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ORIGINAL ARTICLE
Pulmonary circulation

Non-steroidal anti-inflammatory drugs and risk of pulmonary embolism in patients with inflammatory joint disease—results from the nationwide Norwegian Cardio-rheuma registry

Eirik Ikdahl[1,*], Silvia Rollefstad[1], Amirhossein Kazemi[1], Sella A. Provan[1,2], Trine-Lise Larsen[3] and Anne Grete Semb[1]

[1]Center for treatment of Rheumatic and Musculoskeletal Diseases (REMEDY), Diakonhjemmet Hospital, 0319 Oslo, Norway; [2]Department Public Health and Sport Sciences, Inland Norway University of Applied Sciences, 2406 Elverum, Norway; and [3]Department Hematology, Medical Division, Akershus University Hospital, 1478 Lørenskog, Norway

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Aims Patients with inflammatory joint diseases (IJD), including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) have increased rates of pulmonary embolism (PE). Non-steroidal anti-inflammatory drugs (NSAIDs) use is associated with PE in the general population. Our aim was to evaluate the association between NSAIDs use and PE in IJD patients.

Methods and results Using individual-level registry data from the whole Norwegian population, including data from the Norwegian Patient Registry and the Norwegian Prescription Database, we: (1) evaluated PE risk in IJD compared to non-IJD individuals, (2) applied the self-controlled case series method to evaluate if PE risks were associated with use of traditional NSAIDs (tNSAIDs) and selective cox-2 inhibitors (coxibs). After a one-year wash-out period, we followed 4 660 475 adults, including 74 001 with IJD (RA: 39 050, PsA: 20 803, and axSpA: 18 591) for a median of 9.0 years. Crude PE incidence rates per 1000 patient years were 2.02 in IJD and 1.01 in non-IJD individuals. Age and sex adjusted hazard ratios for PE events were 1.57 for IJD patients compared to non-IJD. Incidence rate ratios (IRR) [95% confidence interval (CI)] for PE during tNSAIDs use were 0.78 (0.64–0.94, $P = 0.010$) in IJD and 1.68 (1.61–1.76, $P < 0.001$) in non-IJD. IRR (95% CI) for PE during coxibs use was 1.75 (1.10–2.79, $P = 0.018$) in IJD and 2.80 (2.47–3.18, $P < 0.001$) for non-IJD.

Conclusion Pulmonary embolism rates appeared to be higher in IJD than among non-IJD subjects in our study. Traditional NSAIDs may protect against PE in IJD patients, while coxibs may associated with increased PE risk.

Keywords Pulmonary embolism • Venous thromboembolism • Non-steroidal anti-inflammatory drugs • Inflammatory joint diseases • Rheumatoid arthritis • Psoriatic arthritis • Axial spondyloarthritis

Introduction

Pulmonary embolism (PE) is a common condition associated with significant morbidity and mortality.[1,2] The wide range of risk factors for PE can be summarized by the Virchow's triad: abnormal blood flow, hypercoagulability, and vessel wall damage.[3]

Previous studies suggest that patients with inflammatory joint diseases (IJD), including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA), are predisposed to develop PE.[4–6] While the underlying mechanisms have not been fully elucidated, the high rates of PE in IJD patients are hypothesized to be result of common risk factors such as smoking, systemic inflammation which affects coagulability and vessel wall function, as well as blood stasis due to pain and sedentary lifestyles.[4,6–9] Potential roles of anti-rheumatic and anti-inflammatory drugs have also been discussed, particularly after reports of increased PE risk in users of Janus kinase inhibitors.[10,11]

* Corresponding author. Tel: +47 905 05 926, Fax: + 47 22 45 17 69, Email: eirik.ikdahl@gmail.com

Non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used in treatment of pain, inflammation and stiffness in IJD patients, have also been implicated.[7,12,13]

Non-steroidal anti-inflammatory drugs are a group of drugs that mainly exert their pharmacological effects by inhibiting cyclo-oxygenase (COX) enzymes. Cyclo-oxygenase enzymes are found in two isoforms, COX- and COX-2, with varying properties in terms of constitutive expression and inducibility by inflammation.[14,15] Non-steroidal anti-inflammatory drugs that show non-selective COX inhibition are known as traditional NSAIDs (tNSAIDs), while drugs that block COX-2 selectively are known as coxibs.[14] Previous studies from the general population have revealed a substantially increased risk of PE and atherosclerotic cardiovascular disease in NSAIDs users.[7,16] Interestingly, emerging data suggest that NSAIDs use is not associated with cardiovascular risk in IJD populations and in fact, may even lower the risk.[17–20] A possible explanation could be that suspected thrombogenic adverse effects of NSAIDs are counteracted by their anti-inflammatory, and thus cardio-protective, actions.[18] Whether NSAIDs use is a risk factor for PE in IJD patients or may be a protective factor has not been clarified.

