Missed opportunities in the trial on proton-pump inhibitor therapy in bleeding peptic ulcers [4]

ARTICLE *in* ANNALS OF INTERNAL MEDICINE · OCTOBER 2009

Impact Factor: 17.81 · DOI: 10.7326/0003-4819-151-8-200910200-00022 · Source: PubMed

1 AUTHOR:

Alejandro Piscoya

Universidad Peruana de Ciencias Aplicadas (…

65 PUBLICATIONS **89** CITATIONS

SEE PROFILE

References

1. US Preventive Services Task Force. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;150:396-404. [PMID: 19293072]
2. Medical College of Wisconsin. Risk Assessment Tool. Accessed at http://healthlink.mcw.edu/article/923521437.html on 20 March 2009.
3. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-47. [PMID: 9603539]
4. National Cholesterol Education Program. 10-year CVD Risk Calculator. 19 March 2009. National Heart Lung and Blood Institute. Accessed at http://hp2010.nhlbihin.net/atpiii/calculator.asp on 11 September 2009.
5. Lenz M, Mühlhauser I. [Cardiovascular risk assessment for informed decision making. Validity of prediction tools]. Med Klin (Munich). 2004;99:651-61.
6. Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. Heart. 2006;92:1752-9. [PMID: 16621883]
7. PROCAM risk calculator. Accessed at www.chd-taskforce.com on 20 March 2009.

IN RESPONSE: We appreciate the thoughtful letters from Dr. Budhraja and Dr. Mohan and colleagues regarding the USPSTF recommendation on aspirin prophylaxis for the prevention of cardiovascular disease. Dr. Budhraja calls attention to subgroups of women in whom the effect of aspirin in preventing cardiovascular disease may differ from that of the general population. In general, the USPSTF is cautious when considering unplanned subgroup analyses of randomized trials, which are the basis for Dr. Budhraja's comment. The authors of the original report from the Women's Health Study (1) mention multiple comparisons as an additional caution in interpreting this subgroup analysis. All subgroup analyses should be considered hypothesis-generating rather than independently persuasive.

The possibility suggested by Dr. Budhraja that the higher risk for peptic ulcer disease in smokers might place them at higher risk for hemorrhage when taking aspirin merits further research.

Dr. Mohan and colleagues raise many valuable points. The inadequate and contradictory information derived from Web-enabled coronary and cardiovascular disease risk calculators has been a matter of great concern for the USPSTF. The calculator referenced in the recommendation was selected primarily because it is easy to use and does not require information about high-density lipoprotein cholesterol concentration. As of this writing, the calculator has been removed from the Medical College of Wisconsin's Web site and reportedly is being revised.

The USPSTF felt that making a recommendation meant to be tailored to estimation of cardiovascular disease risk without making any suggestions to help clinicians use the recommendation would be worse than mentioning an imperfect calculator. Research in this field is sorely needed. The development of a "gold standard" cardiovascular disease risk calculator to aid in predicting contemporary rates of cardiovascular disease in the United States should be a pressing priority for analysis of data derived from large cohort studies done in the past decade, perhaps pooling individual-level data across studies. The Agency for Healthcare Research and Quality has funded a project to evaluate the models currently available for risk calculation for cardiovascular disease. The results will be available soon. The use of risk-prediction models, and the tools based on them, to guide decisions about use of preventive and therapeutic medications, as well as decisions about screening, will become increasingly important in the emerging era of personalized medicine.

Ned Calonge, MD, MPH
Diana Petitti, MD, MPH
Mary Barton, MD, MPP
U.S. Preventive Services Task Force
Rockville, MD 20850

Potential Conflicts of Interest: None disclosed.

Reference

1. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352:1293-304. [PMID: 15753114]

Missed Opportunities in the Trial on Proton-Pump Inhibitor Therapy in Bleeding Peptic Ulcers

TO THE EDITOR: In their article on prevention of recurrent ulcer bleeding, Sung and colleagues (1) conclude that theirs is the first international trial supporting the efficacy of high-dose intravenous proton-pump inhibitor (PPI) therapy in white patients with acute peptic ulcer bleeding. We have several concerns with this statement. First, Sung and colleagues' initial intent was to study a multiethnic population, which would have been enlightening because trials to date have only focused on Asian and non-Asian populations. However, this trial was primarily composed of white participants. This population has been studied many times before (13 trials in 3219 patients) (2), and Sung and colleagues' trial adds little to existing evidence.

