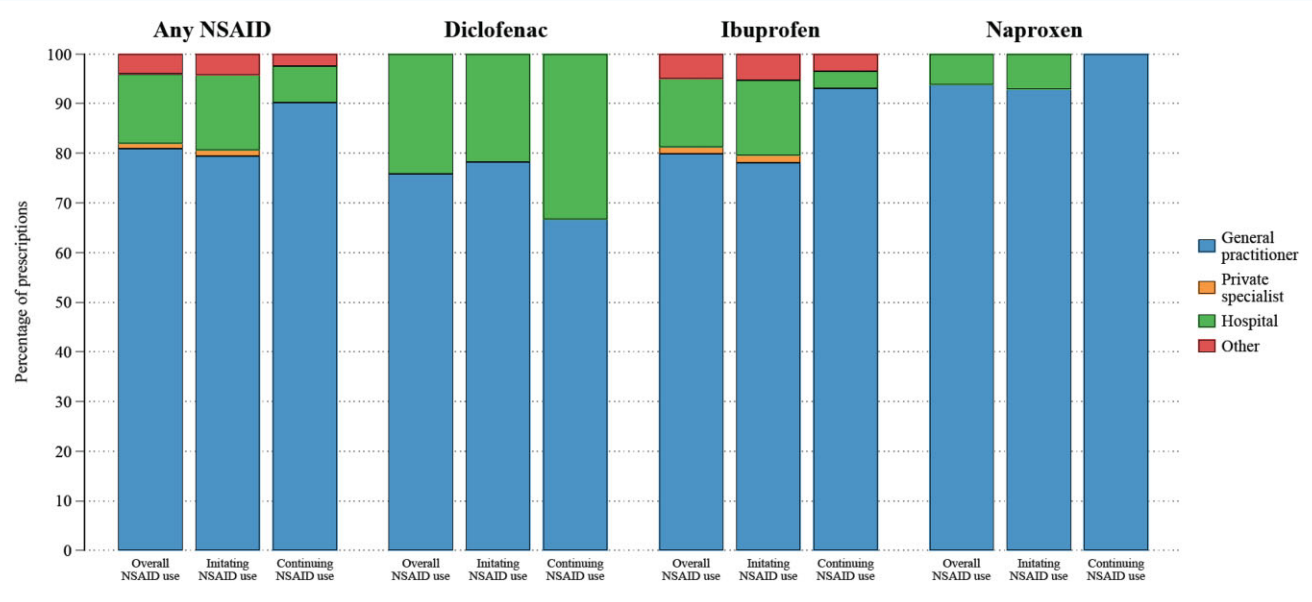

Figure 2 Entities responsible for continuing and initiating NSAID use within 1 year after first-time myocardial infarction or heart failure (2019).

Table 2 Cardiovascular risks associated with continuing and initiating NSAIDs after first-time myocardial infarction or heart failure in Denmark (1996–2018)

	Unexposed		Exposed		Hazard ratio	
NSAID use* and outcomes	**Number of events**	**Rate per 1000 PY**	**Number of events**	**Rate per 1000 PY**	**Crude**	**Adjusted†**
Overall NSAID use						
Composite outcome	173 903	144	15 904	202	1.39 (1.37–1.41)	1.25 (1.23–1.27)
MI	24 909	21	2281	29	1.39 (1.33–1.45)	1.35 (1.30–1.41)
HF hospitalization	68 983	57	5963	76	1.31 (1.28–1.35)	1.22 (1.19–1.25)
All-cause death	81 772	68	7855	100	1.47 (1.43–1.50)	1.25 (1.23–1.28)
Continuing NSAID use						
Composite outcome	16 568	163	4886	211	1.07 (1.03–1.10)	1.03 (1.00–1.07)
MI	2271	22	779	34	1.21 (1.12–1.32)	1.19 (1.09–1.29)
HF hospitalization	6305	62	2034	88	1.08 (1.02–1.13)	1.04 (0.99–1.09)
All-cause death	8153	80	2133	92	1.02 (0.97–1.07)	1.00 (0.95–1.05)
Initiating NSAID use						
Composite outcome	157 335	142	11 018	198	1.51 (1.48–1.54)	1.39 (1.36–1.41)
MI	22 638	20	1502	27	1.42 (1.35–1.50)	1.42 (1.34–1.49)
HF hospitalization	62 678	57	3929	71	1.41 (1.36–1.46)	1.34 (1.30–1.39)
All-cause death	73 619	67	5722	103	1.62 (1.58–1.67)	1.40 (1.36–1.44)

Abbreviations: HF, heart failure; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug.
*Defined by prescription filling ≤60 days before index date, NSAID use was categorized as continuing (= re-filling) or initiating (= new filling) use.
†Adjusted for age, sex, calendar period, DANCAMI, and comedication categories listed in *Table 1*.

for ibuprofen, and 1.11 (CI: 1.03–1.20) for naproxen. The HR was stronger among initiators, increasing to 1.63 (CI: 1.57–1.69) for diclofenac, 1.31 (CI: 1.27–1.35) for ibuprofen, and 1.19 (CI: 1.08–1.31) for naproxen. Among continuing users, however, re-filling of NSAIDs was only associated with a slightly increased outcome rate for diclofenac (HR = 1.11, CI: 1.05–1.18), and no increased rate for ibuprofen (HR = 1.00, CI: 0.96–1.05) or naproxen (HR = 0.98, CI: 0.86–1.12).

