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Ibuprofen for Acute Pericarditis and Associated Cardiovascular Risks: A Danish Nationwide, Population-Based Cohort Study

Jakob Kjølby Eika[1,2,*], Kasper Bonnesen[1,2,*], Lars Pedersen[1,2], Vera Ehrenstein[1,2], Henrik Toft Sørensen[1,2], Morten Schmidt[1–3]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; [3]Department of Cardiology, Gødstrup Regional Hospital, Herning, Denmark

*These authors contributed equally to this work

Correspondence: Morten Schmidt, Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark and Department of Clinical Medicine, Aarhus University, Olof Palmes Allé 43–45, Aarhus, 8200, Denmark, Tel +45 87 16 72 12, Email morten.schmidt@clin.au.dk

Purpose: Ibuprofen is used to treat acute pericarditis, but high-dose ibuprofen has also been associated with increased cardiovascular risks. We examined the cardiovascular safety of using ibuprofen for acute pericarditis.

Patients and Methods: A Danish nationwide, population-based cohort study including patients ≥18 years with first-time acute pericarditis (n=12,381) during 1996–2020 was conducted. Ibuprofen use was modelled in two ways: First, we considered patients exposed based on the tablet strength of their first ibuprofen filling (a proxy for an *intention-to-treat* analysis). Second, we considered patients exposed in a time-varying manner (a proxy for an *as-treated* analysis). The primary outcome of major adverse cardiovascular events (MACE) was a composite of myocardial infarction, ischemic stroke, congestive heart failure, and cardiovascular death.

Results: In the *intention-to-treat* analysis, the 1-year risk of MACE was 1.37% (95% confidence interval [CI]: 1.03–1.79) for ibuprofen initiators and 4.32% (95% CI: 3.89–4.78) for non-initiators. Compared with non-initiators within 1-year follow-up, the adjusted hazard ratio for MACE was 0.75 (95% CI: 0.67–0.85) for initiators overall, 0.38 (95% CI: 0.28–0.52) for initiators of >400 mg tablets, and 0.87 (95% CI: 0.76–0.99) for initiators of ≤400 mg tablets. In the *as-treated* analysis, compared with no use, the hazard ratio associated with ibuprofen use was 0.69 (95% CI: 0.54–0.89) for MACE, 0.82 (95% CI: 0.54–1.26) for myocardial infarction, 0.74 (95% CI: 0.45–1.22) for ischemic stroke, 0.67 (95% CI: 0.47–0.96) for congestive heart failure, and 0.60 (95% CI: 0.31–1.17) for cardiovascular death.

Conclusion: Ibuprofen use for acute pericarditis was not associated with increased cardiovascular risks, supporting its safety in current practice.

Keywords: Pericarditis, Anti-Inflammatory Agents, non-steroidal, Cohort Study, Epidemiology

Introduction

Acute pericarditis is an inflammatory disease of the pericardium due to both infectious and non-infectious causes.[1,2] In the general population, around three per 100,000 are hospitalized with acute pericarditis annually.[3] In uncomplicated cases, acute pericarditis causes chest pain and fever,[1] but can in complicated cases result in pericarditis recurrence, pericardial constriction, and cardiac tamponade.[1,4] Conventional medical treatment of acute pericarditis includes non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, and/or colchicine, with ibuprofen, a non-selective NSAID,[5] in monotherapy being the most common treatment.[1]

Ibuprofen use has been linked to an increased risk of myocardial infarction, ischemic stroke, and congestive heart failure.[6–8] The relative increase in cardiovascular risk is highest around treatment initiation.[9] NSAIDs, in general, achieve their anti-inflammatory effects through inhibition of the cyclooxygenase (COX) enzymes of which there are at least two major isoforms, COX-1 and COX-2.[10] Ibuprofen is categorized as a non-selective NSAID although slightly favoring

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COX-1 inhibition.[5] The COX-enzymes catalyze the conversion of arachidonic acid into bioactive lipids. In turn, these lipids modulate the tendency of atherogenesis, thrombosis, arrhythmicity, and blood pressure.[10] Consequently, NSAIDs, in general, are not recommended for individuals with established or at high risk of cardiovascular disease.[10] However, acute pericarditis is an exception to this rule, as ibuprofen reduces inflammation and associated symptoms.[1] Whether this benefit comes at the cost of other increased cardiovascular risks remains unclear as neither the efficacy nor safety of using ibuprofen to treat acute pericarditis has been evaluated in a randomized controlled trial.[11,12] We, therefore, examined whether ibuprofen use after acute pericarditis was associated with adverse cardiovascular events.

