MJ - Decision on Manuscript ID BMJ.2015.029885

Body: 08-Dec-2015

Dear Prof. Corrao

Manuscript ID BMJ.2015.029885 entitled "Non-steroidal anti-inflammatory drugs and the risk of heart failure: a nested case-control study from four European countries in the SOS Project"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Jose Merino
jmerino@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Julie Morris (statistical consultant), Tiago Villanueva, Georg Roeggla, Wim Weber, José Merino

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. In particular, please pay special attention to the comments of the statistical reviewer (reviewer 6 below).

Most editors found that the scale of the study was a plus but there are questions over novelty. In the end, however, there was consensus that the focus on so many individual NSAIDs was clinically useful.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
Very interesting analysis of real-world data. The study's aims, the outcomes being measured, and the issues and questions the paper addresses, are relevant not only to high-risk HF individuals, but to broader worldwide public health.
Over the counter NSAIDs are mentioned on manuscript page 13, and that led me to wonder if the NSAIDs tracked in the study were all prescription strength, or if they varied in strength from prescription to OTC. If the increased HF risk applies only to prescription strength NSAIDs, then knowledge of this risk needs to focus on providers - if the increased risk is the same if taking OTC NSAIDs, then there is a larger public health education campaign that needs to occur.
I would have liked to have seen gender differences reported in the results - e.g. men are at greater for risk for HF if prescribed diclofenac, while women are at greater risk if prescribed indomethacin.
In the results section of the abstract, the "estimated adjusted odds ratio of...of HR hospitalization associated with current use of any NSAID was 1.20" - is that 1.20 a decimal expression of the ratio? Should it be written as a ratio instead - 12:10 ? Or change to percent increased risk (roughly 20%) ?

Additional Questions:

Please enter your name: Erica Lake

Job Title: Associate Librarian

Institution: Spencer S. Eccles Health Sciences Library, University of Utah, United States

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Reviewer: 2

Recommendation:

Comments:
General comments
- Thank you for the opportunity to review. The authors present a nested case-control study examining the risk of hospitalization for heart failure among users of NSAIDs and COX-2 inhibitors across healthcare databases from four European countries. The number of NSAIDs and COX-2 inhibitors examined as well as the sample size in this study is robust and a strength of the study. This study examines patients using these medications in the 'real-world' and appears to add to the body of literature on this topic.
Major comments
- Methods: Because the comparison group here are non-users of these medications, it is possible that patients using NSAIDs or COX-2 inhibitors may be more likely to be hospitalized due to increased exposure to their provider and the healthcare system. Is it possible to identify an control group (e.g., acetaminophen or aspirin users) that is not thought to be associated with an increased risk of HF to see whether the associations persist? Comparisons without an active comparator group may be tricky due to inherent differences in the study populations.
- Methods: Please provide more information on the control group. Did they ever experience a HF hospitalization? Or just not in that period of time that they were matched?
- Methods: While mentioned in the discussion, please clarify more that the patients included in the study could have diagnosed HF at baseline. The motivation for the study appears to be the association between NSAID/COX-2 use and clinically-significant HF (defined here as 'hospitalization for HF'); however, if HF differs substantially between the case and control groups at baseline, naturally there would be differences in hospitalizations for HF (and it may not be possible to fully control for this). Why not also examine the association among patients without any HF at baseline? This information might help provide information to answer the key biological questions presented in the introduction.
Minor comments
- Methods: Is it possible to capture previous use of NSAIDs or COX-2 inhibitors (and the extent to which that may affect the 'control' population)?
- Methods: To help the reader interpret the study findings, please provide information per medication (in the Appendix) about what was considered to be "low", "medium", "high" and "very high" dose class.
- Discussion: Please provide a biological rationale here for why NSAIDs might be associated with increased risk of a HF hospitalization.
- Discussion: Is there any information on the extent to which any dispensations of NSAIDs or COX-2 inhibitors may not be captured within the healthcare databases? In the US, because traditional NSAIDs are usually (and most often) dispensed without a prescription (over-the-counter), so they are frequently not captured in databases. If there are medications that are not captured in the databases, this could potentially affect the study results through misclassification of exposure, but agree that this would likely bias towards the null.
Discretionary comments
- Abstract: If space permits, please provide motivation for this work here.
- Abstract: Please define "current use" in the abstract as well as the cases and controls used for the comparisons.
- Methods: With 27 different NSAID comparisons, please address whether there is any risk of multiple comparisons affecting the study results.
- Methods: Please consider whether a sensitivity analysis of any diagnosis of HF in the outpatient

