BMJ

BMJ 2011;343:d3450 doi: 10.1136/bmj.d3450

RESEARCH

Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study

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Abstract

Objectives To examine the risk of atrial fibrillation or flutter associated with use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclo-oxygenase (COX) 2 inhibitors.

Design Population based case-control study using data from medical databases.

Setting Northern Denmark (population 1.7 million).

Participants 32 602 patients with a first inpatient or outpatient hospital diagnosis of atrial fibrillation or flutter between 1999 and 2008; 325 918 age matched and sex matched controls based on risk-set sampling.

Main outcome measures Exposure to NSAID use at the time of admission (current use) or before (recent use). Current use was further classified as new use (first ever prescription redemption within 60 days before diagnosis date) or long term use. We used conditional logistic regression to compute odds ratios as unbiased estimates of the incidence rate ratios.

Results 2925 cases (9%) and 21 871 controls (7%) were current users of either non-selective NSAIDs or COX 2 inhibitors. Compared with no use, the incidence rate ratio associating current drug use with atrial fibrillation or flutter was 1.33 (95% confidence interval 1.26 to 1.41) for non-selective NSAIDs and 1.50 (1.42 to 1.59) for COX 2 inhibitors. Adjustments for age, sex, and risk factors for atrial fibrillation or flutter reduced the incidence rate ratio to 1.17 (1.10 to 1.24) for non-selective NSAIDs and 1.27 (1.20 to 1.34) for COX 2 inhibitors. Among new users, the adjusted incidence rate ratio was 1.46 (1.33 to 1.62) for non-selective NSAIDs and 1.71 (1.56 to 1.88) for COX 2 inhibitors. Results for individual NSAIDs were similar.

Conclusions Use of non-aspirin NSAIDs was associated with an increased risk of atrial fibrillation or flutter. Compared with non-users, the association was strongest for new users, with a 40-70% increase in relative risk (lowest for non-selective NSAIDs and highest for COX 2 inhibitors). Our study thus adds evidence that atrial fibrillation or flutter needs to be added to the cardiovascular risks to be considered when prescribing NSAIDs.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat inflammatory conditions and pain.[1] By inhibiting cyclo-oxygenase (COX)-1 mediated production of prostaglandins,[1] non-selective NSAIDs are known to cause gastrointestinal toxicity[1] and a variety of nephrotoxic syndromes.[2] An alternative is selective COX 2 inhibitors, available in the form of older or newer agents.[3] The newer COX 2 inhibitors, introduced into clinical practice in 1998, were developed as NSAIDs with an improved gastrointestinal side effect profile.[1] The cardiovascular safety of all marketed newer COX 2 inhibitors requires thorough evaluation in view of the increased cardiovascular[4-6] and renal risk[2] reported for several of these drugs.

Atrial fibrillation is the most common rhythm disorder observed in clinical practice. It more than doubles in prevalence during each advancing decade of life, from 0.5% at age 50-59 years to

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Webappendix: Registry codes
Webfigure: Required strength of an unmeasured confounder
Webtable 1: Characteristics of cases with atrial fibrillation or flutter and controls from northern Denmark, 1999-2008, according to their NSAID use
Webtable 2: Adjusted incidence rate ratios with 95% confidence intervals associating NSAID use and atrial fibrillation or flutter, stratified by age group, cardiovascular disease, chronic kidney disease, and rheumatoid arthritis
Webtable 3: Adjusted incidence rate ratios for atrial fibrillation or flutter comparing use of individual NSAIDs with ibuprofen as referent exposure
Webtable 4: Association between NSAID use and atrial fibrillation or flutter, overall and restricted to patients without systemic inflammatory conditions
Webtable 5: Association between NSAID use by type of medication and atrial fibrillation or flutter, overall and restricted to patients without systemic inflammatory conditions

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above 10% at age 80-89 years.[7] It is associated with increased mortality and morbidity, mainly due to haemodynamic impairments that exacerbate or even cause heart failure,[8] and a threefold to fourfold increased risk of thromboembolic stroke.[9]

Use of NSAIDs may increase the risk of atrial fibrillation through its adverse renal effects—for example, fluid retention, electrolyte disturbances, and blood pressure destabilisation [2 6]—but the evidence for such effects is limited.[10 11] Although no original research has been published on COX 2 inhibitors and atrial fibrillation, a meta-analysis summarised data from 114 clinical trials and found that rofecoxib was associated with an increased risk of cardiac arrhythmias (relative risk 2.90, 95% confidence interval 1.07 to 7.88).[10] Because the meta-analysis included only 286 incident arrhythmias, precision was low and risk of arrhythmia subtypes such as atrial fibrillation could not be examined.[10] Recently, traditional NSAIDs (that is, non-selective NSAIDs and older COX 2 inhibitors) have been associated with increased risk of chronic atrial fibrillation (incidence rate ratio 1.44, 1.08 to 1.91).[11]

Any confirmed association between use of NSAIDs and atrial fibrillation would have major clinical and public health implications. Older people are of special concern because the prevalence of use of NSAIDs and the incidence of atrial fibrillation increase with age. To address the limitations of the existing literature, we conducted a large population based case-control study examining whether and to what extent use of NSAIDs increases the risk of atrial fibrillation or flutter.