Using the nationwide Norwegian Cardio-Rheuma Registry (NCRR), our goal was to describe the use of NSAIDs over a 10-year period and investigate if PE rates are associated with NSAIDs use in IJD and non-IJD populations.

Methods

Data source

The NCRR has previously been described in detail.[21,22] In short, the registry is based on data from individual-level Norwegian nationwide registers linked by the unique personal identifier given to all Norwegian citizens. The NCRR includes the whole Norwegian adult population (age ≥18 years) during a 10-year period from 1 January 2008 to 31 December 2017. Data includes: (a) Diagnostic code data (International Classification of Diseases, 10th revision [ICD-10] codes) from specialized healthcare (public and private) retrieved from the Norwegian Patient Registry (NPR). Norwegian Patient Registry has excellent data quality with regard to completeness: In 2015, the main diagnosis was recorded in 100% of contacts.[23] (b) Data from the Norwegian National Population Register, which includes birth, sex, yearly income data, yearly highest attained educational level, and immigration/emigration status. (c) Dispensed prescription data according to anatomical therapeutic classification (ATC) codes from the Norwegian Prescription Database (NorPD). For the present project, observation start was either 1 January 2008, date of immigration, or the date of 18th birthday if the two latter had occurred after 1 January 2008. Observation end was the date of first PE event, date of emigration, date of death, or 31 December 2017, whichever occurred first.

Ethical approval information, institution(s), and number(s)

The study was approved by the Norwegian General Data Protection Regulation (16/00482-11/CDG), the South East Health Authority Ethical Committee (2016/588), and the Data Protection Officers at Oslo University Hospital (2016/924) and Diakonhjemmet Hospital (7/12–2019). The NCRR comprises routinely recorded administrative data, and no written consent from study subjects was required.

Identification of IJD patients

The process of identifying and validating individuals with IJD diagnoses in the NCRR has previously been described in detail.[22] In brief, IJD diagnoses were based on the presence of ≥2 relevant ICD-10 code diagnoses (RA: M05 to M06; PsA: M07.0 to M07.3, and L40.5; axSpA: M45, M46.0, M46.1, M46.8, and M46.9) during the 10-year period, of which at least one ICD-10 code had to be the main diagnostic code. We did not have data to determine if the first appearance of an IJD ICD-10 code was also the time of diagnosis, or if there had been a diagnostic delay with potentially high levels of systemic inflammation that would increase PE risk. Therefore, individuals with IJD diagnoses were considered as IJD patients during the whole observation period, regardless of when the first IJD ICD-10 code appeared.

Definition of PE events

Pulmonary embolism events were based on both main and contributory ICD-10 codes of PE (I26.0–I26.9). The reliability of PE coding has not been studied in Norway, but has recently been reported to show acceptable accuracy in a Swedish RA patient cohort.[24] Because the same ICD-10 is used for the PE events as for further follow-up of PE patients, only the first instance was used and the patient was removed from the data set after this event.

Data on dispensed prescriptions

Non-steroidal anti-inflammatory drugs treatment data were derived from NorPD data which includes ATC codes, dosage forms and strengths, number of pills dispensed, defined daily doses , as well as dispension dates in the form of month and year. The following tNSAIDs (ATC code) were dispensed during the 10-year period: Traditional non-selective NSAIDs (tNSAIDs): Indometacin (M01AB01), sulindac (M01AB02), diclofenac (M01AB05, M01AB55), ketorolac (M01AB15), aceclofenac (M01AB16), piroxicam (M01AC01), meloxicam (M01AC06), ibuprofen (M01AE01), naproxen (M01AE02, M01AE52), ketoprofen (M01AE03), dexibuprofen (M01AE14), dexketoprofen (M01AE17), tolfenamic acid (M01AG02), and nabumetone (M01AX01). Furthermore, three coxibs were dispensed: celecoxib (M01AH01), parecoxib (M01AH04), and etoricoxib (M01AH05). Information on NSAIDs for topical use was not obtained. Disease-modifying antirheumatic drugs (DMARD) use was obtained from NorPD and/or from the NPR if given in hospitals.