The sensitivity analyses using varying definitions of pre-index NSAID use (Supplementary material online, *eTable 5*), using a maximum of 5 years of follow-up (not shown), using the start of follow-up at discharge date (data not shown), stratifying by calendar period

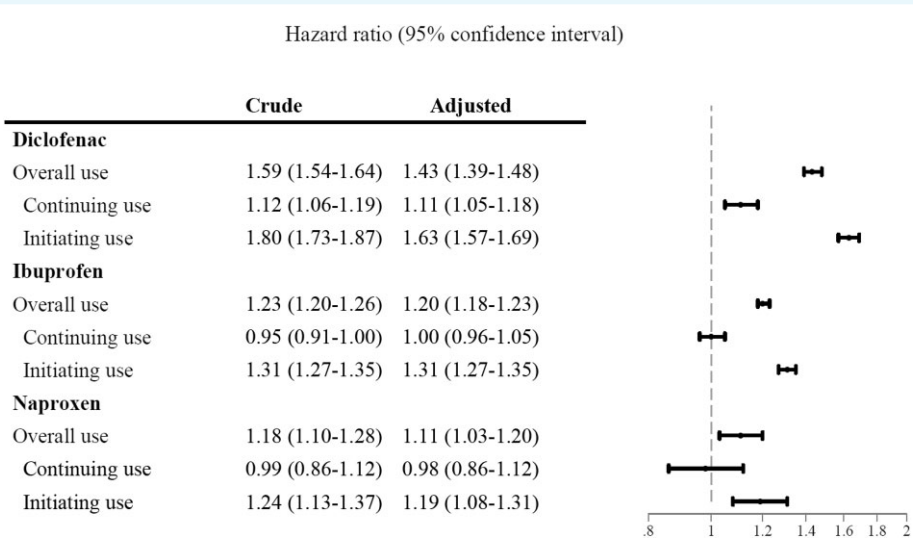

Figure 3 Cardiovascular risks associated with continuing and initiating individual NSAIDs after first-time myocardial infarction or heart failure in Denmark (1996–2018).

(Supplementary material online, *eTable 6*), and adjusting for individual comorbidities instead of DANCAMI (Supplementary material online, *eTable 7*) all showed consistent results.

Discussion

Despite contraindications, our study showed that NSAIDs were commonly prescribed to patients with first-time MI and HF. Reflecting the large primary care sector in the Danish health care system, this prescribing behavior was observed mainly in general practice and to a lesser extent in the hospital sector. Thus, half of the patients using NSAIDs up to their diagnosis for MI or HF were re-prescribed NSAIDs within only 3 months, increasing to two-thirds within 1 year. However, more than four out of five of all NSAID users after MI or HF initiated treatment without recent use. This frequent de novo initiation of NSAID was a concern because the magnitude of the NSAID-associated rate of adverse cardiovascular outcomes differed substantially between patients continuing and initiating use. Thus, the key finding of this study was that the cardiovascular risk associated with NSAID use was predominantly observed among initiators with relative risk increases of 60% for diclofenac, 30% for ibuprofen, and 20% for naproxen. In contrast among continuing users, only diclofenac users had a slightly elevated risk whereas ibuprofen and naproxen users had not.

Previous literature

The recommendation from the European Society of Cardiology to consider NSAIDs contraindicated in patients with MI and HF is clear.[3] The prevalence of NSAID use after newly-diagnosed MI or HF was therefore above expected. Part of the explanation for this apparent contraindicated use is likely that NSAIDs previously were thought to be risk-neutral in low doses and short treatment periods. Both assumptions are incorrect.[15] While ibuprofen in low doses (≤1200 mg/day) is considered safe for low-risk populations according to European Medicines Agency recommendations, it is not the case in the presence of cardiovascular disease.[3] The cardiovascular risks of diclofenac are clinically relevant even at low doses and short treatment duration.[15]

While the cardiovascular risk of NSAID use after MI and HF has previously been shown,[16,17] the importance of whether the index hospitalization is NSAID exposed or not has not. In many respects, our findings are counterintuitive. Conditioning on the index MI occurring during NSAID exposure would be expected to select individuals who are prone to developing MI while taking NSAIDs and such persons would be particularly liable to develop MIs if exposed again. Subjects, whose index MI is unexposed would have shown no such liability a priori and would be expected to have a lower risk of NSAID exposure than the former group. We found the opposite pattern. Whether there is some biological tolerance development when having an MI while taking NSAIDs is unknown. It should be noted, however, that with weak associations like the NSAID-MI relationship, the attributable proportions are low. For example, if an HR of 1.5 is assumed for the NSAID-MI association, only one-third (= (1.5–1.0)/1.5) of those MIs that developed during NSAID exposure is caused by the drug. We would therefore not expect large differences in the biological profiles of those patients whose MIs occurred during NSAID exposure and those whose MI did not.

