

## Importance of adherence to gastroprotection during cyclooxygenase 2 inhibitor treatment

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**Title:** Adherence to gastroprotection during cyclooxygenase 2 inhibitor treatment and the risk of upper gastrointestinal tract events

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### Summary

Evidence shows that suboptimal adherence to gastroprotective agents (GPAs) decreases the beneficial effects on the risk of upper gastrointestinal (GI) complications (UGIC) associated with the use of traditional non steroidal anti-inflammatory drugs (NSAIDs) [1]. There is less evidence about the role of GPA adherence for lowering the risk of UGIC in selective cyclooxygenase (COX)-2 inhibitors users.

A recent nested case-control study by Valkhoff *et al* [2] aimed to determine the association between GPA adherence and upper GI (UGI) tract events (an UGIC or a symptomatic ulcer) among selective COX-2 inhibitors users. Authors obtained the data from three dynamic population-based primary care databases of UK, The Netherlands and Italy. Three kinds of exposure cohorts were created. The first was the total selective COX-2 treated cohort, which was split into the other 2 cohorts: selective COX-2 minus GPA-treated cohort and selective COX-2 plus GPA treated cohort. The case-control study nested within selective COX-2 inhibitors plus GPA treated cohort. Cases were patients who were newly starting treatment with selective COX-2 inhibitors plus GPA (at least 1 day of GPA exposure) and had a UGI tract event during the selective COX-2 inhibitor treatment or within a maximum of 60 days thereafter. Each case was matched with all eligible patients without UGI events in treatment with selective COX-2 inhibitors and GPA for age, sex, database

and calendar date. Adherence to GPA was calculated as the percentage of days of selective NSAIDs treatment covered by a GPA. Non adherence was defined as <20% of days covered and full adherence as > 80% of days covered.

The study involved 81,000 selective COX-2 inhibitor-treated patients. 14,416 of them were treated with selective COX-2 inhibitors plus GPA, generating 16,442 treatment intervals. Thirty days were the median duration of treatment interval. Overall adherence was 76%. Seventy four patients had a UGI tract event during follow up, with an incidence rate of 11.9 (95% CI 9.4-14.8) per 1,000 years of selective COX-2 inhibitors treatment. Patients who were non-adherent to GPA and those who were moderately adherent had a non-significant 2-fold and 1.5-fold increased risk of UGI events, respectively, (OR 1.97 [95% CI 0.84-4.60] and OR 1.55 [95% CI 0.91- 2.62]), compared to patients who were fully adherent. Therefore, the risk of a UGI event grew significantly by 9%, with every 10% drop in GPA adherence during selective COX-2 inhibitor treatment (OR 1.09 [95% CI 1.00-1.18],  $P=0.045$ ). On the other hand, the level of adherence was higher in patients with higher number of risk factors, but decreased with longer treatment intervals.

In brief, the authors suggest that decreasing GPA adherence among selective COX-2 users is associated with an increased risk of UGI tract events, a similar conclusion to what had been previously reported among traditional NSAID users.

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### Opinion

NSAIDs are the core treatment for many rheumatic diseases, but their use is associated with a broad spectrum of side effects, especially GI ones. Two therapeutic approaches are commonly used to prevent the development of UGI damage in NSAIDs users: 1) co-therapy with GPAs; and 2) substitution of a selective COX-2 inhibitor for a traditional NSAID. A recent systematic review of randomized controlled trials (RCTs) showed that selective COX-2 inhibitors produced

significantly fewer ulcer complications compared with traditional NSAIDs [RR 0.39 (95% CI 0.31-0.50)], although they did not abolish the risk [3].

Several studies have evaluated the effects of co-prescription of selective COX-2 inhibitors and proton pump inhibitors (PPI). Chan *et al* [4] showed that high-risk patients (prior UGI bleeding) who were treated with combined therapy (esomeprazole + celecoxib) for 1 year had no recurrent ulcer bleeding compared with a recurrence rate of 9% in those treated with celecoxib alone. Previously, Scheiman *et al* [5] conducted two RCTs that showed significantly lower gastroduodenal ulcer rates in patients treated with COX-2 inhibitors plus GPA compared with selective COX-2 inhibitors alone. Based on these data, guidelines for the prevention of NSAID-related ulcer complications recommend that patients at very high GI risk should be treated with alternative therapy to NSAIDs, if possible, or with a selective COX-2 inhibitors plus a GPA to minimize the risk [6]. Unfortunately, in clinical practice these recommendations are not always followed. Today, low rates of prescription of GPA in at-risk NSAID users and poor patient adherence to the prescribed GPA are two major challenges to reduce serious GI complications in these patients. Reported rates of non-adherence broadly range from 9 to 80% [7-10]. Suboptimal adherence to GPAs (defined as adherence <80% of the prescribed days) has been associated with a 2.5- to 4-fold increase in the risk of UGI bleeding in traditional NSAIDs users [7-10].