setting may be possible. While HF is complex, it may be worth exploring any diagnosis to provide additional generalizability to the study.
- Methods: Please provide a motivation for using a nested case-control study rather than a full cohort study.
- Discussion: Was the study 'powered' sufficiently to examine all of the NSAIDs (even in a post-hoc analysis)?
- Discussion: The study appears to be potentially underpowered for some dose classes (Figure 3). Please provide this as a limitation.

Additional Questions:
Please enter your name: Julie Lauffenburger

Job Title: Research Fellow

Institution: Brigham and Women's Hospital

Reimbursement for attending a symposium?: No

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Reviewer: 3

Recommendation:

Comments:
Name: Kristian Filion
Position: Assistant Professor of Medicine
Institution: McGill University

GENERAL COMMENTS:
In this nested case-control study from four European countries, Arfe and colleagues examine the association between non-steroidal anti-inflammatory drugs (NSAIDs) and the risk of heart failure (HF). This study, conducted as part of the larger SOS project, has several strengths, including the use of 5 population-based healthcare databases, which produced precise estimates and results that are likely highly generalizable. Other strengths include the inclusion of both a common data analysis (using a single database) and site-specific analyses with random-effects meta-analysis; the presentation of both provides key information regarding potential residual confounding and increases the transparency of such multi-site studies. However, there are several methodological issues that require clarification; these issues are described in detail in the specific comments below.

SPECIFIC COMMENTS:
1. The study cohorts consisted of new users of NSAIDs, with past users of NSAIDs (i.e., those with no use in the 183 days before the index date) as the reference group for all analyses. This reference group renders the results somewhat difficult to interpret. These past users will have discontinued use for a variety of reasons, including improved symptoms, the occurrence of side effects, and poor adherence. Did the authors consider using current users of one of the individual NSAIDs are the reference group? Such a comparison may also be more clinically relevant, particularly given the information presented in the second to last paragraph of the introduction.

2. It is also likely that some of the past users were prescribed short-term NSAID therapy for an acute event (e.g., sports injury, dental work), and these patients may have an inherently different risk of HF relative to those who are using NSAIDs long-term to treat chronic conditions. Similarly, different NSAIDs may be prescribed preferentially for different indications. Some discussion of confounding by indication is warranted.

3. Was a minimum duration of NSAID prescription required for cohort entry? In addition, was inclusion restricted based on route of NSAID administration? For example, could a patient enter the cohort due to a prescription of a topical NSAID?

4. Controls were selected using incidence density sampling, matching on database, sex, age at cohort entry, and date of index prescription. With all patients entering the cohort on an NSAID prescription (and thus initially exposed), person-moments earlier during follow-up were thus more likely to be exposed to an NSAID than those later during follow-up. Did the authors consider also matching on duration of follow-up (via risk set sampling) to ensure that cases and controls had the same opportunity for exposure?

5. In the Introduction, the authors discuss that current guidelines limit the use of NSAIDs in patients predisposed to HF and prohibit their use in patients with diagnosed HF. With approximately 9% of cases and 2.5% of controls having a history of HF, the inclusion of some subgroup analyses and/or tests for interaction would be informative.

6. In site-specific analyses, covariates should be included in the model based on substantive knowledge and not p-values. If an automated variable selection process is used, the use of AIC or BIC is preferred.

