Risk of hospital admissions for heart failure with non-steroidal anti-inflammatory drugs

A European nested case-control study including 92,163 cases and 8,246,403 controls found that current use of any non-steroidal anti-inflammatory drug (NSAID) increased the risk of admission to hospital for heart failure by nearly 20% compared with past use. The study suggests a dose-response effect with very high doses of etoricoxib and diclofenac more than doubling the risk of admission to hospital for heart failure. Prescribers should continue to follow MHRA prescribing advice on use of NSAIDs, and base prescribing on assessment of a person’s individual risk factors (including cardiovascular and gastrointestinal), ensuring that the lowest effective dose is used for the shortest possible time.

Overview and current advice

Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic and anti-inflammatory properties and can be used for many painful conditions. There are long-standing and well-recognised gastrointestinal and renal safety concerns with all NSAIDs. There is also substantial evidence confirming an increased risk of cardiovascular events with many NSAIDs, including COX-2 selective inhibitors and some traditional NSAIDs such as diclofenac. In the June 2015 edition of Drug Safety Update, the MHRA gave prescribing advice on the use of all NSAIDs:

- The decision to prescribe an NSAID should be based on an assessment of a person's individual risk factors, including any history of cardiovascular and gastrointestinal illness.
- Naproxen (1000 mg a day or less) and low-dose ibuprofen (1200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.
- The lowest effective dose should be used for the shortest duration necessary to control symptoms. A person's need for symptomatic relief and response to treatment should be re-evaluated periodically.

The risk of heart failure with NSAID use has been highlighted in previous randomised controlled trials and observational studies. However the risk with individual NSAIDs and whether the effect is dose-dependent is largely unknown. The NICE clinical knowledge summary on NSAIDs-prescribing issues recommends that NSAIDs are not prescribed for anyone with severe heart failure, and that COX-2 selective inhibitors, diclofenac and high-dose ibuprofen (2400 mg or more daily) should not be prescribed for people with mild, moderate or severe heart failure. The May 2009 edition of Drug Safety Update reminded prescribers of the renal safety concerns with NSAIDs and highlighted that people with conditions including congestive heart failure may be at a particular risk of experiencing these.
New evidence

A nested case-control study investigated the risk of hospital admission for heart failure with individual NSAIDs.

The study used data from 5 electronic databases from the UK, Italy, Germany and the Netherlands. A cohort of new users of NSAIDs consisting of 7,690,181 adults aged 18 years and over who received at least 1 prescription or dispensation of NSAIDs between the years 2000–2010 was formed from the databases. People were excluded if they did not have at least 1 year of uninterrupted observation before cohort entry, if they received 1 or more NSAIDs within the year previous to cohort entry (to exclude prevalent NSAID users), if they received a diagnosis of malignant cancer (except non-melanoma skin cancer), or if they had been admitted to hospital with a primary diagnosis of heart failure in the year before cohort entry. Each cohort member was followed up until the date of first hospital admission for heart failure, end of registration in the database because of death or emigration, diagnosis of malignancy or the end of database-specific data availability.

A case-control study was nested into the cohort. A total of 92,163 cohort members were admitted to hospital for heart failure during follow up (cases; the date of the first hospital admission for heart failure admission was the index date). Cases (mean age 77 years) were matched to 8,246,403 controls (mean age 76 years) based on age at cohort entry, gender and date of cohort entry. Compared with controls, cases had more comorbidities (mainly cardiovascular) and received concomitant drug treatment more often. A total of 9.1% of cases and 2.5% of controls had a history of heart failure diagnosis recorded as either outpatient diagnosis or secondary hospital diagnosis in the year before cohort entry. All NSAIDs received by cohort members during follow-up were identified. People were classified as current NSAID users if they had used NSAIDs at or within the previous 14 days of the index date, recent users if they have used NSAIDs 15–183 days before the index date, or past users otherwise. A dose-response analysis based on defined daily doses was performed using databases which recorded dose (Netherlands and UK databases).

