responses. In the absence of randomized trial data, our timely controlled study—small numbers notwithstanding—provides supportive evidence that SLIT protects susceptible individuals from ETA. We suggest consideration of preseasonal Oralair for 3 years for patients with SAR meeting SLIT guidelines (13). The 2016 Melbourne ETA disaster must drive radical change in the management of SAR and asthma. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Nonsteroidal Antiinflammatory Drug Use and Clinical Outcomes of Community-acquired Pneumonia

To the Editor:

Nonsteroidal antiinflammatory drugs (NSAIDs) may negatively affect local airway immunity and may also attenuate warning signs, including inflammation, fever, and pain, during the course of community-acquired pneumonia (CAP) (1–3). This may result in delayed antibiotic therapy and other clinical care. There is a growing body of evidence linking NSAID intake to pleuropulmonary complications of CAP, but large-scale epidemiological data remain scarce (1–8). We therefore undertook a population-based study in northern Denmark (1.8 million residents) to evaluate NSAID use as a prognostic factor for clinical outcomes in patients hospitalized with CAP.

Methods

We used the Danish National Patient Registry to identify all patients (>15 yr old) with hospitalized CAP in the period 1997–2011, defined as a first-time incident hospital admission with a primary diagnosis of pneumonia, lung abscess, pyothorax, or pleural effusion coded with secondary pneumonia (International Classification of Diseases, 10th revision: J10–J18, A37, A481, A709, J85, J86, and J90). We excluded patients with any recent inpatient hospitalization within 1 month before CAP admission (the index date). Complete information on comorbidities, medications, complications, and death was obtained from medical databases.

We defined current NSAID users as persons who had filled an NSAID prescription within 60 days before the index date. We further categorized current users into two groups: longer-term users (current users who had filled a previous NSAID prescription 61–365 days before the index date) and new users (current users with a first-ever NSAID prescription within 60 days before the index date). Former NSAID users were defined as patients who had redeemed their most recent prescription 61–365 days before the index date. Nonusers were persons with no redeemed NSAID prescriptions 365 days before the index date (reference group).

We computed adjusted rate ratios (aRRs) of pleuropulmonary complications (pleural empyema or lung abscess) and adjusted 30-day mortality RRs (aMRRs) associated with exposure to NSAID use, using Poisson regression analyses to adjust for age, sex, Charlson comorbidity index score, alcoholism, and use of immunomodulatory drugs, antibiotics, or paracetamol. We applied

Author Contributions: Concepts, manuscript review, and final approval of the manuscript: all authors. Literature search: D.B. and R.W.T. Data analysis and interpretation: D.B., R.W.T., M.M., C.A., V.J., and H.T.S. Manuscript preparation: D.B., R.W.T., C.A., V.J., and H.T.S.

Originally Published in Press as DOI: 10.1164/rccm.201802-0229LE on February 20, 2018

Table 1. Rates of Pleuropulmonary Complications (Empyema or Lung Abscess) in Community-acquired Pneumonia according to NSAID Use, Overall and Stratified by Age and Comorbidity