Methods

Setting

We conducted this population based case-control study in northern Denmark, which has 1.7 million inhabitants (30% of the Danish population). Since 1998 complete computerised prescription records have been available for this population.[12] Our study period encompassed 1 January 1999 to 31 December 2008, which yielded at least one year of prescription history for all study participants.

The Danish National Health Service provides universal tax supported healthcare, guaranteeing unfettered access to general practitioners and hospitals and partial reimbursement for prescribed medications, including NSAIDs.[13] Most patients with atrial fibrillation or flutter are diagnosed during a hospital admission or at a hospital outpatient clinic.[14] Very few cardiologists work outside the public hospital system in Denmark. Linkage among national registries is possible using the unique central personal registry number assigned to each Danish citizen at birth and to residents on immigration.[15]

Patients with atrial fibrillation or flutter

We used the Danish National Registry of Patients,[16] covering all non-psychiatric hospitals since 1977 and emergency room and outpatient clinic visits since 1995, to identify all patients with a first time inpatient or outpatient diagnosis of atrial fibrillation or flutter during the study period. Because atrial fibrillation and flutter share risk factors and to some degree pathophysiology,[17 18] we collapsed them into one disease entity.[17 18] More than 90% of patients registered with these codes had atrial fibrillation.[19] We considered the date of the first diagnosis of atrial fibrillation or flutter to be the index date for cases.

Population controls

We used the Danish Civil Registration System to select 10 population controls for each case, matched for age and sex.[15] This registry has recorded vital statistics for the Danish population since 1968 with daily updates.[15] We selected controls using risk set sampling.[20] Controls were assigned an index date identical to that of corresponding cases.

Non-steroidal anti-inflammatory drug use

We used the prescription database in the region[12] to identify prospectively all prescriptions of NSAIDs redeemed by cases and controls before their index date. Except for ibuprofen in the 200 mg tablet dose, all non-aspirin NSAIDs are available by prescription only.[13] Regular users of ibuprofen typically are registered in the database because the cost automatically is partly refunded when the drug is prescribed by a doctor.[13]

We identified prescriptions for non-aspirin non-selective NSAIDs (ibuprofen, naproxen, ketoprofen, dexibuprofen, piroxicam, and tolfenamic acid), older COX 2 inhibitors (diclofenac, etodolac, nabumeton, and meloxicam), and newer COX 2 inhibitors (celecoxib, rofecoxib, valdecoxib, parecoxib, and etoricoxib).[3 21] Because of overlapping COX 2 selectivity, we collapsed the groups of older and newer COX 2 inhibitors into one group.[3] Associated ATC (Anatomical Therapeutic Chemical Classification System) codes are provided in the web appendix.

We defined current users of NSAIDs as people who redeemed their most recent prescription within 60 days before their index date. We chose an exposure window of 60 days to capture most current users, as prescriptions of NSAIDs are seldom provided for more than 60 days at a time in Denmark.[22] Some side effects may arise shortly after starting treatment[2 6] and inclusion of long term users, who are more likely to tolerate the drug, could lead to underestimation of the association with atrial fibrillation or flutter.[23] We therefore categorised current users into two groups: new users, defined by having redeemed their first ever prescription within 60 days before the index date, and long term users, defined by having redeemed their first prescription more than 60 days before the index date. We defined people who had redeemed their most recent prescription 61-365 days before the index date as recent users. We defined people with no redeemed prescriptions 365 days before their index date as non-users (reference group).

Patient characteristics

Because a number of risk factors for atrial fibrillation or flutter can also be associated with use of NSAIDs,[24 25] we obtained data from the Danish National Registry of Patients on any previous hospital diagnosis since 1977 of diseases that may increase the risk of atrial fibrillation or flutter (listed in table 1).[24 25] To increase the sensitivity of the diagnoses, we used the prescription database[12] to obtain data on any use since 1998 of relevant drugs. Furthermore, we identified current use of oral glucocorticoids, because these are associated with increased risk of atrial fibrillation or flutter.[26] Associated ICD (International Classification of Diseases) and ATC codes are provided in the web appendix.

