Reviewer's report

Title: Risk of new acute myocardial infarction hospitalization associated with use of oral and parenteral non-steroidal anti-Inflammation drugs (NSAIDs): A case-crossover study of Taiwan’s National Health Insurance claims database and review of current evidence

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Reviewer: Paola Patrignani

Reviewer's report:

In the present manuscript, Shau et al studied the risk of new acute myocardial infarction (AMI) hospitalization resulting from current use of a variety of oral and parenteral NSAIDs in a nationwide population and compared their results with existing evidence.

They conducted a retrospective case-crossover study by using the claims database of Taiwan’s National Health Insurance, identifying patients hospitalized for a new episode of AMI in 2006. They defined the case period as 1 to 30 days before hospital admission, and the matched control period as 91 to 120 days prior to admission for each patient. Uses of NSAIDs during case and control periods were compared using conditional logistic regression and adjusted for use of co-medications in the respective periods.

They found that the risk of AMI significantly increased with use of oral and parenteral non-selective NSAIDs, the adjusted odds ratio, aOR (95% confidence interval), were 1.42 (1.29, 1.56) and 3.35 (2.05, 4.47) respectively. The use of parenteral and some oral NSAIDs, especially ketorolac, are associated with increased risk of acute myocardial infarction. The strength of adjusted association between current use of celecoxib and the risk of new AMI hospitalization was moderate and comparable to the ORs with other oral ns-NSAIDs. However, a great limitation was that the total number of patients in the celecoxib group with MI was limited to 79 for all the 39 trials included in the meta-analysis.

This study is exploring a clinically relevant issue however I think that the methodology used, ie case-crossover design, is not valid to study the association between NSAIDs and AMI. The reasons are well discussed in the paper by Hernández-Díaz et al (Am J Epidemiol 2003;158:385–391).

“Case-crossover designs are appropriate only to evaluate transient exposures with immediate and transient effects in relation to abrupt outcomes (abrupt outcomes being defined as outcomes with a short sensitive time period). Although some drugs are given for acute illnesses (e.g., a 7-day course of trimethoprim for urinary tract infection), others are given for chronic conditions (e.g., carbamazepine for epilepsy).
Since NSAIDs are given quite frequently (over 50% above the age of 50 years) for long durations case-crossover designs seem inappropriate to study the association between NSAIDs and AMI.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests