Citation: Clin Transl Sci (2020) 13, 1103–1107; doi:10.1111/cts.12904

ARTICLE

Association Between Prescribed Ibuprofen and Severe COVID-19 Infection: A Nationwide Register-Based Cohort Study

Kristian Kragholm[1,2,*], Thomas A. Gerds[3], Emil Fosbøl[4], Mikkel Porsborg Andersen[5], Matthew Phelps[6], Jawad H. Butt[4], Lauge Østergaard[4], Casper N. Bang[5,6], Jannik Pallisgaard[7], Gunnar Gislason[6,7], Morten Schou[7], Lars Køber[4] and Christian Torp-Pedersen[5]

Recommendations regarding ibuprofen use in relation to coronavirus disease 2019 (COVID-19) have been conflicting. We examined the risk of severe COVID-19 between ibuprofen-prescribed and non-ibuprofen patients with COVID-19 in a nationwide register-based study of patients with COVID-19 in Denmark between the end of February 2020 and May 16, 2020. Patients with heart failure (n = 208), < 30 years (n = 575), and prescribed other nonsteroidal anti-inflammatory drugs (n = 57) were excluded. Patients with ibuprofen prescription claims between January 1, 2020, and before COVID-19 diagnosis or April 30, 2020 (last available prescription) were compared with patients without ibuprofen prescription claims. Outcome was a 30-day composite of severe COVID-19 diagnosis with acute respiratory syndrome, intensive care unit admission, or death. Absolute risks and average risk ratios comparing outcome for ibuprofen vs. non-ibuprofen patients standardized to the age, sex, and comorbidity distribution of all patients were derived from multivariable Cox regression. Among 4,002 patients, 264 (6.6%) had ibuprofen prescription claims before COVID-19. Age, sex, and comorbidities were comparable between the two study groups. Standardized absolute risks of the composite outcome for ibuprofen-prescribed vs. non-ibuprofen patients were 16.3% (95% confidence interval (CI) 12.1–20.6) vs. 17.0% (95% CI 16.0–18.1), P = 0.74. The standardized average risk ratio for ibuprofen-prescribed vs. non-ibuprofen patients was 0.96 (95% CI 0.72–1.23). Standardized absolute risks of the composite outcome for patients with ibuprofen prescription claims > 14 days before COVID-19 vs. ≤ 14 days of COVID-19 were 17.1% (95% CI 12.3–22.0) vs. 14.3% (95% CI 7.1–23.1). In conclusion, in this nationwide study, there was no significant association between ibuprofen prescription claims and severe COVID-19.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Recommendations regarding ibuprofen use in relation to coronavirus disease 2019 (COVID-19) have been conflicting and to date, no studies have addressed the risk of severe COVID-19 between ibuprofen and non-ibuprofen users.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Is ibuprofen prescription redemption associated with severe outcome of COVID-19?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ In this nationwide study, there was no significant association between ibuprofen prescription claims and severe COVID-19.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Ibuprofen prescription to patients with COVID-19 does not appear to be associated with severe COVID-19 trajectory.

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to substantial changes in healthcare utilization, morbidity, intensive care resources, and mortality.[1–7] The entry point for this novel coronavirus for its further pathogenesis in humans is thought to be through an angiotensin-converting enzyme 2 receptor found in the lungs, arteries, heart, kidneys, and intestines.[8] Nonsteroidal anti-inflammatory drugs (NSAIDs) might facilitate and aggravate infection with COVID-19.[9,10] The mechanisms may include upregulation of the angiotensin-converting enzyme 2 enzyme expression and delayed diagnostics