7. The inclusion of duration-response analyses would also be helpful. For example, some evidence suggests that the increase in myocardial infarction with rofecoxib only occurred after 18 months of use.

8. Minor comments:
a. Abstract, methods: Please mention how cases were matched to controls.
b. Abstract, results: Please mention that the reference group was past users of NSAIDs.
c. It would be helpful to mention in the "Harmonization and Data Processing" section that a common data model was used in the primary analysis.
d. Covariates: Some of the descriptions of covariates are somewhat vague (e.g., "other drugs for CV diseases", "specific drugs as proxies for certain diseases and conditions not well recorded in the databases"). Please provide a complete list as an appendix.

Additional Questions:
Please enter your name: Kristian Filion

Job Title: Assistant Professor of Medicine

Institution: McGill University

Reimbursement for attending a symposium?: No

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Reviewer: 4

Recommendation:

Comments:
This study investigated the association between non-steroidal anti-inflammatory drugs and the risk of heart failure using data from 4 population-level hospital databases. The authors did a very thorough job. My only question is that why DB-specific results were not provided for the dose-response analysis? Why a similar verification approach as the main analysis was not used for the dose-response analysis?

Additional Questions:
Please enter your name: Yujie Wang

Job Title: Biostatistician

Institution: UNC

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 5

Recommendation:

Comments:
Manuscript ID: bmj.2015.029885 -" Non-steroidal anti-inflammatory drugs and the risk of heart failure: a nested case-control study from four European countries in the SOS Project"

This study by Arfe et al is a multinational case-control study including data from 4 different countries in 5 databases, investigating the risk of hospitalization for heart failure associated with incident NSAID use. The study included 92,163 cases hospitalized for heart failure that were matched with 8,246,403 controls. The main results of the study that both traditional NSAIDS and selective COX-2 inhibitors were associated with increased risk of heart failure hospitalizations and there was evidence for dose-related increase in risk. Notably, the selective COX-2 inhibitor celecoxib was not associated with increased risk of heart failure hospitalization.

General comments
This is a carefully conducted study addressing an important topic related to the safety of NSAIDs in the general population. Although the results of the study are not novel, the study adds to the accumulating body of evidence linking NSAIDs with unfavourable cardiovascular safety.
The study design is nested case-control study and suffers from the caveats encountered in such study design, but the authors carefully address weaknesses and potential confounders in the manuscript. The main strength of the study is that it includes a large cohort of cases and controls but data are from heterogeneous and multiple data sources that are sought harmonized during data management.

Specific comments
1. I had some problems understanding the datasets used for the study and how participants entered the database's and the completeness of follow-up. This is a major issue and could influence detection of the primary outcome as well as exposure to NSAIDs. Please clarify.
2. In the methods section you describe how you excluded individuals who did not have at least one year of uninterrupted observation prior to the index prescription date. How does this affect your prior history of e.g. heart failure or cardiovascular disease?
3. There is lot of heterogeneity in data between the individual databases and you describe that you harmonized data during data management and before pooling datasets. Did that in any way influence cohort selection or completeness of data?
4. I do not agree with your approach to only include primary discharge code of heart failure to define outcome since heart failure is often associated with other cardiovascular diagnoses, e.g. myocardial infarction or atrial fibrillation, and therefore affect detection of outcome events. Although the effect of this most likely would be non-differential, we know that NSAIDs increase risk of ischemic heart disease and atrial fibrillation which might affect how discharge codes were prioritized and therefore heart failure events missed.
5. We know from other databases that the sensitivity of heart failure diagnosis is notoriously poor, but with acceptable positive predictive value and specificity. This would be even more pronounced by only including primary discharge coding diagnoses.
6. Not all heart failure patients are hospitalized and many are managed as outpatients in specialized heart failure clinics or outpatient clinics. This is being more frequent during the last years and therefore this might affect detection of heart failure events if you only included inpatients.
7. It is intriguing that you do not find any association between celecoxib and increased risk of heart failure hospitalization, which is further supported in the dose response analyses. During the study period, there has been lot of discussion on the unfavourable effect of NSAIDs on CV risk and in particular the selective COX-2 inhibitors. Thus, this could have directed physicians towards more use of non-selective NSAIDs and less use of celecoxib in high-risk patients. Did you see any trend towards change in use of different NSAIDs according to risk profile of patients (e.g. lower CV disease or hypertension in celecoxib users) during the study period?
8. There are some important differences in baseline characteristics between the cases and controls