Material and Methods

Setting

The Danish National Health Service provides universal tax-supported health care for all 5.8 million inhabitants, guaranteeing free access to general practitioners and hospitals, as well as partial reimbursement for the costs of prescribed drugs, including ibuprofen.[13] Individual-level linkage among Danish registries is possible using the unique Civil Personal Register number assigned to all Danish citizens and legal residents at birth or upon immigration.[14]

European guidelines recommend treating acute pericarditis with either NSAIDs or aspirin.[1] Since 2015, colchicine has been added as an adjunctive treatment, as it has been found to improve remission rates and halve the 18-month rate of recurrence.[15,16] Danish guidelines recommend using ibuprofen or aspirin as monotherapy for uncomplicated cases and adding colchicine for severe or prolonged cases.[17] After cessation of symptoms, continuation of ibuprofen or aspirin is recommended for at least one week and continuation of colchicine, if administered, is recommended for at least three months.[17]

Design and Population

We conducted a population-based cohort study of all Danish patients aged 18 years or older who received a first-time primary or secondary inpatient discharge diagnosis of acute pericarditis between January 1, 1996, and December 31, 2020. We identified the diagnoses from the Danish National Patient Registry (DNPR), which contains nationwide data on all non-psychiatric hospital contacts since 1977 and on all psychiatric hospital, outpatient clinic, and emergency room contacts since 1995.[18] Each contact is recorded with one primary diagnosis and potentially several secondary diagnoses classified according to the *International Classification of Diseases, Eighth Edition* (ICD-8) until 1994 and *Tenth Edition* (ICD-10) thereafter.[18] We excluded patients who had filled an NSAID prescription (*Anatomical Therapeutic Chemical Classification system* [ATC] code: M01A) within 180 days prior to hospital discharge for pericarditis because prevalent and new users of NSAIDs might have different cardiovascular risks.

Ibuprofen Use

Ibuprofen use was analysed using proxies for both *intention-to-treat* and *as-treated* approaches. In the *intention-to-treat* analysis, we defined ibuprofen use by the tablet strength of the first filled prescription as ≤400 mg or >400 mg within seven days after hospital discharge for pericarditis. Patients who did not fill a prescription within or later than the seven-day exposure window were considered unexposed. The choice to use a seven-day exposure window was based on a feasibility analysis of 25,060 patients with an in- or outpatient diagnosis of pericarditis, which showed that 76% of all persons filling an NSAID prescription within 60 days after discharge for pericarditis did so within seven days (Supplementary Figure 1). Moreover, ibuprofen accounted for >90% of all NSAID fillings.

In the *as-treated* analysis, ibuprofen was modelled in a time-varying manner. A patient was considered exposed from when a prescription was filled until the end of an exposure period. The exposure period was defined as package size times tablet dose divided by a defined daily dose of 1200 mg per day — the recommended dose for treating fever and pain according to Danish guidelines.[19] If a new prescription was filled within an exposure period plus a 14-day gap period, the exposure period was extended by the number of days provided by the new prescription. The time elapsed from discharge until the first filled prescription was considered unexposed.

The filled prescriptions were identified from the Danish National Prescription Registry, which contains nationwide data on all prescriptions filled at community pharmacies since 1995.[20]

Cardiovascular Outcomes

The primary outcome was a combined outcome of major adverse cardiovascular events (MACE), consisting of cardiovascular events related to ibuprofen use, *ie*, myocardial infarction, ischemic stroke, congestive heart failure, and cardiovascular death. We obtained information on primary and secondary outcome diagnoses from the DNPR,[18] on mortality and migration status from the Danish Civil Registration System,[14] and on the main underlying cause of death from the Danish Register of Causes of Death.[21] The Danish Civil Registration System is updated daily and its records extend back to 1968 for the entire Danish population,[14] and the Danish Register of Causes of Death contains information on the main underlying cause and potential contributory cause(s) of deaths since 1970.[21] The secondary outcomes were the individual components of MACE. In the case of a cardiovascular event, we used the date of hospital admission to define the date of an outcome.