A total of 16,081 (17.4%) cases and 1,193,537 (14.4%) controls were current users of NSAIDs. The most frequently used traditional NSAIDs included diclofenac, nimesulide (an NSAID not available in the UK) and ibuprofen. The most commonly used COX-2 selective inhibitors were celecoxib, rofecoxib (withdrawn from the market in 2004) and etoricoxib.

A pooled analysis found that current users of any NSAID had a greater risk of hospital admission for heart failure compared with past users (odds ratio [OR] 1.19, 95% confidence interval [CI] 1.17 to 1.22). A statistically significant increase in risk of hospital admission for heart failure was found for 7 traditional NSAIDs (ketorolac, indometacin, piroxicam, diclofenac, nimesulide, ibuprofen and naproxen) and 2 COX-2 selective inhibitors (etoricoxib and rofecoxib) compared with past use. A dose-response analysis found that current use of very high doses of diclofenac (more than 200 mg daily) and etoricoxib (more than 120 mg daily) at least doubled the risk of heart failure compared with past use.

This study had several limitations. Firstly, it only captured data on prescribed and dispensed NSAIDs, information on NSAIDs purchased over the counter was not captured. Secondly, heart failure is often associated with other cardiovascular diseases such as myocardial infarction and this could have affected the way in which hospital admissions were coded. Thirdly, the dose-response analysis may have been underpowered because only 2 of the 5 databases recorded information on dose. In addition, there were missing data on dosage in the 2 databases meaning some people were excluded. Fourthly, there were differences in the baseline characteristics between cases and controls. Although the authors attempted to adjust for this, the possibility of residual differences between baseline
characteristics may have accounted for some of the observed differences in relative risk estimates associated with the different NSAIDs. Finally, some diseases and drugs may affect the risk of heart failure. Although the authors tried to adjust for these, the possibility of residual confounding cannot be ruled out.

**Commentary**

**Commentary provided by NICE**

This study found that current use of any NSAID increased the risk of hospital admission for heart failure by nearly 20%, and adds to current knowledge about the increased risk of heart failure associated with NSAID use. It provides information on which specific NSAIDs are associated with increased risk. It was interesting to see that some NSAIDs such as ibuprofen and naproxen, which at lower doses are considered safer in terms of cardiovascular risk, were found to be associated with a statistically significant increase in the risk of hospital admission for heart failure. This suggests that all NSAIDs, even those which are safer in terms of cardiovascular risk, carry risks and prescribers should ensure they take into account a person’s individual risks when considering prescribing any NSAID.

The study included a dose-response analysis which found that very high doses of diclofenac and etoricoxib more than doubled the risk of admission to hospital for heart failure. It should be noted that these doses are greater than the maximum recommended dose for these drugs in the relevant summaries of product characteristics. This highlights the need to ensure doses prescribed are in line with the recommended doses. For etoricoxib, the MHRA has recently issued advice for healthcare professionals on prescribing information for rheumatoid arthritis or ankylosing spondylitis which has been updated to introduce a lower recommended dose of 60 mg daily. For people with insufficient relief from symptoms, an increased dose of 90 mg once daily may improve efficacy, but this should be titrated back down to 60 mg daily once the condition is clinically stabilised.

This study adds to the information on risks of NSAID use. Prescribers should continue to follow MHRA advice on the use of NSAIDs, ensuring that the decision to prescribe should be based on an assessment of a person's individual risk factors, including any history of cardiovascular and gastrointestinal illness. Naproxen and low-dose ibuprofen are considered to have the most favourable thrombotic cardiovascular safety profiles of all non-selective NSAIDs. The lowest effective dose should be used for the shortest duration necessary to control symptoms and the person's need for symptomatic relief and response to treatment should be re-evaluated periodically. NSAIDs should be not prescribed for anyone with severe heart failure, and COX-2 selective inhibitors, diclofenac and high-dose ibuprofen (2400 mg or more daily) should not be prescribed for people with mild, moderate or severe heart failure.

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**References**

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