Second, the Cochrane review (2) quoted by Sung and colleagues addressed the issue of high- versus low-dose PPI therapy and found no advantage to higher doses of PPI therapy on the basis of indirect comparisons.

Third and most important, this trial does not address the issue of oral versus intravenous PPI therapy. Again in the Cochrane review (2), no association was found between PPI route and treatment effect on the basis of indirect comparisons. In addition, a recent head-to-head randomized, controlled trial (3) found oral omeprazole to be as effective as intravenous omeprazole in patients with acute peptic ulcer bleeding in terms of mortality, rebleeding, and surgery. We acknowledge that indirect comparisons and 1 small randomized, controlled trial do not provide sufficient evidence for the equivalent effectiveness of oral therapy. But they do provide an important signal that we need more randomized, controlled trials comparing oral with intravenous therapy.

To justify Sung and colleagues' conclusions, the study should have compared high-dose PPI therapy with low-dose PPI therapy rather than placebo. In terms of missed opportunities, this trial should have included an oral PPI therapy treatment group to fill in the clinically important gaps in existing evidence.

Vivian Yih, BSc(Pharm)
Aaron Tejani, BSc(Pharm), PharmD
Fraser Health
Surrey, British Columbia V3R 7P8, Canada

Potential Conflicts of Interest: None disclosed.

References

1. Sung JJ, Barkun A, Kuipers EJ, Mössner J, Jensen DM, Stuart R, et al; Peptic Ulcer Bleed Study Group. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. Ann Intern Med. 2009;150:455-64. [PMID: 19221370]
2. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev. 2006:CD002094. [PMID: 16437441]
3. Yilmaz S, Bayan K, Tüzün Y, Dursun M, Canoruç F. A head to head comparison of oral vs intravenous omeprazole for patients with bleeding peptic ulcers with a clean base, flat spots and adherent clots. World J Gastroenterol. 2006;12:7837-43. [PMID: 17203530]

TO THE EDITOR: We would like to comment on the article by Sung and colleagues (1), which reaffirmed the clinical effectiveness of infusional esomeprazole as an adjuvant pharmacotherapy for patients at high risk for bleeding peptic ulcers. First, it is extraordinary that the rebleeding and mortality rates in the placebo recipients were 13.6% and 2.1%, respectively, which are noticeably lower than those in most previous reports. A recent Cochrane meta-analysis (2) revealed a rebleeding rate of 19.2% and a mortality rate of 4.9% in the patients with bleeding ulcers who received placebo. Unfortunately, Sung and colleagues did not explain the discrepancy regarding recurrent bleeding rates, and their explanation for the lower mortality rate was confusing. They argued that the lower-than-expected mortality rate was similar to those reported most recently by Lau and colleagues (3). However, Lau and colleagues aimed to explore the effect of preemptive PPI therapy before endoscopy, and therefore their study comprised heterogeneous patients with bleeding. We do not understand how this study is comparable with the study by Lau and colleagues, in which only 60% of the participants bled from peptic ulcers; moreover, most of them (even the preemptive placebo group) did not have high-risk stigmata.

Second, this study did not standardize endoscopic therapy and did not provide sufficient information to ensure that the results were unbiased. The categorization of epinephrine injection, thermocoagulation, and hemoclipping in the same group was inappropriate, because the hemostatic effect of epinephrine injection was inferior to that of the other 2 modalities. In fact, optimal hemostasis can be achieved by thermocoagulation or hemoclipping alone, but not by injection therapy alone. Furthermore, with 764 patients from 91 centers, fewer than 10 patients on average were managed in the same hospital. Because endoscopic therapy depends on the operator's skill, we wonder how the investigators adjusted for probable technical variance across these institutions.

Third, Sung and colleagues missed an opportunity to achieve a greater impact on current practice by choosing placebo as the comparator. We already demonstrated the efficacy of infusional PPI therapy in bleeding peptic ulcers in our study (4) a decade ago, and this efficacy has been supported by compelling evidence by the time the study by Sung and colleagues was initiated. In a meta-analysis published in May 2005, Leontiadis and colleagues (5) already concluded that PPI therapy reduced recurrent peptic ulcer bleeding in both Western and Asian trials, notwithstanding a quantitatively (not qualitatively) greater effect in Asian patients. In our opinion, this study should have used another PPI therapy, a different dosage, or oral administration as the comparator.