[1]Unit of Clinical Biostatistics and Epidemiology, Aalborg University Hospital, Aalborg, Denmark; [2]Departments of Cardiology, North Denmark Regional Hospital and Aalborg University Hospital, Aalborg, Denmark; [3]Department of Biostatistics, Copenhagen University, Copenhagen, Denmark; [4]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; [5]Department of Clinical Research, Nordsjaellands Hospital, Hillerød, Denmark; [6]The Danish Heart Foundation, Copenhagen, Denmark; [7]Department of Cardiology, Herlev-Gentofte Hospital, Copenhagen, Denmark. *Correspondence: Kristian Kragholm (kdks@rn.dk)
Received: July 24, 2020; accepted: September 10, 2020. doi:10.1111/cts.12904

by masking inflammation and fever.[9,10] Initially, the World Health Organization (WHO) and national health boards issued a warning against the use of NSAIDs in patients with COVID-19 and that paracetamol or acetaminophen should be administered instead. However, later and current WHO and European Medicine Agency recommendations do not call for avoidance of ibuprofen to treat COVID-19 symptoms, based on the lack of evidence to support the initially recommended warning.[10] The US Food and Drug Administration (FDA) has stated their awareness of reports of potential worsening of COVID-19 infection based on NSAID use, but the agency also stresses that there is currently insufficient evidence to support that NSAID should worsen the clinical course of COVID-19 infection. Therefore, given the current uncertainty about whether NSAID should be avoided in patients with COVID-19, we performed a nationwide register-based study to evaluate the risk of severe COVID-19 infection with recent ibuprofen prescription claims. Because very few patients were prescribed other NSAIDs, we only studied the association between ibuprofen prescription claims and outcome.

METHODS

Study setting and population

In Denmark, all citizens hold a unique civil registration number used in all healthcare and social contacts and recorded in national administrative registries. From the Danish National Patient Registry, we identified patients positive with COVID-19 between the end of February 2020 and May 16, 2020, through the use of International Classification of Disease-10th edition diagnosis codes DB342, DB342A, and DB972 for unspecific COVID-19 infection and DB972A for COVID-19 infection with severe acute respiratory syndrome.[11] Patients below 30 years of age, as well as patients with heart failure, in whom ibuprofen is not recommended, were excluded. Finally, only 57 patients were prescribed other NSAIDs, and these patients were excluded.

Exposure

From the Danish National Prescription Registry, data on prescription medication was available until April 30, 2020. We assessed ibuprofen prescription claims between January 1, 2020, and April 30, 2020, and the latest filled prescription before COVID-19 diagnosis or April 30, 2020, was used. Ibuprofen prescription claims were further divided into > 14 days before COVID-19 diagnosis vs. ≤ 14 days before COVID-19 diagnosis. Finally, because we do not have exact data on doses available from the Danish National Prescription Registry, we defined strengths of the latest package of 200–400 mg vs. 600–800 mg, respectively, as low-medium vs. high dosage. These 2 groups may be viewed as proxies for daily doses of 600–1,200 mg and 1,800–2,400 mg, respectively. Indications for ibuprofen and concomitant prescription for paracetamol were also assessed.

Covariates

We included information on patient age and sex from the Danish Civil Registration System. We assessed the following comorbidities: hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, hypertension, any malignancy, and rheumatic disease. Hypertension was defined as a redemption of at least 2 antihypertensive drugs in 2 consecutive 100-day periods prior to the COVID-19 diagnosis, as done previously.[12] All other comorbid conditions were identified from the Danish National Patient Registry up to 5 years prior to COVID-19 diagnosis.

Outcome

The study outcome was a 30-day composite of severe COVID-19 diagnosis (International Classification of Disease-10th edition: DB972A), admission to an intensive care unit (ICU), or death. The Danish National Patient Registry was used to identify the first two components of the composite end point, whereas vital status was identified from the Danish Civil Registration System. Patients admitted to an ICU 3 days before the COVID-19 diagnosis up to 30 days after the COVID-19 diagnosis were defined as admitted to an ICU and incorporated into the composite end point. For cases where the ICU admission was ahead of the COVID-19 diagnosis, risk time began at the time of COVID-19 diagnosis.