	Study Population	Complications [*n (%)*]	Crude RR (95% CI)	Adjusted RR (95% CI)
Overall cohort				
NSAID nonusers	40,548	922 (2.3)	1 (referent)	1 (referent)
NSAID former users	9,690	232 (2.4)	1.05 (0.91–1.21)	1.10 (0.95–1.27)
NSAID current users	9,012	344 (3.8)	1.68 (1.49–1.90)	1.81 (1.60–2.05)
NSAID longer-term users	6,718	202 (3.0)	1.32 (1.14–1.54)	1.51 (1.29–1.75)
NSAID new users	2,294	142 (6.2)	2.72 (2.29–3.23)	2.48 (2.09–2.94)
Young adults (18–44 yr)				
NSAID nonusers	5,578	140 (2.5)	1 (referent)	1 (referent)
NSAID former users	1,065	30 (2.8)	1.12 (0.76–1.66)	1.20 (0.82–1.78)
NSAID current users	894	71 (7.9)	3.16 (2.40–4.17)	3.48 (2.64–4.60)
NSAID longer-term users	372	25 (6.7)	2.68 (1.77–4.04)	3.08 (2.03–4.68)
NSAID new users	522	46 (8.8)	3.51 (2.55–4.84)	3.73 (2.71–5.13)
Middle-aged adults (45–64 yr)				
NSAID nonusers	9,824	372 (3.8)	1 (referent)	1 (referent)
NSAID former users	2,408	97 (4.0)	1.06 (0.85–1.32)	1.11 (0.89–1.38)
NSAID current users	2,152	147 (6.8)	1.80 (1.50–2.17)	1.90 (1.58–2.30)
NSAID longer-term users	1,481	81 (5.5)	1.44 (1.14–1.83)	1.57 (1.24–1.98)
NSAID new users	671	66 (9.8)	2.60 (2.02–3.33)	2.53 (1.97–3.24)
Older adults (65–79 yr)				
NSAID nonusers	13,660	285 (2.1)	1 (referent)	1 (referent)
NSAID former users	3,445	65 (1.9)	0.90 (0.69–1.18)	0.97 (0.74–1.27)
NSAID current users	3,156	83 (2.6)	1.26 (0.99–1.60)	1.36 (1.06–1.74)
NSAID longer-term users	2,535	64 (2.5)	1.21 (0.93–1.58)	1.32 (1.00–1.73)
NSAID new users	621	19 (3.1)	1.47 (0.93–2.32)	1.51 (0.95–2.38)
Oldest old adults (⩾80 yr)				
NSAID nonusers	11,486	125 (1.1)	1 (referent)	1 (referent)
NSAID former users	2,772	40 (1.4)	1.33 (0.93–1.89)	1.28 (0.90–1.83)
NSAID current users	2,810	43 (1.5)	1.41 (1.00–1.98)	1.34 (0.95–1.90)
NSAID longer-term users	2,330	32 (1.4)	1.26 (0.86–1.86)	1.21 (0.82–1.77)
NSAID new users	480	11 (2.1)	2.11 (1.14–2.87)	2.02 (1.10–3.71)
Low Charlson comorbidity index score (0)				
NSAID nonusers	18,219	487 (2.7)	1 (referent)	1 (referent)
NSAID former users	3,607	108 (3.0)	1.12 (0.91–1.38)	1.13 (0.92–1.39)
NSAID current users	3,350	195 (5.8)	2.18 (1.85–2.56)	2.29 (1.94–2.70)
NSAID longer-term users	2,109	91 (4.3)	1.61 (1.30–2.01)	1.81 (1.45–2.26)
NSAID new users	1,241	104 (8.4)	3.41 (2.56–3.84)	2.92 (2.39–3.57)
Medium Charlson comorbidity index score (1, 2)				
NSAID nonusers	15,088	306 (2.0)	1 (referent)	1 (referent)
NSAID former users	3,891	81 (2.1)	1.03 (0.81–1.31)	1.05 (0.82–1.34)
NSAID current users	3,678	98 (2.7)	1.31 (1.05–1.64)	1.37 (1.09–1.71)
NSAID longer-term users	2,953	71 (2.4)	1.19 (0.92–1.53)	1.27 (0.98–1.63)
NSAID new users	725	27 (3.7)	1.84 (1.25–2.70)	1.72 (1.17–2.52)
High Charlson comorbidity index score (⩾3)				
NSAID nonusers	7,241	129 (1.8)	1 (referent)	1 (referent)
NSAID former users	2,192	43 (2.0)	1.10 (0.78–1.55)	1.10 (0.79–1.54)
NSAID current users	1,984	51 (2.6)	1.44 (1.05–1.99)	1.49 (1.08–2.05)
NSAID longer-term users	1656	40 (2.4)	1.36 (0.95–1.93)	1.39 (0.98–1.98)
NSAID new users	328	11 (3.4)	1.88 (1.03–3.45)	1.95 (1.06–3.57)

Definition of abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; NSAID = nonsteroidal antiinflammatory drug; RR = rate ratio. NSAID current users: persons who had filled an NSAID prescription within 60 days before the CAP index date. Longer-term users: current NSAID users who had filled a previous NSAID prescription 61–365 days before the index date. New users: current users with a first-ever NSAID prescription within 60 days before the index date. Former NSAID users: patients who had redeemed their most recent prescription 61–365 days before the index date. Nonusers: persons with no redeemed NSAID prescriptions 365 days before the index date. See text.
Rate ratios for pleuropulmonary complications were adjusted for age, sex, Charlson comorbidity index score, alcoholism, and use of immunomodulatory drugs, antibiotics, or paracetamol.

sensitivity analyses with different NSAID exposure windows before CAP to counteract any possible protopathic bias. We also performed stratified analyses by age category and Charlson comorbidity index score. We used SAS software version 9.4 (SAS Institute Inc.).

