Non-Steroidal Anti-Inflammatory Drugs (NSAID) Abuse - An Evolving, Novel Risk Factor for Coronary Artery Disease (CAD)

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Received: October 21, 2019; Published: October 29, 2019

In the ever evolving pathophysiology and epidemiology of Coronary Artery Disease (CAD) there has been a surge in the number of implicated risk factors for CAD. One of the less highlighted risk factor but of greater epidemiological importance (especially in the developing countries) is the nonsteroidal anti-inflammatory drugs (NSAIDs) abuse, as they are used to relieve pain and inflammation in multitude of clinical conditions. There are many studies (case control studies to meta-analysis of observational studies) [1,2] that have reported the association between NSAID intake and the risk of CAD in the past. But the extent of attributable risk could not be ascertained in those studies because of small cohorts size and their poor generalizability [3]. With the widespread use of NSAIDs (especially in the developing countries) and a steep rise in CAD, NSAIDs abuse assumes more important role as a risk factor for CAD in developing countries where NSAIDs are available without prescription as over the counter (OTC) drugs. There have been few case reports of AMI where NSAID abuse was the only risk factor present (no conventional risk factors) [4]. Hence, the need of the hour is to conduct population based observational studies to establish the risk of acute myocardial infarction (AMI) associated with NSAIDs usage, as they reflect the extent of NSAIDs usage/(abuse) in real world practice.

The mechanistic pathway leading to CAD/AMI with NSAIDs usage is by inhibition of Prostaglandin I2 (PGI2) synthesis [5]. PGI2 causes vasodilatation, inhibits platelet aggregation, and prevents the proliferation of vascular smooth muscle cells. Depression of PGI2 formation leads to high blood pressure, accelerated atherogenesis and predisposition to exaggerated thrombotic response to the rupture of an atherosclerotic plaque [5]. Other mechanisms associated with the use of individual NSAIDs, such as effects mediated through the renal system and increases in arterial blood pressure, could be implicated in the variability of the risk of CAD across individual NSAIDs.

NSAIDs abuse and the consequent risk of developing CAD / acute myocardial infarction (AMI) is understated in most of the guidelines [6] (e.g. The “2019 ACC/AHA guideline on the Primary Prevention of Cardiovascular Disease” lists NSAIDS as drugs that predispose to increased bleeding risk alone and not as a risk factor/enhancer for CAD/AMI). The probable cause for the paucity of recommendations for NSAIDs as a risk factor for CAD is lower relative risk (at the prescription doses) as compared to gastrointestinal complications limiting the statistical power to examine variations in the risk in previous studies [7]. Results of some of the studies have shown a higher relative risk associated with current use of NSAIDs in the young [1] which could mean a lot of morbidity and mortality in the young leading to significant economic losses for the developing countries. The relative risk was similar for patients with or without major cardiovascular (CV) risk factors [1].

All NSAIDs do not exhibit the same degree of class effect as far as CAD risk is concerned. Among the NSAIDs, naproxen and low-dose ibuprofen, were found to be the safer NSAIDs (lesser risk of developing AMI) in previous studies [8]. Previous studies have also reported that the NSAIDs with a lesser degree of COX-2 inhibition (e.g. Ibuprofen, Etoricoxib) have a lesser relative risk of AMI compared to those with greater COX-2 inhibition (e.g. Diclofenac, Indomethacin, and Piroxicam) [9]. The results of all the studies done in the past associate Diclofenac (irrespective of the dosage or duration of therapy) and ibuprofen (high dose) with a higher risk of developing CAD/AMI [1,8].

In contradiction to all the previous studies, a recent study by Bally, et al. has shown that current use of any of the traditional NSAIDs, including naproxen, was associated with a significantly increased risk of AMI and that the onset of risk of AMI increased immediately with exposure to NSAIDs with the risk being the maximum in the first month of treatment with higher doses [10].

In conclusion, it is important that the practicing physicians and surgeons be aware of the association of NSAIDs use/abuse with the risk of developing CAD/AMI and should weigh the risks and benefits of prescribing NSAIDs to their patients, particularly at higher doses, till the newer guidelines endorse the strength of association/risk. Safer alternatives for analgesia like acetaminophen and tramadol can be preferentially prescribed in day to day practice. If indicated, Naproxen and low dose - Ibuprofen can be prescribed in patients with low background risk of cardiovascular events, for a shorter duration. People with high risk of CV events should be cautioned against the use of NSAIDs and the probable risk of developing CAD/AMI with their usage.

Bibliography


Volume 6 Issue 11 November 2019
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