Covariables

We used all in- and outpatient information in the DNPR for up to 10 years before the hospital discharge for pericarditis to identify the comorbidities presented in Table 1. Similarly, we used all information on filled prescriptions recorded in the Danish National Prescription Registry for up to 180 days before the hospital discharge for pericarditis to identify the use of the medications presented in Table 1. Because uncomplicated diabetes, hypertension, and recent infections may be treated solely by a general practitioner, we also used drug proxies for these diseases. We estimated the patients' comorbidity burden using the Danish Comorbidity Index for Acute Myocardial Infarction (DANCAMI).[22] All codes used in the study are presented in Supplementary Table 1. Covariates included in the adjusted model were selected based on their association with NSAID use[23] and cardiovascular disease.[24]

Statistical Analyses

We presented categorical variables as numbers with percentages and continuous variables as medians with interquartile ranges. For the *intention-to-treat* analysis, we described the number of patients who filled an ibuprofen prescription within seven days of discharge. For this analysis, we restricted the cohort to patients who survived and did not experience an outcome within seven days from discharge. To avoid immortal time bias,[25] we then followed the patients from day seven after hospital discharge until the occurrence of an outcome; emigration; 30, 180, or 365 days of follow-up; or December 31, 2020, whichever came first. We used an Aalen-Johansen estimator to compute cumulative incidences (*ie*, risks) of a cardiovascular event, considering death due to non-cardiovascular causes a competing event.[26]

For the *as-treated* analysis, we described the median ibuprofen tablet dose and the average length considered exposed to ibuprofen after a filled prescription. In this analysis, we followed patients from hospital discharge for pericarditis until the occurrence of an outcome, emigration, death or December 31, 2020, whichever came first. We estimated the incidence of the outcomes by calculating baseline incidence rates per 1,000 person-years for each outcome.

For both the *intention-to-treat* and the *as-treated* analyses, we used a Cox proportional-hazards regression model to compute crude and adjusted hazard ratios (HRs) of the association between ibuprofen use and the outcomes.[27] The adjusted model included sex, age, DANCAMI category (none, low, moderate, severe), and the comorbidities and comedications presented in Table 1. The time-varying Cox modeling did not allow testing for proportional hazards.[28] We presented the precision of all estimates with a 95% confidence interval (CI). We used STATA for Cox regression models, R for forest plots and SAS for survival curves.

Table 1 Characteristics of Patients with First-Time Acute Pericarditis in Denmark (2016–2020) According to Ibuprofen Initiation Within 7 Days After Discharge