Results

We identified 59,250 patients with a first-time CAP diagnosis. Of these, 9,012 (15.2%) were current NSAID users (including 2,294 [3.9%] new users and 6,718 [11.3%] longer-term users), and 9,690

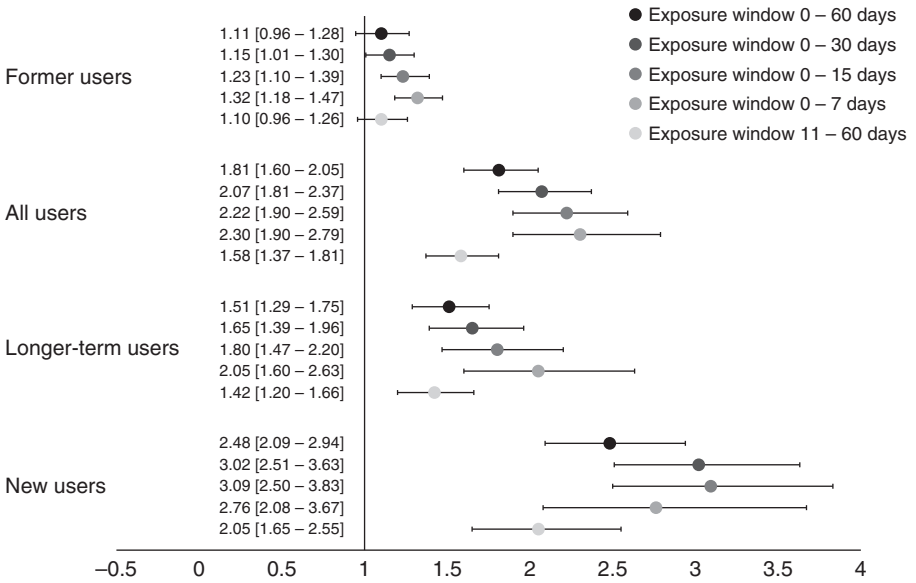

Figure 1. Adjusted rate ratios (aRRs) with 95% confidence intervals of pleuropulmonary complications of community-acquired pneumonia (CAP) according to five exposure definitions of nonsteroidal antiinflammatory drug (NSAID) use. NSAID nonusers were considered as the reference group. The aRRs for the different user groups (all users, new users, and longer-term users) increased when the exposure windows were shortened to include only the days immediately preceding admission. When the last 10 days preceding CAP admission were excluded from the definition of current NSAID use (exposure window 11–60 d), the aRRs were lower but still substantially increased.

(16.4%) were former users. New NSAID users were younger, had fewer comorbid conditions, and used fewer concurrent medications than current longer-term users or former users, but more often received antibiotics before CAP admission.

Current NSAID users had a higher risk of pleuropulmonary complications (3.8%) compared with both former users (2.4%) and nonusers (2.3%). After adjustment for confounders, the aRR was 1.81 (95% confidence interval [CI], 1.60–2.05) for all current NSAID users, 1.51 (95% CI, 1.29–1.75) for current longer-term users, and 2.48 (95% CI, 2.09–2.94) for current new users (Table 1). In contrast, the aRR was 1.10 (95% CI, 0.95–1.27) for former NSAID users. As a point of comparison, the complication aRR associated with current paracetamol use was 0.97 (95% CI, 0.86–1.09). Among current NSAID users, a stratified analysis showed the highest complication aRRs in young patients (18–44 yr; aRR = 3.48 [95% CI, 2.64–4.60]) and in patients without comorbidities (aRR = 2.29 [95% CI, 1.94–2.70]). Results remained robust in several sensitivity analyses with various definitions of the NSAID exposure window (Figure 1), and the highest aRRs were observed for new use with a prescription filled within 0–7 days before CAP. Thirty-day mortality was 11.5% in current NSAID users, 10.1% in former users, and 9.7% in nonusers. Current NSAID intake was not associated with 30-day mortality (aMRR = 1.01 [95% CI, 0.96–1.07]).