Statistical analysis

Initially, we created contingency tables for the main study variables from which we calculated the frequency of cases and controls in categories of exposure and other variables. We then stratified the contingency tables according to each of the

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potential confounding factors listed in table 1.[27] Next we used conditional logistic regression to compute odds ratios for atrial fibrillation or flutter among current, new, long term, and recent users of non-selective NSAIDs or COX 2 inhibitors.[28] Current users of both subclasses of the drugs were treated as a separate group. Because we used risk set sampling of controls, the odds ratios estimated the incidence rate ratios.[28] We fitted models controlling for the potential confounding factors listed in table 1. We repeated the analyses in predefined subgroups of sex, age, and presence or absence of cardiovascular disease, chronic kidney disease, osteoarthritis, rheumatoid arthritis, or systemic connective tissue disease. In the stratified analysis, we disregarded the matching and performed unconditional logistic regression with additional adjustments for the matching factors. We repeated the overall analysis for the six most frequently prescribed NSAIDs. To evaluate clinically relevant heterogeneity across drugs, we then compared individual NSAIDs directly using ibuprofen as the referent exposure. Because all patients needed pain relief, this comparison was likely to reduce confounding by indication. We used the tablet dose from the last redeemed prescription as a proxy for the total daily dose and examined the effect associated with low and high tablet dose.

In four secondary analyses we restricted cases to patients with atrial fibrillation or flutter: who had their diagnosis listed as the first diagnosis in the discharge summary, thereby detecting the potential effect of diagnostic surveillance bias among NSAID users;[28] who had never redeemed a prescription for digoxin or a vitamin K antagonist before their index date, thereby excluding patients with atrial fibrillation or flutter treated by their general practitioner with no previous hospitalisation; who underwent cardioversion within one year after the index date, thereby relating use of NSAIDs to disease severity; or who had no cancer, chronic obstructive pulmonary disease or asthma, inflammatory bowel disease, rheumatoid or psoriatic arthritis, or systemic connective tissue disease, thereby reducing confounding from systemic inflammation. Finally, using a rule-out approach,[29] we estimated how strongly a single unmeasured binary confounder would need to be associated with use of NSAIDs and atrial fibrillation or flutter to fully explain our findings.[29]

Results

Patient characteristics

Descriptive data are presented in table 1 for the 32 602 cases and 325 918 population controls (web table 1 divides cases and controls according to their use of NSAIDs). Among the cases, 27 984 (85.8%) were diagnosed with atrial fibrillation or flutter during hospital admission, 4220 (12.9%) at an outpatient clinic, and 398 (1.2%) at an emergency department. The median age was 75 years, and 54% were male. Among cases, 80.1% had been diagnosed previously with cardiovascular disease compared with 58.7% of controls. Cancer, chronic obstructive pulmonary disease or asthma, diabetes mellitus, glucocorticoid use, hyperthyroidism, and osteoarthritis were also more common among cases than controls.

Risk of atrial fibrillation or flutter

As table 2 shows, the age and sex matched incidence rate ratio associating current drug use with atrial fibrillation or flutter was 1.33 (95% confidence interval 1.26 to 1.41) for non-selective NSAIDs and 1.50 (1.42 to 1.59) for COX 2 inhibitors compared with non-users. The crude incidence rate ratios, dissolving the matched sets, were similar to the matched incidence rate ratios, indicating that the matched factors were on balance not associated with the exposure. Adjustment for confounders reduced the incidence rate ratio to 1.17 (1.10 to 1.24) for non-selective NSAIDs and 1.27 (1.20 to 1.34) for COX 2 inhibitors. Older and newer COX 2 inhibitors had similar estimates of effect. The increased risk was driven by new users with an adjusted incidence rate ratio of 1.46 (1.33 to 1.62) for non-selective NSAIDs and 1.71 (1.56 to 1.88) for COX 2 inhibitors.

The stratified analyses showed no observable sign of modified measure of effect by sex, osteoarthritis, or systemic connective tissue disease (data not shown). The data indicated that the risk of atrial fibrillation or flutter associated with use of NSAIDs was highest in the elderly (web table 2). Among patients with chronic kidney disease, the adjusted incidence rate ratio was 2.87 (1.53 to 5.38) for new users of COX 2 inhibitors and 1.75 (1.11 to 2.77) for long term users of non-selective NSAIDs (fig 1). Among patients with rheumatoid arthritis, the adjusted incidence rate ratio was 2.49 (1.40 to 4.42) for new users of COX 2 inhibitors and 1.44 (1.01 to 2.03) for long term users of non-selective NSAIDs). Similar to the overall results, the adjusted incidence rate ratio in the secondary analysis restricted to patients without systemic inflammatory conditions was 1.45 (1.29 to 1.63) for new users of non-selective NSAIDs and 1.64 (1.46 to 1.84) for new users of COX 2 inhibitors.