Characteristics	Total n=12,381 (100)	Ibuprofen initiators* n=3,673 (100)	Non-initiators* n=8,156 (100)
Female sex	3,623 (29)	801 (22)	2,613 (32)
Hospitalization in days†	1 (0–3)	1 (0–2)	1 (0–4)
Age in years†	51 (36–65)	44 (32–57)	53 (37–67)
18–49	6,035 (49)	2,250 (61)	3,658 (45)
50–59	2,263 (18)	671 (18)	1,496 (18)
60–69	1,982 (16)	467 (13)	1,386 (17)
≥70	2,101 (17)	285 (7.8)	1,616 (20)
Year of pericarditis discharge			
1996–2000	1,729 (14)	403 (11)	1,255 (15)
2001–2005	2,202 (18)	689 (19)	1,402 (17)
2006–2010	1,756 (14)	539 (15)	1,140 (14)
2011–2015	3,390 (27)	967 (26)	2,280 (28)
2016–2020	3,304 (27)	1,075 (29)	2,079 (25)
Comorbidity burden‡			
None	6,478 (52)	2,488 (68)	3,860 (47)
Low	3,097 (25)	836 (23)	2,137 (26)
Moderate	918 (7.4)	138 (3.8)	694 (8.5)
Severe	1,888 (15)	211 (5.7)	1,465 (18)
Conditions with chronic pain			
Inflammatory rheumatic disease	633 (5.1)	134 (3.7)	469 (5.8)
Degenerative rheumatic disease	2,117 (17)	592 (16)	1,431 (18)
Soft tissue disorders	1,063 (8.6)	325 (8.9)	696 (8.5)
Osteoporosis	259 (2.1)	41 (1.1)	203 (2.5)
Cancer, low-risk§	969 (7.8)	164 (4.5)	741 (9.1)
Cancer, high-risk§	554 (4.5)	30 (0.82)	474 (5.8)
Headache	153 (1.2)	104 (1.3)	46 (1.3)
Other comorbidities			
Aortic disease	226 (1.8)	20 (0.54)	186 (2.3)
Valvular heart disease	846 (6.8)	63 (1.7)	712 (8.7)
Hypertension	2,545 (21)	406 (11)	1,931 (24)
Venous thromboembolism	306 (2.5)	47 (1.3)	230 (2.8)
Diabetes, uncomplicated	743 (6.0)	122 (3.1)	575 (7.1)
Diabetes, end-organ damage	295 (2.4)	34 (0.93)	230 (2.8)
Chronic kidney disease	414 (3.3)	19 (0.52)	356 (4.4)
Ulcer disease	199 (1.6)	14 (0.38)	166 (2.0)
Infection within three months	4,511 (36)	1,022 (28)	3,251 (40)
Comedication			
Angiotensin-converting enzyme inhibitors	919 (7.4)	155 (4.2)	678 (8.3)
Angiotensin II receptor blockers	559 (4.5)	101 (2.8)	425 (5.2)
Beta blockers	1,671 (14)	245 (6.7)	1,294 (16)
Calcium channel blockers	1,342 (11)	197 (5.4)	1,041 (13)
Diuretics	1,788 (14)	207 (5.6)	1,401 (17)
Statins	1,531 (12)	278 (7.6)	1,146 (14)
Selective serotonin reuptake inhibitors	560 (4.5)	126 (3.4)	385 (4.7)
Anticoagulants	1,031 (8.3)	100 (2.7)	858 (11)
Antiplatelets	1,475 (12)	243 (6.6)	1,098 (13)
Antiulcer drugs	2,059 (17)	582 (16)	1,361 (17)

Note: The cells present numbers (%) unless specified otherwise.*Ibuprofen use measured within 0–7 days after discharge among 7-day survivors without myocardial infarction, ischemic stroke, congestive heart failure, or cardiovascular death in the first 7 days after discharge.†Median (interquartile range). ‡Categorized according to the Danish Comorbidity Index for Acute Myocardial Infarction as none (score: 0), low (score: 1–3), moderate (score: 4–5), or severe (score: ≥6). §Five-year survival ≥30% for low-risk and <30% for high-risk.

Results

Baseline Characteristics

From 1996 through 2020, we identified 12,381 patients with a first-time acute pericarditis hospitalization. Table 1 presents the characteristics of these patients at the time of hospital discharge. There was no missing data on any variables. The median age of the patients was 51 (interquartile range: 36–65) and 3,623 (29%) were females.

In the *intention-to-treat* analysis, 3,673 patients filled an ibuprofen prescription within seven days of hospital discharge: 2,709 filled a prescription for a ≤400 mg tablet and 967 for a >400 mg tablet. Compared with patients that did not fill an ibuprofen prescription, patients that did fill a prescription were younger (median age: 44 years vs 53 years), less comorbid (severe comorbidity burden: 5.7% vs 18%) and used fewer prescription medications (Table 1). In the *as-treated* analysis, the median ibuprofen tablet dose was 400 mg (interquartile range: 400–533) and the median length considered exposed after a filled ibuprofen prescription was 36 days (interquartile range: 29–49) (Supplementary Figure 2).