Hwai-Jeng Lin, MD
Changhua Christian Hospital
Changhua 500, Taiwan

Yao-Chun Hsu, MD, MSc
Lotung Poh-Ai Hospital
Ilan 265, Taiwan

Potential Conflicts of Interest: None disclosed.

References

1. Sung JJ, Barkun A, Kuipers EJ, Mössner J, Jensen DM, Stuart R, et al; Peptic Ulcer Bleed Study Group. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. Ann Intern Med. 2009;150:455-64. [PMID: 19221370]
2. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: Cochrane collaboration meta-analysis of randomized controlled trials. Mayo Clin Proc. 2007;82:286-96. [PMID: 17352364]
3. Lau JY, Leung WK, Wu JC, Chan FK, Wong VW, Chiu PW, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med. 2007;356:1631-40. [PMID: 17442905]
4. Lin HJ, Lo WC, Lee FY, Perng CL, Tseng GY. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. Arch Intern Med. 1998;158:54-8. [PMID: 9437379]
5. Leontiadis GI, Sharma VK, Howden CW. Systematic review and meta-analysis: enhanced efficacy of proton-pump inhibitor therapy for peptic ulcer bleeding in Asia—a post hoc analysis from the Cochrane Collaboration. Aliment Pharmacol Ther. 2005;21:1055-61. [PMID: 15854166]

TO THE EDITOR: I read with interest the article by Sung and colleagues (1). However, it's not news that PPI therapy is better than placebo in the treatment of ulcer bleeding. This was assessed more than a decade ago, and even some cost-effectiveness studies (2) support this conclusion. In addition, some studies (3–5) used low-dose PPI therapy and found no differences between high or low doses of PPI therapy.

Is it ethical to continue to use placebo as a control when enough evidence exists that PPI therapy should be used in peptic ulcer bleeding? Perhaps the only new studies on this issue should compare different doses or evaluate the cost-effectiveness of these different doses.

Alejandro Piscoya, MD
Universidad Peruana de Ciencias Aplicadas
Lima, Peru

Potential Conflicts of Interest: None disclosed.

References

1. Sung JJ, Barkun A, Kuipers EJ, Mössner J, Jensen DM, Stuart R, et al; Peptic Ulcer Bleed Study Group. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. Ann Intern Med. 2009;150:455-64. [PMID: 19221370]
2. van Zanten SV. Cost-effectiveness of intravenous proton pump inhibitors in high-risk bleeders. Can J Gastroenterol. 2004;18:749-50. [PMID: 15605141]
3. Udd M, Miettinen P, Palmu A, Heikkinen M, Janatuinen E, Pasanen P, et al. Regular-dose versus high-dose omeprazole in peptic ulcer bleeding: a prospective randomized double-blind study. Scand J Gastroenterol. 2001;36:1332-8. [PMID: 11761026]
4. Hung WK, Li VK, Chung CK, Ying MW, Loo CK, Liu CK, et al. Randomized trial comparing pantoprazole infusion, bolus and no treatment on gastric pH and recurrent bleeding in peptic ulcers. ANZ J Surg. 2007;77:677-81. [PMID: 17635283]
5. Andriulli A, Loperfido S, Focareta R, Leo P, Fornari F, Garripoli A, et al. High- versus low-dose proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding: a multicentre, randomized study. Am J Gastroenterol. 2008;103:

3011-8. [PMID: 19086953]

IN RESPONSE: We thank all the correspondents for their considered comments. Ms. Yih and Dr. Tejani, Drs. Lin and Hsu, and Dr. Piscoya raised concerns about the use of placebo as a comparator in our study of patients with peptic ulcer bleeding. When this study was planned, the efficacy of intravenous PPI therapy for treatment of peptic ulcer bleeding was still in question, and no approved comparator treatment existed. After full discussion of the design with the U.S. Food and Drug Administration and the European Medicines Agency, it was agreed that the study should be placebo-controlled, which resulted in the first approval of intravenous PPI therapy for this indication in several countries. Now that the efficacy of intravenous PPI therapy has been accepted by health authorities, we agree that it is logical to explore different doses of intravenous therapy and the possible utility of oral PPI therapy. A comparison of oral with intravenous therapy may require many patients, however, even if a noninferiority design is chosen to demonstrate similar efficacy.

