

1 Q: What are FDA labeling requirements for NSAIDs, and what does FDA recommend regarding their dosing?

A: In 2005, FDA required manufacturers of all marketed prescription NSAIDs to revise the labeling for their products to include a Boxed Warning and a Medication Guide¹:

- The Boxed Warning highlighted the potential for increased risk of serious cardiovascular (CV) events with these drugs, as well as the increased risk of serious gastrointestinal (GI) events including bleeding, ulceration, and perforation of the stomach and intestines
- FDA recommended using the lowest effective dose for the shortest duration consistent with individual patient treatment goals

In July 2015, FDA strengthened the Boxed Warning to include statements that nonaspirin NSAIDs increase the chance of a heart attack or stroke. According to this safety communication, prescription NSAID labels were revised to reflect the following information²:

- The risk of heart attack or stroke can occur as early as the first weeks of using an NSAID
 - The risk may increase with longer use of the NSAID
- The risk appears greater at higher doses
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease

2 Q: What are the most recent updates from FDA on NSAID risks and dosing?

A: In 2016, FDA continues to recommend using the lowest effective NSAID dose for the shortest duration consistent with individual patient treatment goals. FDA also required that NSAID labels be updated with the following information:

- Increased CV thrombotic risk has been observed most consistently at higher NSAID doses
- There is an increased risk of heart failure with NSAIDs
- There is an approximate 2-fold increase in hospitalizations for heart failure in NSAID-treated patients compared to placebo-treated patients

3 Q: How did FDA arrive at its recommendations on NSAID dosing?

A: FDA reviewed data from multiple observational studies, meta-analyses of clinical trials, and other scientific publications. In February 2014, FDA held a public advisory committee meeting at which it reviewed data from more than 130 randomized controlled trials and more than 50 observational studies.²⁻⁴

4 Q: What factors should I consider when prescribing an NSAID?

A: FDA warnings highlight the potential for increased risk of CV and GI adverse events when using NSAIDs. These warnings also indicate that nonaspirin NSAIDs increase the risk of heart attack and myocardial infarction (MI) as well as GI bleeding, ulcers, and perforation.^{1,2} Research shows that the risk of serious CV, GI, and renal adverse events increases with dose⁵⁻⁷ and can occur within the first week of treatment.⁷⁻⁹ Additionally, FDA recommends using the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.²

5 Q: Do other medical organizations or advocacy groups also support FDA recommendations on NSAID dosing?

A: Yes. The American College of Cardiology,¹⁰ the American Heart Association,¹⁰ the American College of Rheumatology,¹¹ the National Kidney Foundation,¹² and the Alliance for Rational Use of NSAIDs¹³ are health care groups who support using NSAIDs at the lowest effective dose for the shortest duration.

6 Q: What evidence supports the claim that NSAIDs increase the risk for serious CV, GI, and renal adverse events and that this risk is dose related?

A: Many observational studies have demonstrated that the risk of certain serious adverse events from NSAIDs can be dose related and life-threatening in nature. In one study, high NSAID doses increased the risk of CV events by 28% compared to low-medium doses.⁵ In another study, high NSAID doses increased the risk of upper GI complications by 104% compared to low-medium doses.⁶ In a third study, high NSAID doses increased the risk of acute renal failure by 35% compared to low-medium doses.⁷

7 Q: Are there still risks with using COX-2 selective inhibitors or NSAIDs with gastroprotective agents?

A: Yes. Studies have demonstrated that using selective COX-2 inhibitors or nonselective NSAIDs in combination with gastroprotective agents can decrease the risk of GI adverse events.¹⁴ However, this does not preclude the possibility of other serious adverse events, such as CV events. Clinical trials of several COX-2 selective and nonselective NSAIDs of up to 3 years' duration have shown an increased risk of serious CV thrombotic events, including MI and stroke, which can be fatal.⁴

8 Q: The risk of serious CV, GI, and renal adverse events associated with NSAID use has been shown to be dose related.⁵⁻⁷ However, aren't high doses required to provide a therapeutic dose for my patients who need it most?

A: NSAIDs are presumed to possess an analgesic ceiling effect in which additional increases in dose provide no further analgesic benefit.^{15,16} However, the risk of certain serious adverse events may continue to grow with increasing doses.⁵⁻⁷

9 Q: I'd like to keep my patients who suffer from acute pain on high NSAID doses for a few weeks. What does the literature say about that?