Absolute Cardiovascular Risk

Figure 1 presents the absolute risks of MACE within one year of follow-up for patients initiating and not initiating ibuprofen treatment. In the *intention-to-treat* analysis, the risk of a cardiovascular event for patients initiating ibuprofen treatment was 0.44% (95% CI: 0.26–0.70) after 30 days of follow-up, 0.91% (95% CI: 0.64–1.26) after 180 days of follow-up, and 1.37% (95% CI: 1.03–1.79) after 365 days of follow-up (Supplementary Table 2). The corresponding risk for patients not initiating ibuprofen treatment was 1.61% (95% CI: 1.35–1.95) after 30 days of follow-up, 3.35% (95% CI: 2.97–3.76) after 180 days of follow-up, and 4.32% (95% CI: 3.89–4.78) after 365 days of follow-up (Supplementary Table 2). In the *as-treated* analysis of MACE, we observed 66 cardiovascular events during periods with and 1,593 events during periods without ibuprofen use corresponding to an incidence rate per

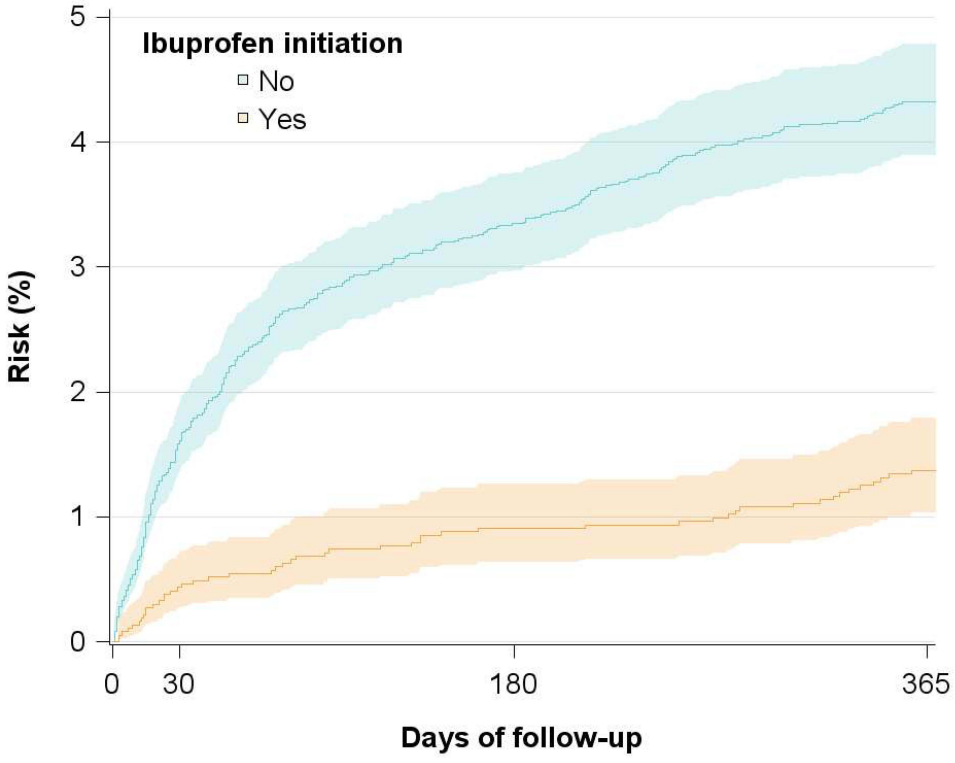

Figure 1 Cumulative incidence of adverse cardiovascular events after acute pericarditis according to ibuprofen initiation.*
Notes: Day zero reflects seven days after acute pericarditis discharge, and ibuprofen initiation reflects an ibuprofen dispensing within seven days from discharge. *Composite of myocardial infarction, ischemic stroke, congestive heart failure, and cardiovascular death.

Table 2 Time at Risk, Number of Events, and Incidence of Cardiovascular Events Using a Proxy for an as-Treated Approach

Outcome	Ibuprofen use			Ibuprofen non-use		
	Years at risk	No. of events	Rate per 1,000 PY (95% CI)	Years at risk	No. of events	Rate per 1,000 PY (95% CI)
MACE*	3,351	66	19.7 (15.4–25.1)	96,588	1,593	16.49 (15.7–17.3)
Myocardial infarction	3,476	24	6.90 (4.63–10.3)	102,011	506	4.96 (4.55–5.41)
Ischemic stroke	3,503	17	4.85 (3.02–7.81)	103,456	526	5.08 (4.67–5.54)
Congestive heart failure	3,504	34	9.70 (6.93–13.6)	102,024	840	8.23 (7.69–8.81)
Cardiovascular death	3,577	9	2.52 (1.31–4.84)	105,980	441	4.16 (3.79–4.57)

Note: *Major adverse cardiovascular events, a combined outcome consisting of myocardial infarction, ischemic stroke, congestive heart failure, or cardiovascular death.
Abbreviations: CI, Confidence interval; MACE, major adverse cardiovascular event; PY, person-years.