Statistics

Continuous variables are reported using median and 25–75 percentiles. Categorical variables are reported using counts and percentages. Thirty-day absolute risks and average risk ratios (treatment effects) for the ibuprofen vs. non-ibuprofen COVID-19 patient groups standardized to the age, sex, and comorbidity distribution of all patients were derived from multivariable Cox regression.[13] The models included the following covariates: age (in groups 30–50, > 50–60, > 60–70, > 70–80, and > 80 years), sex, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, hypertension, cancer, and rheumatic disease. Data management and analyses were performed using SAS, version 9.4 (Cary, NC) and R version 3.6.1.[14]

Ethics

According to Danish legislation, register-based studies do not require ethical committee approval or patient consent. In accordance with the General Data Protection Regulation, the data responsible institute in the Capital Region of Denmark has approved the use of the data sources for research purposes (approval number P-2019-191). Data are accessed on secure servers under Statistics Denmark and cannot be shared according to Danish legislation.

RESULTS

Patients

Of a total of 4,842 patients with COVID-19 infection between the end of February and May 16, 2020, 4,002 patients formed the study population. A total of 264 patients (6.6%) filled an ibuprofen prescription claim prior to COVID-19 diagnosis. Patients with pre-existing heart failure (n = 208), < 30 years of age (n = 575), or who filled a prescription for other nonsteroidal anti-inflammatory drugs (n = 57) were excluded.

Characteristics

Characteristics of age, sex, and comorbidities were generally comparable between the two study groups (**Table 1**). Patients with ibuprofen prescription claims tended to be

Table 1 Characteristics of patients with COVID-19 with vs. without an ibuprofen prescription claim prior to COVID-19

Variable	Ibuprofen prescription claim (*n* = 264)	No ibuprofen prescription claim (*n* = 3,738)	*P* value
Age, median [25%–75%]	58 [46–68]	57 [45–73]	0.67
Age ≤ 50 years, *n* (%)	87 (33.0)	1,359 (36.4)	
Age > 50–60 years, *n* (%)	62 (23.5)	769 (20.6)	
Age > 60–70 years, *n* (%)	56 (21.2)	528 (14.1)	
Age > 70–80 years, *n* (%)	31 (11.7)	575 (15.4)	
Age > 80 years, *n* (%)	28 (10.6)	507 (13.6)	0.007
Male sex, *n* (%)	118 (44.7)	1,773 (47.4)	0.43
Diabetes, *n* (%)	35 (13.3)	414 (11.1)	0.32
Prior MI, *n* (%)	7 (2.7)	94 (2.5)	0.99
COPD, *n* (%)	17 (6.4)	197 (5.3)	0.50
Hypertension, *n* (%)	64 (24.2)	815 (21.8)	0.40
Cancer, *n* (%)	19 (7.2)	362 (9.7)	0.22
Rheumatic disease, *n* (%)	13 (4.9)	171 (4.6)	0.91

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; MI, myocardial infarction.

older and more likely to have hypertension, although insignificant, as well as the prevalence of diabetes, myocardial infarction, chronic obstructive pulmonary disease, and cancer were numerically higher for patients with ibuprofen prescription claims. Characteristics between patients with ibuprofen prescription claims > 14 days before COVID-19 vs. ≤ 14 days before COVID-19 were also comparable (**Table 2**). Indications for ibuprofen prescription were available for 220 patients of 264 patients who were prescribed ibuprofen: 13 patients (5.9%) were prescribed ibuprofen due to rheumatic disease/inflammation and the remaining 207 patients (94.1%) due to pain. Of these 220 patients, 156 (70.9%) were also prescribed paracetamol.

Absolute risks

A total of 688 patients met the 30-day composite end point, 42 patients (15.9%) in the ibuprofen group, and 646 patients (17.3%) in the non-ibuprofen group (**Table 3**). Absolute risks for the composite end point for patients with vs. without an ibuprofen prescription claim standardized to the age, sex, and comorbidity distribution of all patients were 16.3% (95% CI 12.1–20.6) vs. 17.0% (95% CI 16.0–18.1), $P = 0.74$. Corresponding risks for an ibuprofen prescription claim > 14 days before COVID-19 diagnosis vs. ≤ 14 days before diagnosis of COVID-19 were 16.0% (95% CI 11.9–20.9) vs. 14.4% (95% CI 6.7–23.0), $P = 0.70$ (**Table 4**).