Statistical analysis

Patient characteristics are expressed as percentages for dichotomized variables, while the non-normally distributed age variable was presented as median with interquartile ranges (IQR). The *t*-test for independent samples and the chi-square test were used as appropriate to compare baseline variables in the IJD subgroups to non-IJD individuals. Age was log-transformed before the analyses were conducted.

To reduce the risk of analysing a follow-up visit after PE as a PE event, the first year of the 10 year-follow up period was used as a wash-out period where all patients who experienced a PE event were excluded from further analyses.

In order to confirm that our data were comparable to previous studies in terms of there being an increased risk for PE in IJD patients compared to non-IJD individuals, we performed the following analyses: PE incidence rates were calculated per 1000 patient years. Cox proportional hazard (PH) regression was applied to estimate hazard ratios (HR) with 95% confidence intervals (CI) for PE during the observation period in the whole IJD patient group and the individual IJD diagnostic groups, compared to non-IJD individuals. In addition to a crude model, two adjusted Cox PH regression models were analysed: one including only sex and age, and one that also included income level and educational status. The variables in the latter model was chosen as surrogates for lacking data on classical PE risk factors, such as physical inactivity, obesity, and smoking. Our dataset did not include information on important risk factors for PE, such as fractures/traumas and other major surgery, central venous lines, hormone replacement therapy, malignancy, thrombophilia, obesity, pregnancy, varicose veins, and immobility or sedentary lifestyles.

Proportional hazard assumptions were tested and confirmed both graphically (log–log plots) and with Schoenfeld residuals. The groups were also compared using Kaplan–Meier time-to-event plots in which PE was plotted against patient age to correct for age differences between groups.

Table 1 Baseline patient characteristics

	IJD (n = 74 001)	RA (n = 39 050)	PsA (n = 20 803)	axSpA (n = 18 591)	Non-IJD (n = 4 660 475)
Age, median (IQR)	53.2* (40.6–64.3)	59.9* (48.1–69.7)	49.6* (39.7–59.3)	42.7* (31.8–54.2)	40.0 (24.9–57.1)
Female	59.6%*	69.7%*	53.8%*	44.9%*	49.6%
Income					
– Lowest tertile	22.8%*	26.1%*	17.8%*	20.4%*	33.5%
– Highest tertile	33.2%*	27.8%*	37.9%*	40.1%*	33.3%
Highest educational attainment					
– Middle school	30.8%*	33.0%*	28.6%*	27.6%*	36.3%
– High school	46.5%*	46.4%*	48.5%*	44.5%*	37.8%
– College/University	22.7%*	20.6%*	22.9%*	27.9%*	26.0%
bDMARD (%)					
– Any	27.8%	27.3%	25.7%	35.4%	–
– TNFi	23.7%	21.2%	22.4%	33.8%	–
csDMARD					
– Any	42.3%	57.1%	44.3%	13.4%	–
– MTX	35.5%	48.4%	38.3%	8.9%	–

IJD: Inflammatory joint disease, RA: Rheumatoid arthritis, PsA: Psoriatic arthritis, SpA: Spondylosing arthritis, n: number, IQR: Inter-quartile ranges, TNF: tumour necrosis factor inhibitors, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, and MTX: Methotrexate. *: $P < 0.001$ for comparisons with non-IJD individuals.

To ensure patient anonymity, the Kaplan–Meier plot was truncated at 100 years of age.

The self-controlled case series (SCCS) method was applied to test if NSAIDs treatment was associated with increased PE rates in IJD populations and non-IJD individuals. In the SCCS method, only patients who develop PE are sampled and the incidence during NSAIDs exposure is compared to the incidence in periods without treatment.[25] The multinomial model is fitted as an associated Poisson model with log link function. Since NorPD does not provide the precise day (only year and moth) of drug dispension, 30 days (1 month) were added to all NSAIDs exposure intervals. We applied the SCCS method to evaluate if PE was associated with use of (1) any type NSAIDs, (2) tNSAIDs, (3) coxibs, and (4) the largest individual NSAIDs types, defined as >5000 annual prescriptions in both the IJD and the non-IJD group. Separate analyses were performed for the whole IJD population, for the non-IJD group, as well as for RA, PsA, and axSpA, separately. Based on previous findings from the general population that PE rates are highest during the first 30 days after NSAIDs treatment,[13] we also performed sensitivity analyses where the exposure intervals were extended to include 60 and 90 days after NSAIDs treatment.