1,000 person-years of 19.7 (95% CI: 15.5–25.1) during periods with and 16.5 (95% CI: 15.7–17.3) during periods without ibuprofen use. (Table 2).

Relative Cardiovascular Risk

In the *intention-to-treat* analysis, the adjusted short- and long-term risks of a cardiovascular event was lower for patients initiating ibuprofen treatment compared with patients not initiating ibuprofen treatment (Figure 2). Compared with non-initiation, the HRs associating ibuprofen initiation with a cardiovascular event was lower for those initiating a tablet dose >400 mg than for those initiating a tablet dose ≤400 mg during both 30 days of follow-up (0.20, 95% CI: 0.08–0.54 for >400 mg vs 0.52, 95% CI: 0.36–0.73 for ≤400 mg), 180 days of follow-up (0.31, 95% CI: 0.20–0.49 for >400 mg vs 0.81, 95% CI: 0.69–0.96 for ≤400 mg), and 365 days of follow-up (0.38, 95% CI: 0.28–0.52 for >400 mg vs 0.87, 95% CI: 0.76–0.99 for ≤400 mg) (Figure 2). We observed no noteworthy differences in the association between ibuprofen initiation and a cardiovascular event between the sexes (Supplementary Table 3). When stratifying by age, initiation as compared with non-initiation of ibuprofen, was associated with a larger decrease in cardiovascular risk in older than in younger patients (HR: 0.57, 95% CI: 0.42–0.77 for patients ≥70 years of age vs HR: 1.03, 95% CI: 0.85–1.25 for patients 18–49 years of age) (Supplementary Table 3).

In the *as-treated* analysis, ibuprofen use was associated with a 31% reduced cardiovascular event rate compared with non-use (HR: 0.69, 95% CI: 0.54–0.89) (Figure 3). The corresponding HRs for the secondary outcomes were 0.82 (95% CI: 0.54–1.26) for myocardial infarction, 0.74 (95% CI: 0.45–1.22) for ischemic stroke, 0.67 (95% CI: 0.47–0.96) for congestive heart failure, and 0.60 (95% CI: 0.31–1.17) for cardiovascular death (Figure 3).