The results for the individual NSAIDs are shown in table 3. The adjusted incidence rate ratio for atrial fibrillation or flutter among new drug users was 1.43 (1.28 to 1.59) for ibuprofen, 1.44 (0.97 to 2.12) for naproxen, 1.73 (1.53 to 1.97) for diclofenac, 1.51 (1.17 to 1.95) for etodolac, 1.83 (1.44 to 2.34) for celecoxib, and 1.59 (1.24 to 2.02) for rofecoxib. In the direct drug comparison (web table 3), no NSAIDs were associated with a lower risk than ibuprofen, and diclofenac in particular conferred higher risk (1.19, 1.00 to 1.40 for new use). The increased effect estimates associated with use of the individual NSAIDs remained raised for both high dose and low dose tablets. High dose tablets of ibuprofen, naproxen, and diclofenac, however, were associated with higher risks than low dose tablets (data not shown).

Supporting the robustness of our findings, the results of the remaining three secondary analyses were similar to the overall results (web tables 4 and 5 show the results for patients without systemic inflammatory conditions). Finally, we estimated that an unmeasured confounder that was twice as frequent among users of NSAIDs as non-users would need to increase the risk of atrial fibrillation or flutter by a factor of six or more to fully explain the results, if no increased risk actually existed (web figure).

Discussion

In this large population based case-control study, we found that patients starting treatment with non-aspirin NSAIDs were at increased risk of atrial fibrillation or flutter compared with those not using NSAIDs. The relative risk increase was 40-70%—equivalent to approximately four extra cases per year of atrial fibrillation per 1000 new users of non-selective NSAIDS and seven extra cases per year of atrial fibrillation per 1000 new users of COX 2 inhibitors.[7] The risk appeared highest in older people. Patients with chronic kidney disease or rheumatoid arthritis were at particularly increased risk when starting treatment with COX 2 inhibitors.

Several issues should be considered when interpreting our results. The study's population based design within the setting of a tax supported universal healthcare system largely removed

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selection biases. The positive predictive value of a diagnosis of atrial fibrillation or flutter has been reported to be as high as 97% in the Danish National Registry of Patients.[19] Coding errors were thus unlikely to have had any important influence on our results. We considered cases of atrial fibrillation and flutter together, but our results were driven by atrial fibrillation. Although our findings also related to people treated with cardioversion within one year after first diagnosis, our study was limited by its inability to separate paroxysmal, persistent, and permanent atrial fibrillation.

Data in the prescription database are virtually complete.[12] Although we had to use prescription data as a proxy for actual use of NSAIDs, we did not base drug exposure information on written prescriptions,[11] but on actual dispensing at pharmacies.[12] Requirement of co-payment increased the likelihood of compliance.[13] We lacked information on over the counter use of low dose (200 mg/tablet) ibuprofen, which accounted for 30% of total ibuprofen sales and 15% of total NSAID sales during the study period.[13] This misclassification of drug exposure would most likely have been non-differential and thus would have biased the effect estimates towards the null. Therefore, to the extent such misclassification occurred, our effect estimates are underestimates.

Our results may be affected by confounding from unmeasured variables, particularly by underlying inflammatory conditions leading to use of NSAIDs. Although our estimates did not change when patients with systemic inflammatory conditions were excluded in a subanalysis, we cannot rule out that new users may have more severe underlying inflammation, which may increase the risk of atrial fibrillation.[30] Finally, we lacked data on lifestyle factors, including smoking and body size. Nevertheless, we note that we did adjust partly for lifestyle factors by controlling for history of cancer, chronic obstructive pulmonary disease, and ischaemic heart disease, and that our findings could not be explained by even a strong single unmeasured confounder.

Our study is the first on NSAIDs and atrial fibrillation to include both non-selective NSAIDs and COX 2 inhibitors. A case-control study of patients in the United Kingdom diagnosed in 1996 with chronic atrial fibrillation (n=1035) or paroxysmal atrial fibrillation (n=525) found that contemporary use of traditional NSAIDs was associated with an increased risk of chronic atrial fibrillation (incidence rate ratio 1.44, 95% confidence interval 1.08 to 1.91) and modestly associated with paroxysmal atrial fibrillation (1.18, 0.85 to 1.66)—that is, with magnitude of the association similar to our results.[11] By contrast with our findings, however, in the UK study, long term use of NSAIDs was associated with the largest risk increase for atrial fibrillation.