Drs. Lin and Hsu also raised concerns about the low mortality and rebleeding rates observed in our study. Although the study by Lau and colleagues (1) focused on preemptive therapy with omeprazole and thus had a different design, it did have a placebo group, permitting comparison of mortality rates with our study, although we do accept that patients in Lau and colleagues' study were probably in a lower risk group. However, other recent studies (2, 3) in patients with peptic ulcer bleeding have reported similarly low mortality rates. We also attempted to provide other explanations for the low mortality rates, such as exclusion of patients with the worst prognosis (that is, highest American Society of Anesthesiologists scores). Some earlier studies also included more patients who first bled as "inpatients" rather than "outpatients," making them clinically high-risk patients.

Concerning the low rebleeding rates that we observed, we emphasized efficient endoscopic treatment, which we consider to be one of its strengths because even with such state-of-the-art therapy, profound acid suppression still provided additional benefit. The issue of whether to standardize endoscopic therapy in our study was thoroughly discussed within the steering committee, with the view that various endoscopic approaches were used in different centers. We made a deliberate decision to allow "real world" endoscopic treatment, to evaluate the true value of adjuvant esomeprazole therapy in current clinical practice. If one controls too many variables in a study, they may be criticized for making the design remote from reality.

Finally, Ms. Yih and Dr. Tejani raised an issue concerning multiethnicity in our study. Although our study population was largely white, a sufficient number of Asians were included to permit separate analyses of their data, allowing them to be examined as an "internal control" group.

Joseph J.Y. Sung, MD, PhD
Prince of Wales Hospital, Chinese University of Hong Kong
Hong Kong, China

Alan Barkun, MD
McGill University Health Centre
Montreal, Quebec H3G 1A4, Canada

Ernst J. Kuipers, MD
Erasmus MC University Medical Center
Rotterdam 3015 GD, The Netherlands

Potential Conflicts of Interest: None disclosed.

References

1. Lau JY, Leung WK, Wu JC, Chan FK, Wong VW, Chiu PW, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med. 2007;356:1631-40. [PMID: 17442905]
2. Jensen DM, Pace SC, Soffer E, Comer GM; 315 Study Group. Continuous infusion of pantoprazole versus ranitidine for prevention of ulcer rebleeding: a U.S. multicenter randomized, double-blind study. Am J Gastroenterol. 2006;101:1991-9; quiz 2170. [PMID: 16968504]
3. van Rensburg C, Barkun AN, Racz I, Fedorak R, Bornman PC, Beglinger C, et al. Clinical trial: intravenous pantoprazole vs. ranitidine for the prevention of peptic ulcer rebleeding: a multicentre, multinational, randomized trial. Aliment Pharmacol Ther. 2009;29:497-507. [PMID: 19053987]

Universal Insurance Coverage and Health Care Inequity

TO THE EDITOR: We read with interest the editorial by Sehgal (1), in which he concludes that universal insurance coverage is the key factor, compared with other health care reform efforts, in reducing the sizable and persistent health disparities in the United States. We argue that universal insurance is a necessary condition for health equity, but not the only one.

Some literature attests to our opinion. Bratu and colleagues (2) found that despite free, universal health care access in Canada, children with lower socioeconomic status had increased appendiceal rupture rates, which indicated health disparities. Somkotra and Detsomboonrat (3) assessed the socioeconomic inequality and horizontal inequity in oral health care use among Thai adults after universal coverage policy was implemented nationwide. The result was also sad: Inequality and inequity in oral health care use continued. Evidence from Allin's (4) research pointed to persisting socioeconomic inequity in health care use in Canada, although Canadian provinces have provided universal public insurance for hospitals and physician care for more than 30 years. Their national trends showed that the rich were more likely to visit a general practitioner, specialist, or dentist. In these studies, except for income, the main socioeconomic determinants associated with inequity are education, type of insurance entitlement, and geographic characteristics.

In China, the health system has much inequality. Recently, the government approved guidelines and an action plan to reform the health care system. The government will provide insurance coverage for nearly the entire population, but we do not think this will eliminate the health disparities. The precondition for solving this problem should be increasing the supplies of health resources, because the demands of health services expand faster than the mobilization of supplies here in China. How can the limited health resources be shared fairly among the diverse socioeconomic groups? Rich persons can take priority of receiving health care by spending more money. Bureaucrats are able to use their social relationships in hospitals to get services more easily. Gabillat (5) may have been right: "Health is victim to social inequalities."