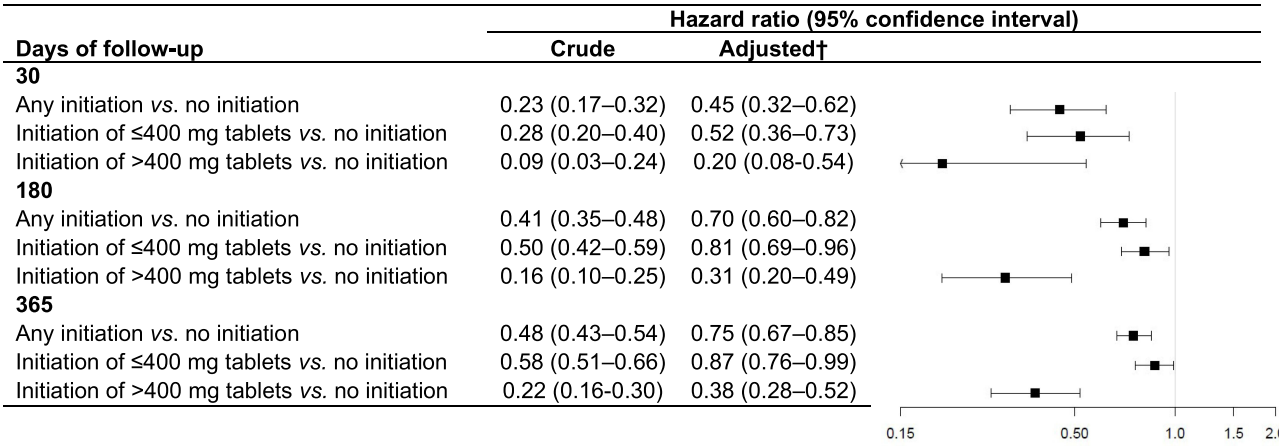

Figure 2 Association between initiation of ibuprofen after acute pericarditis and adverse cardiovascular events (a proxy for an intention-to-treat analysis).
Notes: *Major adverse cardiovascular events (MACE), a combined outcome consisting of myocardial infarction, ischemic stroke, congestive heart failure, or cardiovascular death. †Adjusted for sex, age, the Danish Comorbidity Index for Acute Myocardial Infarction categorized comorbidity burden, and use of the medications listed in Table1.

Outcome	Hazard ratio (95% confidence interval)	
	Crude	Adjusted*
Combined outcome†	0.43 (0.34–0.56)	0.69 (0.54–0.89)
Myocardial infarction	0.62 (0.40–0.95)	0.82 (0.54–1.26)
Ischemic stroke	0.54 (0.33–0.88)	0.74 (0.45–1.22)
Congestive heart failure	0.35 (0.25–0.50)	0.67 (0.47–0.96)
Cardiovascular death	0.28 (0.14-0.55)	0.60 (0.31–1.17)

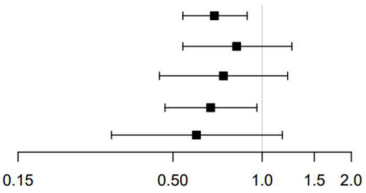

Figure 3 Association between time-varying use of ibuprofen after acute pericarditis and adverse cardiovascular events (a proxy for an as-treated analysis).
Notes: *Adjusted for sex, age, the Danish Comorbidity Index for Acute Myocardial Infarction categorized comorbidity burden, and use of the medications listed in Table1. †Major adverse cardiovascular events (MACE), a combined outcome consisting of myocardial infarction, ischemic stroke, congestive heart failure, or cardiovascular death.

Discussion

In this first nationwide study focusing on the cardiovascular risks of ibuprofen use after acute pericarditis, we found that the absolute risk of experiencing an adverse cardiovascular event after acute pericarditis was low for ibuprofen initiators. Moreover, the use of ibuprofen was not associated with any increased relative risk of adverse cardiovascular events compared with no use. In fact, the effect estimates for cardiovascular events indicated a decreased risk associated with ibuprofen initiation compared with non-initiation. This reduced risk was most pronounced in the immediate post-discharge period and was diluted, but persisted, during longer follow-up. Our results were robust when modelling ibuprofen use both *as-intended* and *as-treated* and consistent independent of dose.

Previous Literature

The rationale for treating acute pericarditis with ibuprofen comes from its anti-inflammatory effects, potentially leading to reduced pericardial inflammation and thereby reduced pain, recurrence, pericardial constriction, and cardiac tamponade.[1] However, such potential benefits could potentially be outweighed by the previously described potential cardiovascular hazards of high-dose ibuprofen related to increased thrombogenesis, blood pressure, and atherosclerotic plaque formation.[10] Indeed, three systematic reviews highlighted the lack of safety data on the use of ibuprofen to treat acute pericarditis.[11,12,29] A single placebo-controlled randomized controlled trial compared ibuprofen with indomethacin treatment for the post-pericardiotomy syndrome.[30] The study evaluated efficacy based on resolution within 48 hours of initiation of at least two of the following: fever, anterior chest pain, and friction rub, and safety based on the occurrence of side effects, including nausea, vomiting, renal failure, and fluid retention. In accordance with our results, the authors reported that treatment with ibuprofen was safe and further also effective as compared with indomethacin and placebo.[30]

Some degree of concomitant myocardial inflammation, *ie*, myopericarditis, is expected to have been present in some of the patients in this study.[1] Use of NSAIDs for myocarditis is generally not recommended due to its potential worsening of myocarditis symptoms in animal models.[31] The safety and efficacy of ibuprofen treatment of cases of myopericarditis and perimyocarditis (the latter denoting a predominantly myocardial clinical picture) remain controversial.[32] However, recent data from case-control studies on the safety of ibuprofen use for myopericarditis indicate that the use of NSAIDs does not worsen patient outcomes, nor reduce the left ventricular ejection fraction, or increase the risk of in-hospital complications.[33,34]