The meta-analysis,[10] involving 116 094 patients using newer COX 2 inhibitors, had 6394 composite renal outcome events but only 286 composite arrhythmia outcome events, of which ventricular fibrillation, cardiac arrest, and sudden cardiac death accounted for most.[10] Although rofecoxib was associated with an increased relative risk for the composite renal outcome of 1.53 (95% confidence interval 1.33 to 1.76) and the composite arrhythmia outcome (2.90, 1.07 to 7.88),[10] the small number and types of arrhythmias available for analysis did not allow for examination of atrial fibrillation as an outcome. In the present study, we found an increased risk of atrial fibrillation or flutter associated with older and newer COX 2 inhibitors. Notably, COX 2 inhibitors, in particular diclofenac, were associated with higher risks than non-selective NSAIDs, indicating the important pharmacological role of COX 2 inhibition.[3 5]

Use of NSAIDs may increase the risk of atrial fibrillation or flutter through renal and cardiovascular related actions. Five per cent of patients treated with NSAIDs experience nephrotoxic syndromes.[2] Both COX enzymes are expressed in distinct anatomic regions of adult kidney tissue.[2] Thus, inhibition of synthesis of COX derived prostaglandin impairs inflammation and a variety of physiological processes.[2] These changes may induce increases in blood pressure due to expansion of plasma volume, increased peripheral resistance, attenuation of diuretic and antihypertensive drug effects,[2 6] and fluctuation of serum potassium as a result of decreased potassium excretion in the distal nephron.[2] Thus, the increased risk among new users may be attributable to short term adverse renal effects of NSAIDs, which subsequently trigger atrial fibrillation.[24] The finding that patients with chronic kidney disease have a markedly higher risk when starting treatment with COX 2 inhibitors supports this hypothesis.[2 6]

In conclusion, we found that use of non-aspirin NSAIDs was associated with an increased risk of atrial fibrillation or flutter. Compared with non-users, the association was strongest for new users, with a 40-70% relative risk increase (lowest for non-selective NSAIDs and highest for COX 2 inhibitors). Our study thus adds evidence that atrial fibrillation or flutter need to be added to the cardiovascular risks under consideration when prescribing NSAIDs.

Contributors: MS, CFC, and HTS conceived the study idea. All authors designed the study. FM and HTS collected the data. MS, CFC, and HTS reviewed the literature. MS, CFC, FM, and HTS analysed the data. All authors participated in the interpretation of the findings. MS wrote the initial draft. All authors participated in critical revision of the manuscript for important intellectual content and approved the final version. HTS is the guarantor.

Funding: The study was supported by the Danish Medical Research Council (grant 271-05-0511), the Clinical Epidemiological Research Foundation, Denmark, the Danish Heart Association, and an Aarhus University scholarship. Department of Clinical Epidemiology collaborates within the EU Seventh Framework Programme: Arrhythmogenic potential of drugs (ARITMO). None of the funding sources had a role in the study design, conduct, analysis, or reporting.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any company for the submitted work, although the Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, none of which has any relation to the present study; no relation with organisations that might have an interest in the submitted work in the previous three years, except KJR, who received payment from Bayer for a lecture on venous thromboembolism; no non-financial interests that may be relevant to the submitted work.

Ethical approval: This study was approved by the Danish Data Protection Agency (record no 2004-41-4693) and the Aarhus University Hospital registry board. The study does not involve any contact with patients or any intervention, and it is not necessary to procure permission from the Danish Scientific Ethics Committee.

Data sharing: No additional data available.

1 Laine L. The gastrointestinal effects of non-selective NSAIDs and COX-2-selective inhibitors. *Semin Arthritis Rheum* 2002;32:25-32.
2 Whelton A. Renal aspects of treatment with conventional non-steroidal antiinflammatory drugs versus cyclooxygenase-2-specific inhibitors. *Am J Med* 2001;110:33S-42S.
3 Capone ML, Tacconelli S, Di Francesco L, Sacchetti A, Sciulli MG, Patrignani P. Pharmacodynamic of cyclooxygenase inhibitors in humans. *Prostaglandins Other Lipid Mediat* 2007;82:85-94.
4 Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.

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What is already known on this topic

Atrial fibrillation is the most commonly sustained rhythm disorder observed in clinical practice, and NSAIDs are among the most widely used drugs worldwide.

No previous study has examined whether use of COX 2 inhibitors increases the risk of atrial fibrillation.

What this study adds

Use of non-selective NSAIDs or selective COX 2 inhibitors was associated with an increased risk of atrial fibrillation or flutter.