Considerations among the NSAID prescribers of a potentially causative effect of NSAID use at the time of first-time event[15,18] was not reflected in re-prescribing rates. Individuals with pre-index use were substantially more often prescribed NSAIDs again after MI/HF diagnosis than those without previous use, indicating that the cardiovascular hazards of NSAID use in patients with newly-diagnosed MI/HF[16,17] were either not considered by the prescribing physician or that the beneficial anti-inflammatory and analgetic effects of continuous use were prioritized above potential risks. It appeared that the cardiovascular risk associated with continuous use of the most frequent NSAIDs, except diclofenac, was not substantial after first-time MI or HF. There may be several explanations for this finding. Long-term use of a drug may imply a tolerance to a drug. This fact may explain why the effect appeared weaker (diclofenac) or even disappeared (ibuprofen and naproxen) among continuing users. The higher underlying absolute outcome rates among continuing users, likely due to their higher comorbidity burden, may also have reduced the magnitude of any NSAID-associated risks (confounding by baseline rate). Still, our data imply that special concerns relate to NSAID-naïve patients initiating therapy after their first-time diagnosis

of MI or HF because the relative cardiovascular risk increase of starting therapy was substantially elevated and applied to all NSAID types, but especially diclofenac.

Strengths and limitations

The population-based design in the setting of a tax-supported, universal healthcare system largely removed selection biases stemming from the selective inclusion of specific hospitals, health insurance systems, or age groups.[5] The prescription data, including prescriber information, are considered valid.[10,13] Moreover, NSAID use was not based on written prescriptions, but on actual dispensing at pharmacies.[10] Re-filling could represent either active re-prescribing or re-iterating of existing prescriptions. Unfortunately, our data source does not allow us to identify the underlying mechanism. Required co-payments increased the likelihood of compliance, although any noncompliance would not influence the estimated proportion of patients prescribed NSAIDs. Any OTC use of ibuprofen or diclofenac would only underestimate results and is of a magnitude insignificant to influence the effect estimates.[8] The algorithms identifying the individual cardiovascular diseases have been validated and found adequate with positive predictive values of 97% for MI,[11] 88% for recurrent MI, 84% for HF,[19] and 76% for HF readmission.[11] It was not possible to stratify on HF severity as data on, e.g. NYHA classification and left ventricular ejection fraction were not available. The mortality and migration data were accurate and complete.[6]

We cannot exclude unmeasured confounding due to the lack of baseline randomisation. However, the overall link between NSAID use and MI and HF is well established.[18] Moreover, we focused on comparing the effect estimates for continuing and initiating users, both of which have indications for NSAID use. Importantly, the comorbidity burden was less severe among initiators and therefore cannot explain the higher risk in this group compared with continuing users.

Conclusion

The persistent high-prevalent contraindicated NSAID use in patients with newly diagnosed MI or HF is a major public and clinical health concern that needs attention from healthcare authorities and relevant medical societies. Our assessment of prescriber responsibility documents the central role of general practice in health care systems like the Danish. Although general practitioners should be acknowledged for their contributions to reducing treatment intensity, minimizing the remaining contraindicated NSAID use also lies in general practice given that the vast majority of prescriptions are issued here. Before initiating NSAIDs in patients with MI or HF without recent use, special attention should be given. Thus, patients with MI or HF patients represent a high-risk group, in which not even nonselective NSAIDs (ibuprofen and naproxen) seem safe to initiate and where other analgetic regimens therefore should be prioritized. Diclofenac was a cardiovascular hazard in all patients independent of whether it was continued or initiated and should therefore always be avoided.

Supplementary material

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

Author contributions

All authors contributed in conceived the study idea and designing the study. M.S., A.P., and J.H. designed the study. A.P. collected the data and M.T.E. carried out the analyses. M.S. organized the writing and wrote the initial draft. All authors participated in the discussion and interpretation of the results. All authors critically revised the manuscript for intellectual content and approved the final version before submission. The corresponding author attests that all authors meet authorship criteria and that no others meeting the criteria have been omitted. M.S. is the guarantor.

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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

Not allowed. Statistical codes may be shared upon reasonable request.

Patient and public involvement

No patient involvement.

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