A: Research shows that the risk of heart attack, stroke, GI complications, or renal failure can occur as early as the first weeks of using an NSAID,⁷⁻⁹ and appears to be greater at higher doses.⁵⁻⁷

10 Q: What considerations do I need to make when prescribing NSAIDs for patients with a history of heart disease?

A: There is an increased risk of heart failure with NSAID use. Avoid use of NSAIDs in patients with a recent MI or severe heart failure unless benefits are expected to outweigh risk of CV events.³ Safety language released by FDA indicates an approximately 2-fold increase in hospitalization for heart failure in NSAID-treated patients compared to placebo-treated patients.

Additionally, FDA strengthened its Boxed Warning to include statements that nonaspirin NSAIDs increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease. FDA also indicated that the risk of heart attack or stroke can occur as early as the first weeks of using an NSAID. The risk may increase with longer use of the NSAID and appears greater at higher doses.²

11 **Q:** I only prescribe NSAIDs for patients with no known predisposition for heart disease. Do I still need to be concerned about CV risks?

A: The relative increase in serious CV thrombotic events associated with NSAID use is similar in patients with and without known CV disease or risk factors for CV disease. This risk increases with higher doses.²

12 **Q:** Are certain NSAIDs safer with regard to CV thrombotic risks?

A: All nonaspirin NSAIDs have been associated with serious CV adverse events. However, it is unclear if the risk of CV thrombotic events is similar for all nonaspirin NSAIDs.²

References:

1. US Food and Drug Administration. Public health advisory - FDA announces important changes and additional warnings for COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm>. Published April 7, 2005. Accessed August 15, 2016. 2. US Food and Drug Administration Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. <http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm>. Published July 9, 2015. Accessed August 15, 2016. 3. US Food and Drug Administration. Joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee: nonsteroidal anti-inflammatory drugs and cardiovascular thrombotic risk. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM383180.pdf>. Published February 10-11, 2014. Accessed August 15, 2016. 4. Coxib and traditional NSAID Trialists' (CNT) Collaboration; Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet*. 2013;382(9894):769-779. 5. García Rodríguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. *J Am Coll Cardiol*. 2008;52(20):1628-1636. 6. García Rodríguez LA, Hernández-Díaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. *Epidemiology*. 2001;12(5):570-576. 7. Huerta C, Castellsague J, Varas-Lorenzo C, García Rodríguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am J Kidney Dis*. 2005;45(3):531-539. 8. Helin-Salmivaara A, Virtanen A, Vesalainen R, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. *Eur Heart J*. 2006;27(14):1657-1663. 9. Helin-Salmivaara A, Saarelainen S, Grönroos JM, Vesalainen R, Klaukka T, Huupponen R. Risk of upper gastrointestinal events with the use of various NSAIDs: a case-control study in a general population. *Scand J Gastroenterol*. 2007;42(8):923-932. 10. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol*. 2007;50(7):e1-e157. 11. American College of Rheumatology Ad Hoc Group on use of Selective and Nonselective Nonsteroidal Antiinflammatory Drugs. Recommendations for use of selective and nonselective nonsteroidal antiinflammatory drugs: an American College of Rheumatology white paper. *Arthritis Rheum*. 2008;59(8):1058-1073. 12. National Kidney Foundation. Pain medicines (analgesics). https://www.kidney.org/atoz/content/painMeds_Analgesics. Accessed May 25, 2016. 13. Alliance for Rational Use of NSAIDs – NSAID Alliance HCP Brochure. Western Pain. 2014. <http://www.nsaidalalliance.com/wp-content/uploads/2014/09/NSAID-Alliance-HCP-Brochure-Web.pdf>. Accessed June 29, 2016. 14. Tuskey A, Peura D. The use of H2 antagonists in treating and preventing NSAID-induced mucosal damage. *Arthritis Res Ther*. 2013;15 Suppl 3:S6. 15. Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen and clinical analgesic response. *Clin Pharma Ther*. 1986;40(1):1-7. 16. Eisenberg E, Berkey CS, Carr DB, Mosteller F, Chalmers TC. Efficacy and safety of nonsteroidal anti-inflammatory drugs for cancer pain: a meta-analysis. *J Clin Onc*. 1994;12(12):2755-2765.