that could influence the results. In particular, there is much more frequent use of cardiac pharmacotherapy in general among cases compared to controls. Use of these drugs could represent risk factors for heart failure (e.g. hypertension or atrial fibrillation) that are being treated, or established heart failure that had not yet been hospitalized and managed in outpatient clinic or primary care. This if quite fundamental and could influence results, therefore the authors could have considered matching fewer controls on each case (it is bit of an overkill to match 100 controls on each case) and tried to achieve better balance in baseline characteristics between cases and controls, for example by using propensity score based matching or matching on more parameters. I would very much like to see results were

Additional Questions:
Please enter your name: Gunnar H. Gislason

Job Title: Professor of Cardiology

Institution: University of Copenhagen

Reimbursement for attending a symposium?: No

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Reviewer: 6

Recommendation:

Comments:
There are a number of statistical concerns about this nested case-control study.

Methodology:

1. The data are pooled from 5 electronic databases covering 4 European countries and were 'harmonised' to obtain comparable "…variable and outcome definitions…"'. What evidence is there to show that the resulting information is equivalent? Also, patients from the databases appear to form quite different cohorts. For example, 16% of cases in the Germany cohort had acute MI as a comorbidity compared to 1% in the UK cohort and 2% in the Italy cohort.

2. Cases were those hospitalised for HF during follow-up. But what percentage of heart failure patients are hospitalised? Does this vary between countries?

3. What is the estimated percentage of 'missed' NSAID drug exposure (due to 'over the counter' prescribing)? Does this vary between countries? If the percentage is large then I am not sure an 'understatement' of the actual association between NSAIDs and HF risk can be claimed.

4. "…up to 100 controls…" were selected for each case identified. Why 100? What is the power of the study, for individual drugs, to detect significant ORs? [Figure 3 shows very wide confidence intervals for dose-response relationships for specific drugs – based on only 2 countries with this data- indicating low power]

5. Cohort subjects were classified into current, recent and past NSAID use. The latter acted as the 'reference group' and included those whose prescription was more than 183 days before the index date. Might this not introduce confounding by indication? What were the possible reasons for stopping?

Analysis:

6. Only covariates available in all databases were used in the statistical analysis. Does this include all features listed in Table 2? Are there any important covariates which could not be included?

7. The primary statistical analysis related to pooling individual data, whereas the secondary

involved pooling summary database estimates. For the latter, results are presented for the individual drugs in the Supplementary tables. However, I could find no estimate for current use of any NSAID using the secondary approach. Was this analysis carried out? It would be useful to compare this result with the estimated OR of 1.20 obtained from the individual pooled data.

8. The dose-response analysis was restricted to 2 countries only (UK and the Netherlands). Was an analysis carried out of the overall (ie. non dose-response) data for these two countries to see how it compared with the 1.20 OR for HF hospitalisation of any NSAID use for all 4 countries?

9. A large number of individual NSAIDs are considered, and hence the problem of multiple testing and the increased possibility of chance statistically significant findings should be acknowledged.

Presentation:

10. Overall (pooled) estimates should be added to Figures 1 and 2.

Additional Questions:
Please enter your name: Julie Morris

Job Title: Head of Medical Statistics

Institution: UHSM

Reimbursement for attending a symposium?: No

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c. Introduction: This should cover no more than three paragraphs, focusing on the research question and your reasons for asking it now.

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END

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