Compared with non-users, the association was strongest for new users, with a 40-70% increase in relative risk (lowest for non-selective NSAIDs and highest for COX 2 inhibitors).

5 Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302-8.
6 Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med* 2005;165:490-6.
7 Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949-53.
8 Stevenson WG, Stevenson LW. Atrial fibrillation and heart failure—five more years. *N Eng J Med* 2004;351:2437-40.
9 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-8.
10 Zhang J, Ding EL, Song Y. Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. *JAMA* 2006;296:1619-32.
11 De Caterina R, Ruigómez A, Rodríguez LA. Long-term use of anti-inflammatory drugs and risk of atrial fibrillation. *Arch Intern Med* 2010;170:1450-5.
12 Ehrenstein V. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol* 2010;2:273-9.
13 Danish Medicines Agency. Reimbursement of medicines. www.dkma.dk.
14 Guidelines for treatment of atrial fibrillation in primary care in Denmark. [In Danish]www.laegehaandbogen.dk/default.aspx?document=1560.
15 Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441-9.
16 Andersen TF, Madsen M, Jorgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263-8.
17 Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. *J Am Coll Cardiol* 2008;51:779-86.
18 Badhwar N, Scheinman MM. Atrial fibrillation after atrial flutter ablation: is atrial fibrillation the primary arrhythmia? *J Cardiovasc Electrophysiol* 2008;19:1151-2.
19 Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med* 2004;164:1993-8.
20 Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. *Am J Epidemiol* 1992;135:1019-28.
21 Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med* 1998;104:413-21.
22 Thomsen RW, Riis A, Munk EM, Norgaard M, Christensen S, Sorensen HT. 30-day mortality after peptic ulcer perforation among users of newer selective COX-2 inhibitors and traditional NSAIDs: a population-based study. *Am J Gastroenterol* 2006;101:2704-10.
23 Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158:915-20.
24 Van der Hooft CS, Heeringa J, van Herpen G, Kors JA, Kingma JH, Stricker BH. Drug-induced atrial fibrillation. *J Am Coll Cardiol* 2004;44:2117-24.
25 Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840-4.
26 Christiansen CF, Christensen S, Mehnert F, Cummings SR, Chapurlat RD, Sørensen HT. Glucocorticoid use and risk of atrial fibrillation or flutter: a population-based, case-control study. *Arch Intern Med* 2009;169:1677-83.
27 Greenland S, Schwartzbaum JA, Finkle WD. Problems due to small samples and sparse data in conditional logistic regression analysis. *Am J Epidemiol* 2000;151:531-9.
28 Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology* . 3rd ed. Lippincott Williams and Wilkins, 2008.
29 Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;15:291-303.
30 Engelmann MD, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *Eur Heart J* 2005;26:2083-92.

Accepted: 4 March 2011

Cite this as: *BMJ* 2011;343:d3450

BMJ: first published as 10.1136/bmj.d3450 on 4 July 2011. Downloaded from http://www.bmj.com/ on 18 January 2020 by guest. Protected by copyright.

Tables

Table 1| Characteristics of patients with atrial fibrillation or flutter and controls from northern Denmark, 1999-2008. Data are number (%)

	Cases (n=32 602)	Controls (n=325 918)
Sex, female	14 993 (46.0)	149 878 (46.0)
Age, years		
0-49	1544 (4.7)	15 506 (4.8)
50-59	3358 (10.3)	33 473 (10.3)
60-69	6277 (19.3)	63 242 (19.4)
70-79	10 273 (31.5)	102 303 (31.4)
>80	11 150 (34.2)	111 394 (34.2)
Comorbidity		
Alcoholism related disorder*	901 (2.8)	6171 (1.9)
Cancer†	4089 (12.5)	31 638 (9.7)
Cardiovascular diseases		
Hospital diagnosis†	26 127 (80.1)	191 200 (58.7)
Use of cardiovascular drugs‡	25 657 (78.7)	188 516 (57.8)
ACE or A2R inhibitors	9820 (30.1)	65 598 (20.1)
Aspirin	14 304 (43.9)	96 294 (29.6)
β blockers	11 598 (35.6)	63 144 (19.4)
Calcium channel blockers	9001 (27.6)	58 259 (17.9)
Diuretics	18 316 (56.2)	126 537 (38.8)
Nitrates	6809 (20.9)	41 147 (12.6)
Statins	3913 (12.0)	27 431 (8.4)
Other antihypertensives	887 (2.7)	6259 (1.9)
Chronic kidney disease†	874 (2.7)	3608 (1.1)
COPD or asthma§	7987 (24.5)	53 448 (16.4)
Current use of oral glucocorticoids‖	2246 (6.9)	10 383 (3.2)
Diabetes mellitus§	3192 (9.8)	22 715 (7.0)
Hyperthyroidism§	1614 (5.0)	10 335 (3.2)
Hypothyroidism§	1263 (3.9)	11 827 (3.6)
Liver disease or chronic pancreatitis†	306 (0.9)	2068 (0.6)
Osteoarthritis†	4249 (13.0)	35 458 (10.9)
Rheumatoid arthritis†	592 (1.8)	4112 (1.3)
Systemic connective tissue disease†	791 (2.4)	5811 (1.8)