There is little evidence on the role of adherence to GPAs in COX-2 selective agent users. Valkhoff *et al* [2] suggest that GPA adherence to reduce UGIC or symptomatic ulcers is as important in selective-COX-2 users as it is in patients treated with traditional NSAIDs. Their study showed that COX-2 selective NSAIDs users with no adherence to GPA had a 2-fold increased risk of UGI event compared to adherent patients, although this difference was not statistically significant. However, in a previous study published by Goldstein [8], the likelihood of UGI tract events remained relatively constant across all GPA adherence levels for COX-2 selective NSAID users. Some differences among both studies could explain these discordant outcomes. The population in Goldstein's study [8] were younger than in Valkhoff's study [2] (mean age 50.2 years versus 69.3 years). Moreover, only 979 patients were treated with selective COX-2 inhibitors plus PPI in Goldstein's study vs. 14,416 patients in Valkhoff's study [2]. Lastly, the dose of rofecoxib routinely used in the US was lower than in Europe.

As mentioned previously, Valkhoff's study [2] used data of 3 European databases which were collected for clinical use and therefore, it described real-world physician behavior, which is very interesting. But this and other studies of the same type, of course, have some limitations. Rates of adherence were calculated with data of prescribed GPAs and COX-2 inhibitors, and not with data of drugs consumed by patients. Moreover, it is not possible to know if GPAs were prescribed for prevention of UGIC or for other reasons. Finally, authors showed the association between several UGI risk factors and UGI tract events, but they did not analyze the influence of

GPA adherence in the particular subgroup of high GI risk patients (previous UGIC, multiple risk factors or concomitant use of anticoagulants or corticosteroids). This data would be of interest since according to current guidelines, selective COX-2 inhibitors plus GPA only should be prescribed to these high-risk patients.

Despite the limitations commented on above, this study adds new information on the current knowledge in the field, concerning the need for improvement in adherence of patients to the prescribed GPAs when associated with NSAID therapy. The fact that in this study, the authors demonstrated that GPA adherence is also important in the reduction in GI events associated with the apparently GI safe COX-2 inhibitors, must reinforce the concept that all traditional NSAIDs and COX-2 selective inhibitors increases the risk of UGIC, and that there is room for improvement in patients with GI risk receiving these drugs. New compounds are now in the market combining in one pill a traditional NSAID plus a GPA, but we may need other compounds combining a COX-2 selective NSAID associated with a GPA for the target population at the highest risk to develop UGIC.

## References

1. Rostom A, Dube C, Wells G, et al. Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev* 2002;**4**:CD002296.
2. Valkhoff VE, van Soest EM, Mazzaglia G, et al. Adherence to gastroprotection during cyclooxygenase 2 inhibitor treatment and the risk of upper gastrointestinal tract events: a population-based study. *Arthritis Rheum* 2012;**64**:2792-2802.
3. Rostom A, Muir K, Dubé C, et al. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. *Clin Gastroenterol Hepatol* 2007;**5**:818-828.
4. Chan FK, Wong VW, Suen BY, et al. Combination of a cyclooxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. *Lancet* 2007;**369**:1621-1626.
5. Scheiman JM, Yeomans ND, Talley NJ, et al. Prevention of ulcers by esomeprazole in at-risk patients using non-selective NSAIDs and COX-2 inhibitors. *Am J Gastroenterol* 2006;**101**:701-710.
6. Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009;**104**:728-738.
7. Sturkenboom MC, Burke TA, Tangelder MJ, et al. Adherence to proton pump inhibitors or H2-receptor antagonists during the use of non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2003;**18**:1137-1147.
8. Goldstein JL, Howard KB, Walton SM, et al. Impact of adherence to concomitant gastroprotective therapy on nonsteroidal-related gastroduodenal ulcer complications. *Clin Gastroenterol Hepatol* 2006;**4**:1337-1345.
9. van Soest EM, Sturkenboom MC, Dieleman JP, et al. Adherence to gastroprotection and the risk of NSAID-related upper gastrointestinal ulcers and haemorrhage. *Aliment Pharmacol Ther* 2007;**26**:265-275.
10. Lanas A, Polo-Tomás M, Roncales P, Gonzalez MA, Zapardiel J. Prescription of and adherence to non-steroidal anti-inflammatory drugs and gastroprotective agents in at-risk gastrointestinal patients. *Am J Gastroenterol* 2012;**107**:707-714.