Results

A total of 74 001 IJD patients (RA: 39 050, PsA: 20 803, axSpA 18 591, and overlapping IJD diagnoses: 4268) were identified among the 4 660 475 individuals aged over 18 years in Norway during the 9 years of observation time after the initial one-year wash-out period. Median (IQR) follow-up time was 9.0 (6.8–9.0) years (data not shown). RA patients were older and more often female, while most axSpA patients were male (*Table 1*). Non-IJD individuals were more likely to be in the in the lowest income tertile and have lower educational attainment, while RA patients were less often in the highest income and educational groups ($P < 0.001$ for all).

Incidence of PE

After exclusion of the 3865 patients with ICD-10 codes of PE during the wash-out period, 35 276 initial PE events were identified in the Norwegian adult population during the 9-year observation period. Crude PE incidence rates per 1000 patient years was 2.02 in IJD patients, ranging from 2.71 in RA patients to 1.16 in axSpA patients, and 1.01 among non-IJD patients (*Table 2*). Age and sex adjusted Cox regression models comparing the risk of PE to that of non-IJD individuals yielded HR (95% CI) of 1.57 (1.49–1.67, $P < 0.001$) in the whole IJD group, ranging from 1.67 (1.56–1.79, $P < 0.001$) in RA, to 1.45 (1.28–1.63, $P < 0.001$) and 1.39 (1.20–1.61, $P < 0.001$) in PsA and axSpA, respectively. Cox regression models that also included income and educational levels yielded relatively similar effect sizes, while unadjusted models returned considerably lower effect sizes for axSpA and higher in RA patients, mainly due to the strong relation between age and PE risk. *Figure 1* shows a Kaplan–Meier plot of the proportion of patients without PE plotted against age.

NSAIDs use

Dispensed NSAIDs prescription data in the IJD and non-IJD populations during the 10-year observation period are plotted in *Figure 2*. Diclofenac, ibuprofen, and naproxen were the most commonly prescribed tNSAIDs in all groups (>5000 annual prescriptions in both the IJD and non-IJD groups). Additional plots of dispensed prescription data for each drug class is available in supplementary data. The median (IQR) number of NSAIDs treatment courses during the observation period per IJD patient was 9 (5–13) compared to 5 (3–10) in the non-IJD population. Median length of each NSAIDs treatment course was also longer in IJD than in non-IJD patients. In total, IJD patients were exposed to any NSAID during 14.0% of the total patient observation time (RA 12.2%, PsA 14.5%, and axSpA 17.7%), non-IJD patients were on NSAIDs for 3.0% of the observation time.

NSAIDs and PE risk

Figure 3 displays the results of the SCCS analyses, shown as incidence rate ratios (IRR) for PE during exposure to NSAIDs vs. non-exposure periods. While the risk of PE during any NSAIDs therapy was significantly reduced in RA patients with IRR (95% CI) of 0.77 (0.61–0.98), $P = 0.031$, the risk was highly significantly increased in non-IJD individuals: 1.77 (1.69–1.84), $P < 0.001$. The IRR for the total IJD, PsA,

Table 2 Pulmonary embolism in IJD patients vs. non-IJD individuals

	Patients with PE events (%)	PE incidence (per 1000 patient years)	Unadjusted model, HR (95% CI)	Adjusted model, HR (95% CI)*	Adjusted model, HR (95% CI)[α]
IJD	1247 (1.69%)	2.02	1.97 (1.86–2.09) $P < 0.001$	1.57 (1.49–1.67) $P < 0.001$	1.57 (1.48–1.66) $P < 0.001$
RA	861 (2.20%)	2.71	2.65 (2.47–2.83) $P < 0.001$	1.67 (1.56–1.79) $P < 0.001$	1.65 (1.54–1.77) $P < 0.001$
PsA	268 (1.29%)	1.49	1.46 (1.30–1.65) $P < 0.001$	1.45 (1.28–1.63) $P < 0.001$	1.46 (1.29–1.65) $P < 0.001$
axSpA	183 (0.98%)	1.16	1.11 (0.97–1.29) $P = 0.137$	1.39 (1.20–1.61) $P < 0.001$	1.39 (1.20–1.61) $P < 0.001$
Non-IJD	34 029 (0.73%)	1.01	–	–	–

PE: Pulmonary embolism, HR: Hazard ratio, CI: Confidence interval, IJD: Inflammatory joint disease, RA: Rheumatoid arthritis, PsA: Psoriatic arthritis, and axSpA: Axial spondylarthritis

*Logistic regression vs. non-IJD. Adjusted for age and sex

[α] Logistic regression vs. non-IJD. Adjusted for age, sex, income level, and educational status.