Average risk ratios

The average risk ratio for patients with vs. without a recent ibuprofen prescription claim prior to COVID-19 diagnosis standardized to the age, sex, and comorbidity distribution of all patients was 0.96 (95% CI 0.72–1.23). The corresponding average risk ratio for ibuprofen prescription claims ≤ 14 days before the COVID-19 diagnosis vs. > 14 days before COVID-19 diagnosis (reference) was 0.90 (95% CI 0.39–1.57).

Table 2 Characteristics of patients with COVID-19 with an ibuprofen prescription claim ≤ 14 days before COVID-19 vs. > 14 days before COVID-19

Variable	Ibuprofen prescription claim ≤ 14 days before COVID-19 (*n* = 64)	Ibuprofen prescription claim > 14 days before COVID-19 (*n* = 200)	*P* value
Age, median [25% MI, 75% MI]	58.5 [47.0, 74.2]	57 [46, 68]	0.50
Age ≤ 50 years, *n* (%)	19 (29.7)	68 (34.0)	
Age > 50–60 years, *n* (%)	16 (25.0)	46 (23.0)	
Age > 60–70 years, *n* (%)	12 (18.8)	44 (22.0)	
Age > 70–80 years, *n* (%)	11 (17.2)	20 (10.0)	
Age > 80 years, *n* (%)	6 (9.4)	22 (11.0)	0.58
Male sex, *n* (%)	35 (54.7)	83 (41.5)	0.089
Diabetes, *n* (%)	10 (15.6)	25 (12.5)	0.67
Prior MI, *n* (%)	4 (6.2)	3 (1.5)	0.11
COPD, *n* (%)	5 (7.8)	12 (6.0)	0.82
Hypertension, *n* (%)	18 (28.1)	46 (23.0)	0.51
Cancer, *n* (%)	6 (9.4)	13 (6.5)	0.62
Rheumatic disease, *n* (%)	NA	11 (5.5)	0.67

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; MI, myocardial infarction; NA, not available (according to Statistics Denmark legislation, cells with number of patients below three cannot be reported).

Table 3 Absolute risks and average risk ratio of the 30-day composite outcome for patients with COVID-19 with vs. without recent ibuprofen prescription claims prior to COVID-19

Ibuprofen group	Unadjusted absolute risk [95% CI]	Age and sex-adjusted absolute risk [95% CI]	Fully adjusted absolute risk [95% CI]	Standardized average risk ratio [95% CI]
No ibuprofen prescription claim	17.3% [16.1–18.6]	17.0% [15.9–18.0]	17.0% [16.0–18.1]	Ref
Ibuprofen prescription claim	16.0% [11.8–20.5]	16.6% [12.7–21.1]	16.3% [12.1–20.6]	0.96 [0.72–1.23]

The 30-day composite outcome consisted of severe COVID-19 diagnosis, intensive care unit admission, or death. The average risk ratio was standardized to the age, sex, and comorbidity distribution of all patients.
CI, confidence interval; COVID-19, coronavirus disease 2019; Ref, reference.

Other analyses

The dosage of ibuprofen was not directly available from the Danish National Prescription Registry. In analyses applying the strength of the ibuprofen, 215 patients were prescribed 200–400 mg ibuprofen pills and 49 patients were prescribed 600–800 mg ibuprofen pills. The absolute risk of the 30-day composite outcome standardized to the age, sex, and comorbidity distribution of all patients was 15.2% (95% CI 10.7–20.1) for the 200–400 mg ibuprofen group vs. 17.2% (95% CI 6.5–27.3) for the 600–800 mg ibuprofen group. The average risk ratio standardized to the age, sex, and comorbidity distribution of all patients for the 600–800 mg ibuprofen group vs. 200–400 mg ibuprofen group (reference) was 1.13 (95% CI 0.42–1.98).

DISCUSSION

In this nationwide study on the association between ibuprofen prescription claims and severe COVID-19 infection, defined as a COVID-19 diagnosis with severe acute respiratory syndrome, ICU admission, or fatal trajectory, we found no significant association between recent ibuprofen prescription claims and the composite end point.