ACE=angiotensin converting enzyme; A2R=angiotensin-2 receptor; COPD=chronic obstructive pulmonary disease.

*Acute alcohol intoxication or alcoholism related disease other than those affecting the liver or pancreas.

†Any hospital diagnosis recorded in the Danish National Registry of Patients since 1977.

‡Any redeemed prescription recorded in the prescription database since 1998.

§Any hospital diagnosis since 1977 or any redeemed prescription since 1998 of associated drugs.

‖Prescription redemption within 60 days before the index date.

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Table 2| **Association between use of NSAIDs and atrial fibrillation or flutter**

		Incidence rate ratio (95% CI)	
	Number of cases/controls	Unadjusted*	Adjusted†
No use‡	24 593/260 139	1.00 (reference)	1.00 (reference)
Non-selective NSAIDs			
Current use§	1 385/10 985	1.33 (1.26 to 1.41)	1.17 (1.10 to 1.24)
New use||	480/3197	1.59 (1.44 to 1.75)	1.46 (1.33 to 1.62)
Long term use¶	905/7788	1.23 (1.14 to 1.32)	1.05 (0.98 to 1.13)
Recent use**	2 315/20 453	1.20 (1.14 to 1.25)	1.09 (1.04 to 1.14)
COX 2 inhibitors			
Current use§	1 540/10 886	1.50 (1.42 to 1.59)	1.27 (1.20 to 1.34)
Older COX 2 inhibitors	977/6 981	1.49 (1.39 to 1.60)	1.31 (1.22 to 1.40)
Newer COX 2 inhibitors	448/3 119	1.51 (1.37 to 1.67)	1.20 (1.09 to 1.33)
New use||	561/3088	1.93 (1.76 to 2.11)	1.71 (1.56 to 1.88)
Long term use¶	979/7798	1.33 (1.24 to 1.43)	1.10 (1.03 to 1.18)
Recent use**	2 078/18 634	1.18 (1.13 to 1.24)	1.04 (0.99 to 1.09)
Older COX 2 inhibitors	1 396/12 892	1.11 (1.05 to 1.17)	1.01 (0.96 to 1.07)
Newer COX 2 inhibitors	596/5 152	1.23 (1.13 to 1.35)	1.02 (0.94 to 1.12)
Combination††	79/468	1.79 (1.41 to 2.27)	1.47 (1.15 to 1.87)

*Age and sex matched.

†Adjusted for all covariates listed in table 1 using conditional logistic regression.

‡No prescription redemption for any NSAID within 365 days before the index date.

§Prescription redemption within 60 days before the index date.

||Current users who redeemed their first ever prescription within 60 days before the index date.

¶Current users who redeemed their first prescription more than 60 days before the index date.

**Most recent prescription redemption within 61-365 days before the index date.

††Current use of both non-selective NSAIDs and COX 2 inhibitors.

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Table 3| **Association between use of NSAIDs by type of medication and atrial fibrillation or flutter**