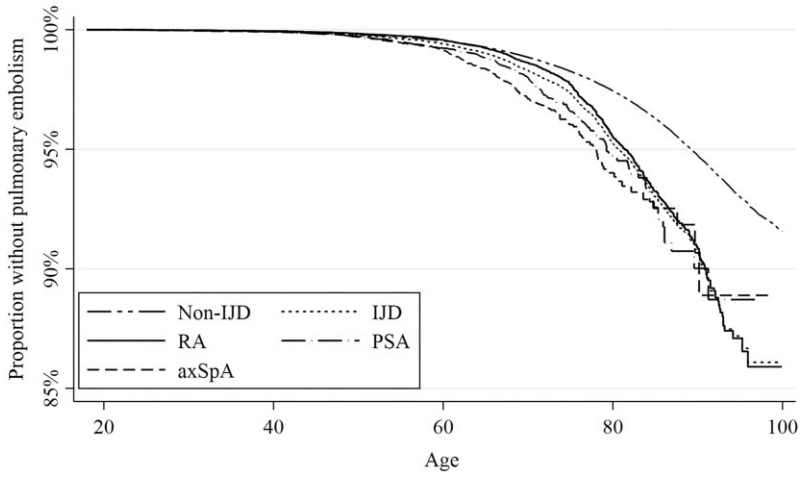

Figure 1 Kaplan–Meier plot of proportion of patients without PE plotted against patient age. IJD: Inflammatory joint disease, RA: Rheumatoid arthritis, PSA: Psoriatic arthritis, and axSpA: Axial spondyloarthropathy.

and axSpA groups were not statistically significant in analyses of all NSAIDs types.

Analyses that included only tNSAIDs exposure yielded significant reduced IRR (95% CI) of 0.78 (0.–0.94), $P = 0.010$, and 0.74 (0.58–0.95), $P = 0.016$ in the whole IJD group and in RA patients, respectively. The IRR estimates for PSA and axSpA patients were comparable to that of IJD and RA, but not statistically significant. Estimates of increased PE risk during tNSAIDs exposure remained highly significant in the non-IJD population, IRR (95% CI) 1.68 (1.61–1.76), $P < 0.001$. There were no statistically significant associations with PE in IJD patients during exposure to the three most commonly prescribed individual tNSAIDs (Diclofenac, Ibuprofen, and Naproxen). On the contrary, all three individual tNSAIDs showed highly significant associations to PE in the non-IJD group, with IRR (95% CI) ranging from 1.75 (1.65–1.85) with diclofenac to 2.14 (1.93–2.36) with naproxen, $P < 0.001$ for all.

PE rates during treatment with coxibs (approximately 2/3 etoricoxib and 1/3 celecoxib, data not shown) were increased in both IJD and non-IJD individuals, with an IRR (95% CI) for PE of 1.75 (1.10–2.79), $P = 0.018$, and 2.80 (2.47–3.18), $P < 0.001$, respectively.

Due to lack of statistical power, analyses of PE incidence and the individual NSAIDs and coxibs were only performed for the IJD group as a whole, and not for the individual IJD subentities. Sensitivity analyses in which the 30 days after NSAIDs treatment was expanded to 60 and 90 days are shown in *Figure 1* of Supplementary material. The IRR for PE remained relatively unchanged in IJD-patients, while it was slightly reduced over time in the non-IJD group. Furthermore, we identified 32 patients in the SCCS-analyses (6 with IJD, 26 non-IJD) who had received NSAIDs for the whole observation period and therefore did not have an observation period without treatment. Additional analyses where these patients were excluded did not affect our results and conclusion.

Discussion

Using registry data from the nationwide NCRR, we have shown that while both tNSAIDs and coxibs are associated with increased PE rates