Respiratory, septic, and cardiovascular complications and prolonged recovery have been linked to NSAID use in COVID-19 infectious disease.[9,15] In addition to the changing recommendations regarding ibuprofen and other NSAID use in the context of COVID-19 from the WHO and several national health boards, several experts have advocated against the use of these drugs in patients infected with COVID-19 and suggested paracetamol or acetaminophen as alternative treatments.[15] Currently, the WHO do not call for avoidance of ibuprofen to treat COVID-19 symptoms. The European Medicine Agency as well as the FDA also do not advocate against the use of ibuprofen, and the FDA calls for more evidence to support the drug safety of NSAIDs, including ibuprofen. Our results do not provide sufficient evidence to change the current recommendations. Reassuringly, the overall results were consistent with results in which ibuprofen prescription claims were divided into > 14 days before COVID-19 diagnosis vs. ≤ 14 days before COVID-19 diagnosis. Finally, although the dosage of ibuprofen was not directly available from the Danish National Prescription Registry, we used the strength of the ibuprofen package of 200–400 mg and 600–800 mg, respectively, to divide patients into low-medium vs. high dosage groups. In these analyses, we did not find any significant differences in severe COVID-19 outcome between the two dosage groups.

In our study, ibuprofen users were defined based on prescription fills and information on whether or how many ibuprofen pills the patients actually took is not available. However, the proxies for ibuprofen dosage mentioned above did not provide evidence to suggest a dose-response relationship between ibuprofen strength and severe COVID-19 outcome. In addition, patients on prescription ibuprofen are presumably more likely to actually use the medication on a more regular and even daily basis. As such, the lack of an association with outcome for patients who claimed a prescription for ibuprofen within 14 days of the COVID-19 diagnosis is likely to be valid. Because ibuprofen also can be purchased as an over-the-counter drug in Denmark, we cannot exclude potential misclassification of ibuprofen exposure, as patients in the non-ibuprofen group may have used over-the-counter ibuprofen. We did not have data on the medication used during hospitalization for COVID-19. As such, we do not have information on whether ibuprofen use was continued or discontinued, which may have had an impact on our results. Whether patients actually were using ibuprofen or they avoided it on

Table 4 Absolute risks and average risk ratio of the 30-day composite end point for patients with ibuprofen prescription claims > 14 days vs. ≤ 14 days before COVID-19 diagnosis

Ibuprofen group	Unadjusted absolute risk [95% CI]	Age and sex-adjusted absolute risk [95% CI]	Fully adjusted absolute risk [95% CI]	Standardized average risk ratio [95% CI]
Ibuprofen prescription claim > 14 days before COVID-19	16.0% [10.9–21.2]	16.0% [11.7–20.9]	16.0% [11.9–20.9]	Ref
Ibuprofen prescription claim ≤ 14 days before COVID-19	15.5% [7.0–25.0]	14.6% [7.7–22.6]	14.4% [6.7–23.0]	0.90 [0.39–1.57]

The composite outcome consisted of severe COVID-19 diagnosis, intensive care unit admission, or death.
The average risk ratio was standardized to the age, sex, and comorbidity distribution of all patients.
CI, confidence interval; COVID-19, coronavirus disease 2019; Ref, reference.

the basis of physician advice and/or the public attention in March 2020 on the potential negative effect on COVID-19 infection severity remain unknown. In support of our study findings, a limited number of recent studies, including reviews, have also not found any evidence suggesting worsening of COVID-19 infection in relation to ibuprofen or NSAID use.[10,16–19] Follow-up data on outcome was limited to May 16, 2020, which may limit the registration of severe COVID-19 infection for patients diagnosed with COVID-19 at the end of the study period. However, the majority of patients hospitalized for COVID-19 were in the hospital in the beginning of April ensuring that the greater majority of the included patients had sufficient follow-up to allow the study of the 30-day outcome measure. Although we adjusted for several confounding factors, we cannot rule out residual or unmeasured confounding. Given the observational design, results, and associations, no conclusions concerning causality can be made. However, we applied average treatment effect analyses with standardization of the age, sex, and comorbidity distribution in an attempt to minimize confounding by indication issues and mimic a randomized controlled trial setting. For these reasons, patients of younger age and with heart failure, in whom ibuprofen was not used, were excluded per study design. In addition to a lack of laboratory data to confirm that each case had a positive swab test, our sample is based on hospital registries, including only cases evaluated for hospitalization needs and/or hospital-based staff. Although most COVID-19 infections in Denmark are located in the capital region and more densely populated areas, the use of nationwide data minimizes selection bias based on geographic differences.