Discussion

We found a clear association between NSAID intake and increased risk of pleuropulmonary complications, especially in young and healthy people. This was observed for both new and longer-term NSAID use, with the highest RRs among new users. The effect size among new NSAID users was consistent with that recently reported in a smaller clinical French cohort based on prospectively collected data from hospitalized individuals with CAP (1).

Previous studies have indicated that NSAID use may delay hospital admission or antibiotic initiation because NSAIDs decrease the occurrence of warning signs such as fever and chest pain (1–3). Our study design did not allow us to investigate this further. Nonetheless, because we did not observe an association with pleuropulmonary complications in users of paracetamol (which has similar effects on warning signs), our results suggest a specific pharmacological action of NSAIDs.

The strengths of this study include a large sample size, use of routinely collected clinical data, and a population-based design with access to individual-level information. Follow-up for pleuropulmonary outcomes and death was virtually complete.

The limitations of this study include its registry-based nature, which prevented us from identifying clinical observations of parapneumonic effusion with reasonable completeness, and led us to restrict our analysis to clinically severe pleuropulmonary complications with well-defined discharge diagnosis codes. The positive predictive value of empyema codes used in our study is documented to be high, that is, 90% (9). The potential of prescription registries to capture individual-level NSAID use in Denmark is estimated at 66% for ibuprofen and 100% for all other nonaspirin NSAIDs (10).

Our sensitivity analyses suggest that some protopathic bias exists, with some patients likely receiving an NSAID at the onset of as yet undiagnosed pleuropulmonary complications to control symptoms such as chest pain and fever. However, even after excluding all patients who redeemed their last NSAID prescription within 10 days before hospital admission, we observed a clear association with pleuropulmonary complications among new NSAID users (Figure 1). Because we also observed a significant association with pleuropulmonary complications in longer-term users, we believe that this association cannot be explained solely by protopathic bias.

In conclusion, we found that NSAID use was associated with an increased risk of pleuropulmonary complications in patients hospitalized with CAP. Our findings may raise a caution regarding the frequent use of NSAIDs in patients with CAP. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Expiratory Flow Limitation Assessment in Patients with Acute Respiratory Distress Syndrome

A Reappraisal

To the Editor:

Expiratory flow limitation (EFL), the lack of an increase in expiratory flow at the same lung volume in response to an increase in the expiratory driving pressure, heralds airway closure (1). As EFL during tidal breathing entails cyclic compression and the reexpansion of peripheral airways with a concurrent risk of lung injury, detecting EFL and abolishing it with the appropriate positive end-expiratory pressure (PEEP) levels are imperative in lung-protective ventilatory strategies. EFL was previously studied during mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) on zero end-expiratory pressure (2). Because the negative expiratory pressure technique (2) is no longer used, we aimed to assess EFL in patients with ARDS at PEEP 5 cm H_2O (PEEP 5) using the atmosphere method, and to compare patients with EFL and those with no flow limitation (NFL) with regard to respiratory mechanics, impact of PEEP, and patient outcomes.

Methods

We performed a secondary analysis of patients with ARDS who were included in a single-center study (3) and a two-center study (NCT02416037) of lung imaging. Sixty-five patients were investigated at PEEP 5, and 51 of these patients were further investigated at PEEP 15 cm H_2O (PEEP 15). The protocol for the two-center study was approved by the ethics committee (No. 2013-AO1116-39), and written informed consent was obtained from the next of kin. Patients who had been intubated, sedated, and paralyzed were given mechanical ventilation in volume-controlled mode at constant flow inflation with an Evita XL (Drager) in a semirecumbent position. Airway pressure and flow were measured proximal to the endotracheal tube. At each PEEP 5 or 15, randomly applied for 10 minutes each, the following protocol was performed: First, arterial blood gas was measured. Then, a 3-second end-expiratory airway occlusion followed by a 3-second end-inspiratory airway occlusion were performed. The low-flow technique at 7 L/min constant flow was then used to obtain the inspiratory pressure–volume (PV) curve from the ventilator, with airway pressure and flow continuously recorded in a data logger. After 10 baseline breaths, the patient was disconnected manually from

Author Contributions: Conception and design: C.G. Analysis and interpretation: H.Y., S.M., C.G., L.B., and A.M. Drafting the manuscript for important intellectual content: H.Y., S.M., L.B., A.M., and C.G.

Originally Published in Press as DOI: 10.1164/rccm.201711-2326LE on February 21, 2018