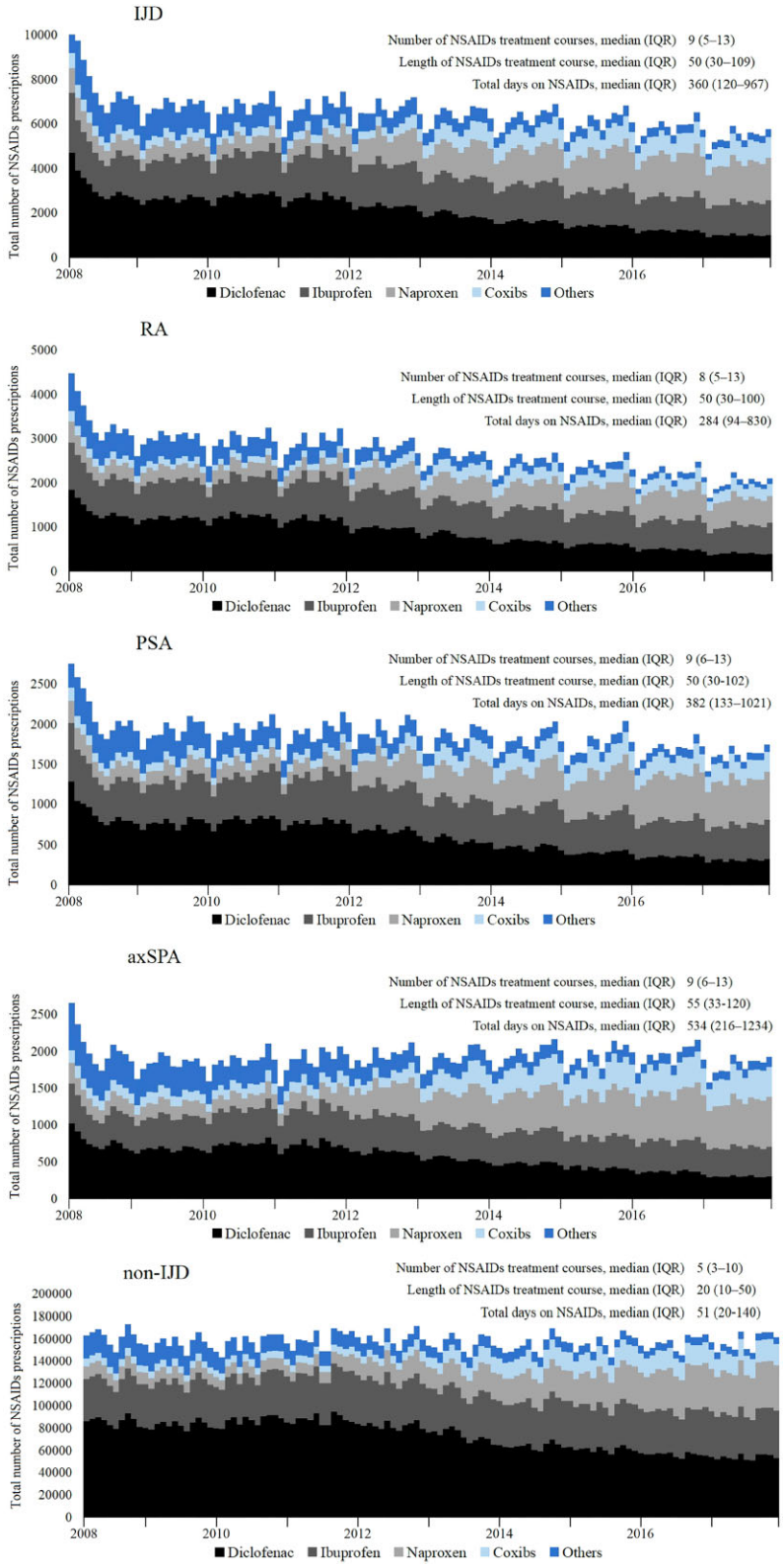

Figure 2 Number of NSAIDs prescriptions across IJD and non-IJD populations.