CONCLUSIONS

In this nationwide study, we did not find recent ibuprofen drug prescription claims prior to COVID-19 diagnosis to be significantly associated with severe, including fatal trajectory of COVID-19 infection.

Funding. No funding was received for this work.

Conflict of Interest. The authors declared no competing interests for this work.

Author Contributions. K.K. wrote the manuscript. K.K., C.T.P., E.F., G.G., M.S., and L.K. designed the research. K.K., T.A.G., E.F., M.P.A., M.P., J.H.B., J.P., C.B., L.Ø., and C.T.P. performed the research. K.K., T.A.G., and C.T.P. analyzed the data.

1. Petrilli, C.M. *et al*. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ* **22**, m1966 (2020).
2. Zhu, N. *et al*. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med*. **382**, 727–733 (2020).
3. Emanuel, E.J. *et al*. Fair allocation of scarce medical resources in the time of Covid-19. *N. Engl. J. Med*. **382**, 2049–2055 (2020).
4. Kinross, P. *et al*. Rapidly increasing cumulative incidence of coronavirus disease (COVID-19) in the European Union/European Economic Area and the United Kingdom, 1 January to 15 March 2020. *Euro Surveill.* **25**, 2000285 (2020).
5. Boccia, S., Ricciardi, W. & Ioannidis, J.P.A. What other countries can learn from Italy during the COVID-19 pandemic. *JAMA Intern. Med.* **180**, 927 (2020).
6. Rubino, S., Kelvin, N., Bermejo-Martin, J.F. & Kelvin, D. As COVID-19 cases, deaths and fatality rates surge in Italy, underlying causes require investigation. *J. Infect. Dev. Ctries.* **14**, 265–267 (2020).
7. Grasselli, G. *et al*. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* **323**, 1574 (2020).
8. Kuba, K. *et al*. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat. Med.* **11**, 875–879 (2005).
9. Fang, L., Karakiulakis, G. & Roth, M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir. Med.* **8**, e21 (2020).
10. Russell, B., Moss, C., Rigg, A. & Van Hemelrijck, M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? *Ecancermedicalscience.* **14**, 1023 (2020).
11. The Danish Health Data Authority. Management of COVID-19 in healthcare cost and financing <https://sundhedsdatastyrelsen.dk/-/media/sds/filer/finansiering-og-afregning/gruppering/noegler/2020/bilag-2-_-haandtering-af-covid_19-i-drg.pdf>. Accessed on August 31, 2020.
12. Krogager, M.L. *et al*. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur. Heart J.* **38**, 104–112 (2017).
13. Grant, R.L. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ* **348**, f7450 (2014).
14. R Core Team. R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria, 2017) <https://www.R-project.org/>.
15. Day, M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ* **17**, m1086 (2020).
16. Vaja, R. *et al*. The COVID-19 ibuprofen controversy: a systematic review of NSAIDs in adult acute lower respiratory tract infections. *Br. J. Clin. Pharmacol.* (2020). https://doi.org/10.1111/bcp.14514.
17. Rinott, E., Kozer, E., Shapira, Y., Bar-Haim, A. & Youngster, I. Ibuprofen use and clinical outcomes in COVID-19 patients. *Clin. Microbiol. Infect.* **26**, 1259.e5–1259.e7 (2020).
18. Nicholas Moore, N., Carleton, B., Blin, P., Bosco-Levy, P. & Droz, C. Does Ibuprofen Worsen COVID-19? *Drug Saf.* **43**, 611–614 (2020).
19. Capuano, A., Scavone, C., Racagni, G. & Scaglione, F., Italian Society of Pharmacology. NSAIDs in patients with viral infections, including Covid-19: victims or perpetrators? *Pharmacol. Res.* **157**, 104849 (2020).