Letters to the Editor

Send letters to Kenneth W. Lin, MD, Associate Medical Editor for *AFP* Online, e-mail: afplet@aafp.org, or 11400 Tomahawk Creek Pkwy., Leawood, KS 66211-2680.

Please include your complete address, e-mail address, telephone number, and fax number. Letters should be fewer than 400 words and limited to six references, one table or figure, and three authors.

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Unsupported Risks of Proton Pump Inhibitor Use

Original Article: Reducing Adverse Effects of Proton Pump Inhibitors

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Available at: http://www.aafp.org/afp/2012/0701/p66.html

TO THE EDITOR: I found this review of proton pump inhibitors (PPIs) to be complete and well written. However, the reported risks of hip fractures associated with PPI use and of cardiac events when PPIs are used in combination with clopidogrel (Plavix) were overstated.

Although case-control studies based on administrative data showed an increased odds ratio for PPI use in persons who sustained hip fractures, this association did not hold for persons without other preexisting fracture risk factors.[1] Prospective cohort studies have not shown an increased hip fracture risk in PPI users. PPI use does not appear to be associated with reduced bone density, which calls into question the hypothetical mechanism of reduced calcium absorption. Any association between PPI use and hip fractures might be explained by other risk factors in patients who tend to require PPIs, such as those who smoke.

As for the suggested increased risk of cardiac events in persons taking clopidogrel and PPIs, more recent cohort studies, a recent randomized controlled trial, and meta-analyses of the highest quality studies have not shown any association.[2] Therefore, I would be reluctant to withhold PPIs from patients who might benefit from them based on undue concerns about unsubstantiated risks.

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Author disclosure: No relevant financial affiliations to disclose.

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1. U.S. Food and Drug Administration. FDA Drug Safety Communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm. Accessed June 29, 2012.
2. Drepper MD, Spahr L, Frossard JL. Clopidogrel and proton pump inhibitors—where do we stand in 2012? *World J Gastroenterol.* 2012;18(18):2161-2171.

IN REPLY: We appreciate the detailed analysis and comments by Dr. Konrad. The goal of our article was to make readers aware of potential adverse effects of long-term PPI use. Clinical data suggest that long-term use needs to be scrutinized, especially in older patients.

Dr. Konrad's reference from the U.S. Food and Drug Administration (FDA) states that over-the-counter (OTC) PPIs "are only intended for a 14 day course of treatment up to 3 times per year. … Healthcare professionals should be aware of the risk for fracture if they are recommending use of OTC PPIs at higher doses or for longer periods of time than in the OTC PPI label."[1]

As we stated, the clinical significance of interactions between PPIs and clopidogrel is unknown. However, retrospective analysis has shown an increased risk of rehospitalization and adverse coronary events with concomitant use of PPIs and clopidogrel. Also, the FDA required a change to the prescribing information for clopidogrel to reflect the increased risk.[2] We agree that patients taking clopidogrel who would clearly benefit from PPI use should be prescribed a PPI. However, selecting a PPI other than omeprazole (Prilosec), administering the PPI at a different time than clopidogrel, or substituting a high-dose histamine H_2 antagonist may be preferred.

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Author disclosure: Dr. Ament serves on the speakers' bureaus of Merck and Pfizer, which manufactures the proton pump inhibitor pantoprazole (Protonix).

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1. U.S. Food and Drug Administration. FDA Drug Safety Communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm. Accessed July 24, 2012.
2. Plavix (clopidogrel) [product information]. Bridgewater, N.J.: Bristol-Myers Squibb/Sanofi Pharmaceutical Partnership; 2009.

Clarification: Failure to Disclose

AFP's conflict-of-interest policy[1] states: "To avoid bias or the perception of bias, *AFP* will not consider manuscripts sponsored directly or indirectly by a pharmaceutical company, medical communications company, or other commercial entity, or those written by an author who has a financial relationship with or interest in any commercial entity that may have an interest in the subject matter of the article within the previous 36 months. It also includes serving on a commercial speaker's bureau or advisory board, or receiving commercial research support related to the subject matter of the article, as well as other relationships detailed in our conflict of interest policy."

It has come to our attention that Dr. Ament, coauthor of the article "Reducing Adverse Effects of Proton Pump Inhibitors" (July 1, 2012, p. 66), failed to disclose his financial relationships with Merck and Pfizer, which existed at the time of submission and publication of his article. He erroneously believed that these relationships, which focused on antibiotic use and stewardship, were not relevant to the subject of the article and did not need to be disclosed. Had we been aware of his relationship with Pfizer, which manufactures the proton pump inhibitor pantoprazole (Protonix), we would have declined to review the article, and it would not have been published. However, because the article has already been published, and because the U.S. National Library of Medicine recommends not removing published articles from their online status,[2] we are publishing this notice of failure to disclose, and have updated the disclosure status of the online version of the article.

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1. *American Family Physician*. Authors' guide. http://www.aafp.org/online/en/home/publications/journals/afp/afpauthors.html. Accessed August 1, 2012.
2. U.S. National Library of Medicine. National Institutes of Health. Fact sheet: errata, retractions, partial retractions, corrected and republished articles, duplicate publications, comments (including author replies), updates, patient summaries, and republished (reprinted) articles policy for Medline. http://www.nlm.nih.gov/pubs/factsheets/errata.html. Accessed August 1, 2012.

Clarification: Updated Recommendations

Although the Practice Guidelines "ACS Releases Updated Guidelines on Cancer Screening" (September 15, 2012, p. 571) accurately reflected the content of the source guideline, the American Cancer Society (ACS) subsequently updated its guidance on screening for cervical cancer in conjunction with the American Society for Colposcopy and Cervical Pathology and the American Society for Clinical Pathology.[1] The updated ACS recommendations are largely consistent with those from the U.S. Preventive Services Task Force (USPSTF), which were also published in the September 15, 2012 issue of *AFP* (p. 555), in advising that cervical cancer screening begin at 21 years of age, regardless of the age of onset of sexual intercourse; that screening occur every three years for women 21 to 29 years of age; and that women 30 to 65 years of age be provided the option of co-testing with cytology and human papillomavirus testing every five years, rather than cytology alone every three years. The editorial "ACS/ASCCP/ASCP Guidelines for the Early Detection of Cervical Cancer" (September 15, 2012, p. 501) reviewed and compared the 2012 guidelines of the ACS and USPSTF.

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REFERENCE

1. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012;62(3):147-172. ■