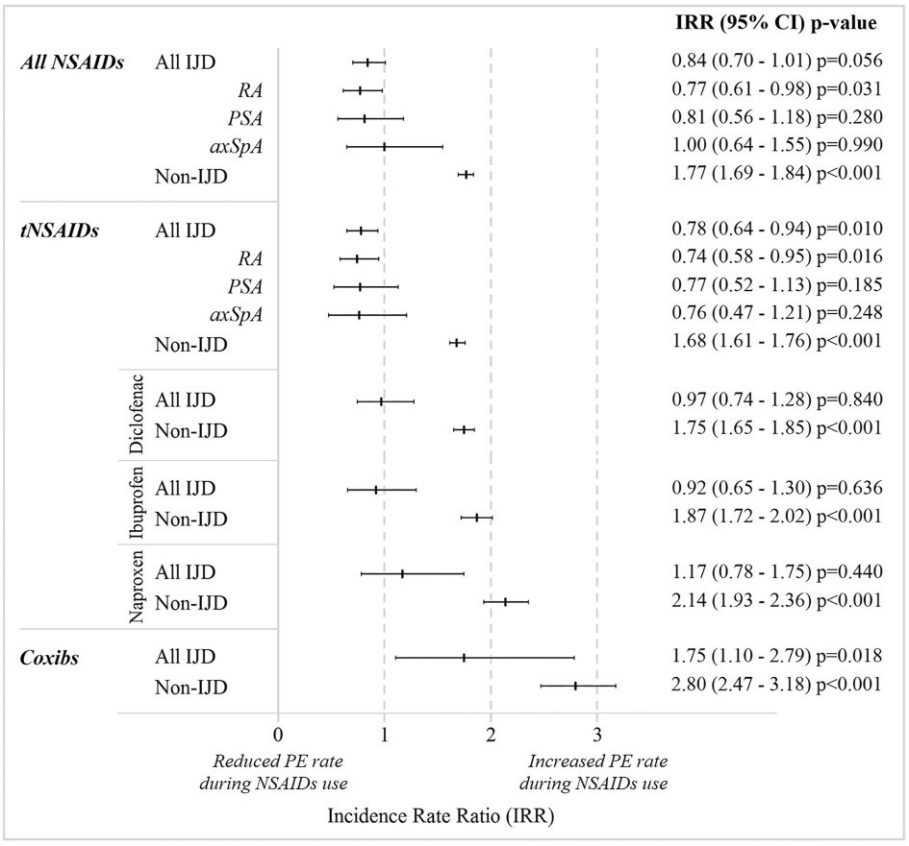

Figure 3 Incidence rate ratios for PE during NSAIDs treatment vs. periods without NSAIDs in IJD and non-IJD populations. NSAIDs: Non-steroidal anti-inflammatory drugs, IJD: Inflammatory joint disease, IRR: Incidence rate ratio, CI: Confidence interval, tNSAIDs: traditional NSAIDs, Rheumatoid arthritis, PsA: Psoriatic arthritis, axSpA axial spondylarthritis, and PE: Pulmonary embolism.

in non-IJD subjects, only coxibs are linked with PE in IJD patients. In fact, tNSAIDs treatment was associated with reduced PE rates in IJD patients in Norwegian nationwide data from 2008 to 2017.

Our results also corroborate previous reports on the increased risk of PE in IJD patients. The existing evidence concerning the increased risk of PE in IJD patients is particularly strong for RA patients. A 2021 meta-analysis by Hu *et al.* presented an OR of 2.15 for PE in RA patients compared to non-IJD individuals.[4] However, the HR for PE from the 6 studies included in the meta-analyses varied from 1.25 to 2.73, with studies including older data generally reporting higher estimates for PE. In fact, the study based on the most recent data (1999–2018) found a HR for PE of 1.57, which is similar to our adjusted results.[26] Further studies are warranted to investigate whether improved therapies for RA over the last decades has resulted in lowered PE rates. The existing documentation on PE risk in PsA and axSpA is less solid. In PsA, two previous studies have reported HR for PE varying from 1.08 to 1.84,[6,26] and for or axSpA, one previous study has reported a HR for PE of 1.62 compared to controls.[5]

It has been two decades since the first report of increased PE risk during NSAIDs treatment in the general population.[12] A meta-analysis compiling evidence from 6 studies revealed a pooled risk ratio of 1.80 for PE in NSAIDs users.[7] The risk appears to be independent of surgery, trauma, and malignancy, and has been reported to be highest during the first 30 days after treatment.[13] We report a quite similar IRR of 1.77 for PE among non-IJD subjects during any NSAIDs treatment.

Based on data from the general population, a thrombogenic effect by NSAIDs has been assumed as a contributing cause to the high rates of venous thromboembolic events (VTE), including PE seen in IJD patients.[4,6,7] Our finding that IJD patients were treated with NSAIDs for 14% of the observation period highlights the important role of these drugs in treatment of IJD.[27–29] Nevertheless, to our knowledge only one previous study has investigated a possible association between VTE and NSAIDs in IJD populations: In a general population-based cohort study by Ogdie *et al.*, multivariable models, including NSAIDs as a covariate revealed a significant hazard ratio of 1.33 risk for VTE among PsA patients who were NSAIDs users.[6] In contrast, our data strongly suggests that no such association exists for IJD patients. In fact, tNSAIDs appeared to protect against PE in the total IJD group and in RA patients. For the smaller PsA and axSpA subgroups, the results were not statistically significant, most likely due to low statistical power for comparisons.