		Incidence rate ratio (95% CI)	
	Number of cases/controls	Unadjusted	Adjusted
No use	24 593/260139	1.00 (reference)	1.00 (reference)
Ibuprofen			
Current use	1044/8484	1.30 (1.22 to 1.39)	1.15 (1.07 to 1.23)
New use	389/2660	1.55 (1.39 to 1.72)	1.43 (1.28 to 1.59)
Long term use	655/5824	1.19 (1.09 to 1.29)	1.02 (0.94 to 1.11)
Recent use	1868/16295	1.21 (1.15 to 1.27)	1.10 (1.05 to 1.16)
Naproxen			
Current use	102/738	1.46 (1.19 to 1.80)	1.28 (1.04 to 1.59)
New use	30/213	1.49 (1.01 to 2.18)	1.44 (0.97 to 2.12)
Long term use	72/525	1.45 (1.13 to 1.85)	1.23 (0.95 to 1.58)
Recent use	171/1390	1.30 (1.11 to 1.53)	1.19 (1.01 to 1.40)
Diclofenac			
Current use	684/4654	1.56 (1.44 to 1.69)	1.38 (1.27 to 1.50)
New use	292/1647	1.88 (1.66 to 2.13)	1.73 (1.53 to 1.97)
Long term use	392/3007	1.38 (1.24 to 1.53)	1.19 (1.07 to 1.33)
Recent use	1021/9527	1.13 (1.06 to 1.21)	1.03 (0.96 to 1.10)
Etodolac			
Current use	223/1730	1.37 (1.19 to 1.57)	1.18 (1.03 to 1.36)
New use	70/451	1.64 (1.28 to 2.11)	1.51 (1.17 to 1.95)
Long term use	153/1279	1.27 (1.07 to 1.50)	1.07 (0.91 to 1.27)
Recent use	285/2605	1.16 (1.03 to 1.31)	1.04 (0.92 to 1.18)
Celecoxib			
Current use	201/1380	1.55 (1.34 to 1.80)	1.22 (1.05 to 1.42)
New use	83/387	2.29 (1.80 to 2.90)	1.83 (1.44 to 2.34)
Long term use	118/993	1.27 (1.05 to 1.53)	0.99 (0.81 to 1.20)
Recent use	287/2487	1.23 (1.09 to 1.40)	1.02 (0.90 to 1.16)
Rofecoxib			
Current use	210/1483	1.51 (1.31 to 1.75)	1.23 (1.06 to 1.43)
New use	80/443	1.93 (1.52 to 2.45)	1.59 (1.24 to 2.02)
Long term use	130/1040	1.33 (1.11 to 1.60)	1.08 (0.89 to 1.30)
Recent use	278/2312	1.29 (1.13 to 1.46)	1.07 (0.94 to 1.22)

See user definitions and description of unadjusted and adjusted model in text and table 2.

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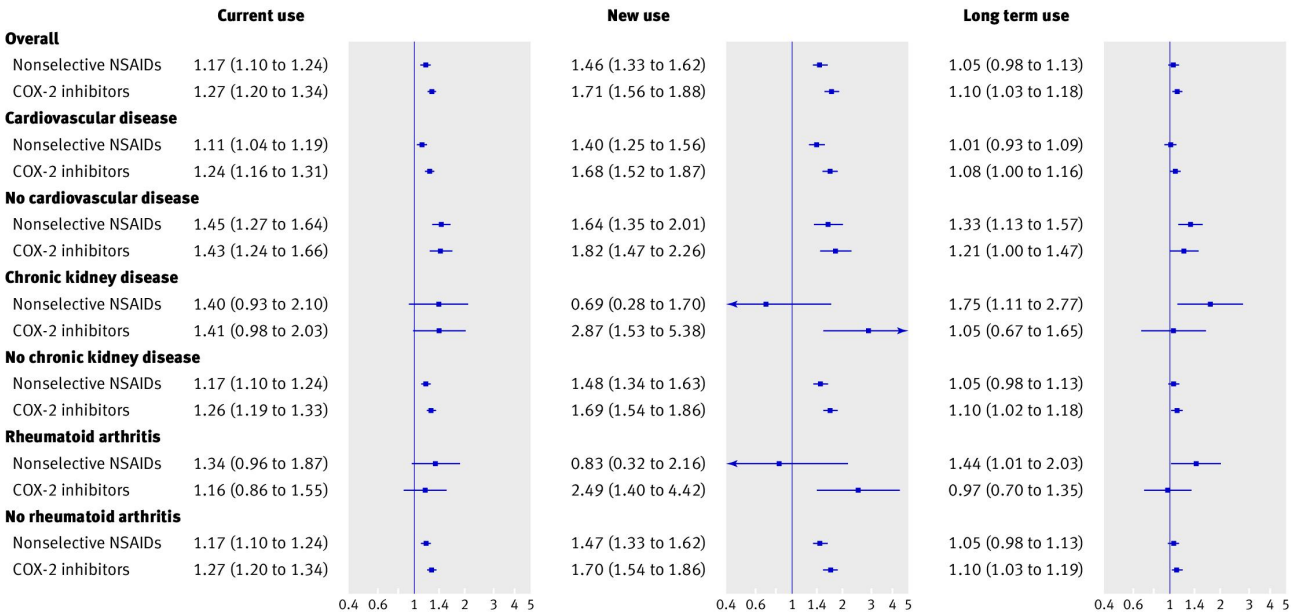
Figure



Adjusted incidence rate ratios (95% confidence intervals) for the association between use of NSAIDs and atrial fibrillation or flutter in patients with or without cardiovascular disease, chronic kidney disease, or rheumatoid arthritis

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