During recent decades, colchicine has received increased attention as an adjunct to conventional acute pericarditis treatment as several randomized controlled trials have demonstrated its effectiveness in improving remission and recurrence rates.[12] Nevertheless, colchicine has been tested in randomized clinical trials only as an adjunct to NSAIDs and never as monotherapy.[12] The latest European guidelines (from 2015) recommend using colchicine as an adjunct in all cases of uncomplicated acute pericarditis, but this was only in the later part of our study period.[1] Thus, too few patients were treated with colchicine in our data to allow for separate risk assessment of colchicine use.

Strengths and Limitations

The large cohort of patients with acute pericarditis allowed for the examination of ibuprofen independently and generated precise results for the primary combined outcome, MACE. Still, the low number of patients prescribed colchicine and aspirin precluded a comparison between the use of ibuprofen and colchicine and/or aspirin. The population-based design in a country with universal tax-supported healthcare and virtually complete long-term follow-up essentially removed all selection biases.[14]

Registration of acute pericarditis in the DNPR has been validated with a positive predictive value of 93%.[35] In general, over-the-counter ibuprofen sales account for around 25% of total ibuprofen sales in Denmark.[36] Importantly, the amount of misclassification due to over-the-counter ibuprofen sales in Denmark has been shown to be too small to substantially bias effect estimates of the association between NSAID use and cardiovascular events.[37] In addition, the prospective data collection in the Danish health registries reduces the risk of differential misclassification of ibuprofen use. In contrast to Danish guideline recommendations, only 30% of the patients initiated ibuprofen use within 7 days after discharge. This fact might partly reflect the usage of stockpiled tablets, over-the-counter or hospital-administered dispensing, the latter of which we did not have information on. Thus, some users may have been misclassified as non-users and the duration of exposure might also to some extent be misclassified. Registration of the study outcomes within the DNPR has also been validated with positive predictive values of 97% for myocardial infarction, 88% for ischemic stroke, and 76% for congestive heart failure.[35,38] Registration of many of the comorbidities has also been validated within the DNPR with high positive predictive values.[35,39–41]

We analysed the data using two different approaches. First, the *intention-to-treat analysis* aimed to reflect clinical practice as ibuprofen use was defined closer in time to pericarditis discharge. This approach further allowed for analyses of dose. Second, the *as-treated analysis* aimed to capture actual ibuprofen use during follow-up. By using the information on the filled number and the dosage of the tablets, we were able to estimate treatment lengths more precisely. As the Prescription registry does not register the intended daily dose as provided by the prescribing doctor, we used tablet doses to approximate daily dose.[19,20] The consistent results from the two approaches supported the robustness of our findings.

The comparisons within a cohort of patients with acute pericarditis likely reduced the potential for confounding. Still, initiators had overall less severe comorbidity burden, why unmeasured confounding, such as confounding by contra-indication, cannot be ruled out. We did not have information on the severity of acute pericarditis. Thus, use compared with no use of ibuprofen could reflect more severe and symptomatic disease, resulting in confounding by indication.[42] However, such confounding would likely bias the effect estimates away from the null and therefore cannot explain our findings.

Conclusions

In patients hospitalized for acute pericarditis, post-discharge ibuprofen use was not associated with increased short- or long-term cardiovascular risks compared with non-use. These findings support the safety of current practice, though a randomized trial is needed to confirm them.

Data Sharing Statement

Data sharing is not applicable to this article as no new data was created or analyzed in this study.

Acknowledgments

The abstract of this paper was presented at the ICPE 39th Annual Conference as a conference talk with interim findings. The poster's abstract was published in 'Abstracts of ICPE 2023, the 39th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), Halifax, Canada, 25–27 August 2023' in Pharmacoepidemiology and Drug Safety: https://doi.org/10.1002/pds.5687.

The study was registered via Aarhus University (record number: 810).

Author Contributions

Jakob Kjølby Eika and Kasper Bonnesen share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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