While Ogdie *et al.* compared PE rates in NSAIDs users and non-users, we applied the SCCS method. The SCCS method is designed to investigate associations between acute outcomes and transient exposures.[25] Since SCCS only uses data on individuals who have experienced the outcome of interest (i.e. PE events), inference is within individuals and thus, fixed covariate effects are controlled for. However, the SCCS method does not take into account possible confounding by indication, i.e. the presence of an indication for the exposure that is the true cause of the outcome. Accordingly, as with previous studies, our results are not proof of a causal relation between

NSAIDs use and PE in non-IJD individuals. However, since most, if not all, indications for NSAIDs are also risk factors for PE (e.g. pain, fever, and inflammation),[3] our result that tNSAIDs may reduce PE rates in IJD populations cannot be explained by such confounding. We cannot exclude the possibility of channelling bias, whereby physicians who recognize an increased risk of PE in patients refrain from prescribing NSAIDs. However, this seems like an unlikely explanation of our findings as PE is difficult to predict for the clinician and as such a bias would apply to both cases and controls. Investigations into underlying mechanisms for a protective role of tNSAIDs with regards to PE risk in IJD patients were beyond the scope of the current study. Previous studies have indicated that even though NSAIDs increase the risk of arterial cardiovascular events in long-term users for analgesic indications, they may in fact be cardioprotective in IJD patients due to their anti-inflammatory properties.[18] Future studies are warranted to explore whether the anti-inflammatory properties of NSAIDs may also counterbalance their possible direct venous thrombogenic effects. Moreover, it would be interesting to see future studies in which similar analyses are applied in cohorts of patients with other disorders, such as osteoarthritis and cancer.

In contrast to the tNSAIDs, coxib use was associated with increased PE rates in both IJD and non-IJD populations. Direct comparisons of tNSAIDs vs. coxibs are not feasible in the SCCS method and application of other statistical methods would entail unacceptable risk of confounding. It could also be a result of channeling bias, meaning that patients could be more likely to be prescribed a coxib than an NSAID during a period of high PE risk. Even with these reservations in mind, it is interesting that PE rates in non-IJD subjects appeared to be even higher during coxib treatment than with tNSAIDs. The latter observation is also in line with results from previous studies.[7] There exist theories regarding the balance of COX-/COX-2 selectivity and COX-2 affinity as the cause of their association with atherosclerotic cardiovascular disease, which remain disputed to date.[30] Our results that selective COX-2 inhibition by coxibs are associated with increased PE rates in IJD patients, when non-selective COX-inhibition appear to lower the risk, may be valuable input into further investigations into this important clinical situation and research question.

There are several limitations to our study. First, we did not have data on important risk factors for PE. Thus, the statistical analyses for comparisons of PE risk in IJD vs. non-IJD did not include important covariates, which could have biased our estimates and interpretation of our results has to be with this in mind. Second, our data only include dispensed prescriptions and not over-the-counter NSAIDs use (naproxen 250 mg, ibuprofen 200, and ibuprofen 400 mg are available over-the-counter NSAIDs in Norway). However, we deem it unlikely that the degree of use of over-the-counter NSAIDs would be so different in IJD and non-IJD individuals that this could have affected our results. Also, we had no information on if and when the NSAIDs were taken. Third, our data only included the month, and not day, that NSAIDs were dispensed, which hampered more precise investigations into temporal relationships. Fourth, since registry data were used, we are not able to ascertain how the PE was diagnosed. However, it is unlikely that PE diagnoses are made without proper investigations. Fifth, we did not have information on other patient characteristics that could influence PE risk, including levels of systemic inflammation. Sixth, the study was performed in a Norwegian population, which may have unique demographic, genetic, lifestyle, and disease activity characteristics which may limit the generalizability of our findings to other IJD populations. Lastly, we had to handle PE, which is a possibly recurrent event, into a non-recurrent event due to previously mentioned problems with ICD-10 codes being used both for the actual event as well as for follow-up. The latter issue also means that we were not able to exclude the possibility that the first event was in fact a contact for follow-up of a previous PE. However, we argue that the chance for this occurring would not be different during periods with and without NSAIDs therapy.

In conclusion, we have shown for the first time that tNSAIDs use may be protective against PE in IJD populations, while coxibs were associated with increased PE rates. Based on our findings, we do not think that clinicians should refrain from prescribing tNSAIDs to IJD patients due to the concern of PE. However, caution may be exercised when prescribing coxibs to IJD patients with other risk factors for PE. Future studies are warranted to investigate the mechanisms underlying the potentially protective role of tNSAIDs for PE in IJD patients.

Supplementary material

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

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Data availability

Due to legal and privacy considerations, the research data that support the findings of this study will not be made available to the public.

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