Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction: A Nationwide Cohort Study

Circulation
May 21, 2011; Vol. 123; No. 20: pp. 2226-2235

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FROM ABSTRACT:
Background—Despite the fact that nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated among patients with established cardiovascular disease, many receive NSAID treatment for a short period of time. However, little is known about the association between NSAID treatment duration and risk of cardiovascular disease. We therefore studied the duration of NSAID treatment and cardiovascular risk in a nationwide cohort of patients with prior myocardial infarction (MI).

Methods and Results—Patients ≥30 years of age who were admitted with first-time MI and their subsequent NSAID use were identified by individual-level linkage of nationwide registries of hospitalization and drug dispensing from pharmacies in Denmark. Risk of death and recurrent MI according to duration of NSAID treatment was analyzed by multivariable time-stratified Cox proportional-hazard models.

Of the 83,677 patients included, 42.3% received NSAIDs during follow-up. There were 35,257 deaths/recurrent MIs.

Overall, NSAID treatment was significantly associated with an increased risk of death/recurrent MI (45% increased risk) at the beginning of the treatment, and the risk persisted throughout the treatment course (55% increased risk after 90 days).

Analyses of individual NSAIDs showed that the traditional NSAID diclofenac [Voltaren] was associated with the highest risk (226% increased risk for death/MI at day 1 to 7 of treatment).

Conclusions—Even short-term treatment with most NSAIDs was associated with increased risk of death and recurrent MI in patients with prior MI.

Neither short- nor long-term treatment with NSAIDs is advised in this population, and any NSAID use should be limited from a cardiovascular safety point of view.

KEY POINTS FROM THESE AUTHORS:

1) Nonsteroidal anti-inflammatory drugs (NSAIDs) increase “cardiovascular risk in healthy individuals and in patients with established cardiovascular disease.”
2) “International guidelines discourage NSAID treatment in patients with established cardiovascular disease, eg, myocardial infarction (MI) and heart failure.”

3) The most commonly used NSAIDs were ibuprofen [Motrin] (23.2%) and diclofenac [Voltaren] (13.4%). Rofecoxib [Vioxx] (4.7%) and celecoxib [Celebrex] (4.8%) were the most commonly used selective COX-2 inhibitors.

4) “In brief, overall NSAID treatment was associated with statistically significantly increased risk of death at the beginning of the treatment, and the increased risk persisted throughout the course of treatment.”

5) “The selective COX-2 inhibitor rofecoxib [Vioxx] was associated with increased risk of death after a treatment duration of 7 to 14 days, whereas celecoxib [Celebrex], another selective COX-2 inhibitor, was associated with increased risk of death after a treatment duration of 14 to 30 days.”

6) “The traditional NSAID diclofenac [Voltaren] was associated with increased risk from the beginning of treatment, and the risk persisted throughout the course of treatment.”

7) Ibuprofen [Motrin] showed an increased risk when used for >1 week.

8) “Overall, NSAID treatment was associated with a significantly increased risk of death/Re-MI from the start of the treatment.”

9) “Rofecoxib [Vioxx] was associated with an increased risk of death/Re-MI already in the first week of the treatment.”

10) “The main results of the study were that the risks of death and death/Re-MI were independent of the duration of NSAID treatment, and that the risk with some NSAIDs became apparent immediately (diclofenac [Voltaren] or early (rofecoxib [Vioxx] and ibuprofen [Motrin]) after treatment onset.”

11) “These results challenge the view that NSAIDs are not harmful during short-term (1 week) treatment and indicate that a revision of current recommendations regarding NSAID treatment in patients with established cardiovascular disease is required.”

12) “Patients with prior MI are at increased risk when taking NSAIDs, especially diclofenac [Voltaren] and the selective COX-2 inhibitors.”

13) “The risk of death and MI during treatment with diclofenac [Voltaren] was increased immediately after the start of treatment, and persisted. It is noteworthy that a commonly used nonselective NSAID like diclofenac [Voltaren] is associated with an even higher risk of death [226%] at the beginning of the course of treatment than the selective COX-2 inhibitor rofecoxib [Vioxx], which was withdrawn from the market in 2004.”
14) “It would seem prudent to limit NSAID use in patients with cardiovascular disease and to get the message out to clinicians taking care of these patients that NSAIDs are potentially harmful, even for short-term treatment.”

15) “Naproxen was not associated with an increased risk of death or MI for the entire treatment duration.” However, naproxen is associated with a higher risk of gastrointestinal bleeding, “and that gastrointestinal bleeding in patients with prior MI is associated with worse prognosis.” “Indeed, the adverse prognostic impact of gastrointestinal bleeding further supports a very conservative approach to use of NSAIDs in patients with prior MI.”

16) “This nationwide study of patients with prior MI demonstrated that short-term treatment with most NSAIDs is associated with increased cardiovascular risk.”

17) “Particularly worrying is the fact that diclofenac [Voltaren]{ which in some countries is available over the counter} was associated with higher cardiovascular risk than the selective COX-2 inhibitor rofecoxib [Vioxx], which was withdrawn from the market in 2004 owing to its unfavorable cardiovascular risk profile.”

18) “The present results indicate that there is no apparent safe therapeutic window for NSAIDs in patients with prior MI and challenge the current recommendations of low-dose and short-term use of NSAIDs as being safe.”

19) “Evidence suggests that we must limit NSAID use to the absolute minimum in patients with established cardiovascular disease.”

20) “We found that short-term treatment with most NSAIDs was associated with increased and instantaneous cardiovascular risk.”

21) “Our results indicate that there is no apparent safe therapeutic window for NSAIDs in patients with prior myocardial infarction and challenge the current recommendations of short-term use of NSAIDs as being safe.”

COMMENTS FROM DAN MURPHY

When reading a study like this, I am reminded of the article by the neurosurgeon from the Pittsburgh Steelers, Joseph Maroon, MD, in 2006. Dr. Maroon found that taking omega-3 essential fatty acids was superior to NSAIDs for pain control 88% of the time, and with none of these side effects. Article Review 21-06:

**Omega-3 Fatty acids (fish oil) as an anti-inflammatory: an alternative to nonsteroidal anti-inflammatory drugs for discogenic pain**

*Surgical Neurology*  
65 (April 2006) 326–331

In fact, Maroon’s fish oil approach probably benefited the heart.