

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Population-based Cohort Study on the risk of pneumonia in nontraumatic intracranial hemorrhage patients with proton pump inhibitor utilization
AUTHORS	Ho, Sai-Wai; Tsai, Ming-Che; Teng, Ying-Hock; Yeh, Ying-Tung; Wang, Yu-Hsun; Yang, Shun-Fa; Yeh, Chao-Bin

VERSION 1 - REVIEW

REVIEWER	Chih-Hsin Tang China Medical University; TAIWAN
REVIEW RETURNED	11-Oct-2014

GENERAL COMMENTS	<p>The study aims to investigate the association between proton pump inhibitors (PPIs) usage and the risk of pneumonia in nontraumatic intracranial hemorrhage (ICH) patients. The authors found that the adjusted HR of the risk of pneumonia for ICH patients who used PPIs was 1.61 (95% CI = 1.40–2.08, $P < .001$). The risk of pneumonia was positively associated with the administration of PPIs. This study indicated that the use of PPIs in nontraumatic ICH patients is associated with an increased risk of pneumonia, and the severity of this risk depends on the DDD.</p> <p>Comments:</p> <ol style="list-style-type: none">1. The author stated that physicians should exercise caution when prescribing PPIs in cumulative doses to nontraumatic ICH patients. But in the results, the risk of pneumonia is related to $DDD < 30$ and $DDD30-60$ only. Higher DDD did not increased risk of pneumonia.2. P8, line33: The authors mentioned newly diagnosed with nontraumatic ICH complicated with pneumonia during the same admission period were excluded. However, why the flow chart in figure 1 has not ruled out that this part of the sample?3. P9, line7: The authors mentioned cumulative dose PPI algorithm before index date, but figure 1 shows a flow chart PPI use was observed after starting, please correct it.4. P13, line10: mentioned in nontraumatic " stoke " patients, please correct it.5. The references 5 and 6 seem not to be represented the epidemiology of pneumonia in Taiwan.
-------------------------	--

REVIEWER	Dan-Ning Hu New York Eye and Ear Infirmary of Mount Sinai Icahn School of Medicine at Mount Sinai USA
REVIEW RETURNED	16-Oct-2014

GENERAL COMMENTS	<p>This is a retrospective analysis of nation-wide administrative data from Taiwan to examine the association between use of PPIs and the subsequent development of pneumonia.</p> <p>Comments:</p> <ol style="list-style-type: none"> 1. The follow-up duration for pneumonia has not been described in the manuscript, only mentioned average years. And how competing risk of death was accounted for remains unclear. 2. The authors mentioned that previous study showed the prophylactic use of PPIs during an acute nontraumatic ICH stroke could increase the risk of nosocomial pneumonia. Please add which kind of pneumonia was studied in the previous report? CAP, HCAP or VAP? 3. It is suggested to use same format for units throughout the manuscript, for example, use $p < 0.001$ or $p < .001$ consistently but not alternatively. 4. Page 5, line 30: GI bleeding and UTI should be “gastrointestinal bleeding” and “urinary tract infection”. 5. Page 11, line 8: “The patients who were not diagnosed with ICH were predominantly male (64.52%).” The word “not” could be deleted. 6. The authors mentioned that the use of PPIs in nontraumatic ICH patients is associated with an increased risk of pneumonia. A related paper (Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. Am J Med. 2010 Jan;123(1):47-53.) should be added to the References and Discussion.
-------------------------	--

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the author:

1. The author stated that physicians should exercise caution when prescribing PPIs in cumulative doses to nontraumatic ICH patients. But in the results, the risk of pneumonia is related to DDD < 30 and DDD 30-60 only. Higher DDD did not increased risk of pneumonia.

Answer: Thanks for your suggestion and to improve this aspect, we correct our conclusion in page 3 line 5 in this revised manuscript. We hope that these changes and replies may meet your requirement for being published.

“Physicians should exercise caution when prescribing PPIs to nontraumatic ICH patients”

2. P8, line33: The authors mentioned newly diagnosed with nontraumatic ICH complicated with pneumonia during the same admission period were excluded. However, why the flow chart in figure 1 has not ruled out that this part of the sample?

Answer: Thanks for your suggestion and to improve this aspect, we correct the sentence in page 8 line 13 in this revised manuscript.

“Patients who had a history of pneumonia within a year before PPI treatment was initiated were also excluded”

3. P9, line7: The authors mentioned cumulative dose PPI algorithm before index date, but figure 1 shows a flow chart PPI use was observed after starting, please correct it.

Answer: Thanks for your suggestion and to improve this aspect, we correct the sentence in page 9 line 3-5 in this revised manuscript.

“Cumulative DDDs were estimated as the sum of the dispensed DDD of any PPI with the final use during the study observation time period”

4. P13, line10: mentioned in nontraumatic " stoke " patients, please correct it.

Answer: Thanks for your suggestion and to improve this aspect, we have corrected it.

5. The references 5 and 6 seem not to be represented the epidemiology of pneumonia in Taiwan.

Answer: Thanks for your suggestion and to improve this aspect, we have corrected the references 5 and 6.

Reference 5: Ramirez JA, Anzueto AR. Changing needs of community-acquired pneumonia. *Journal of Antimicrobial Chemotherapy*. 2011;66:iii3–iii9.

Reference 6: Department of Statistics of Ministry of Health and Welfare in Taiwan. Causes of death in Taiwan (2012) Taipei, Ministry of Health and Welfare in Taiwan.

Reviewer: 2

Comments to the author:

1. The follow-up duration for pneumonia has not been described in the manuscript, only mentioned average years. And how competing risk of death was accounted for remains unclear.

Answer: Thanks for your suggestion and to improve this aspect, we have added phrases “up to 2 years of follow-up duration (page 7 line 11)” and “The average follow-up duration was 1.05 years (page 8 line 9)” and “Track duration (Table 2)” in this revised manuscript. We hope that these changes and replies may meet your requirement for being published.

2. The authors mentioned that previous study showed the prophylactic use of PPIs during an acute nontraumatic ICH stroke could increase the risk of nosocomial pneumonia. Please add which kind of pneumonia was studied in the previous report? CAP, HCAP or VAP?

Answer: Thanks for your suggestion and to improve this aspect, we have corrected the words “nosocomial pneumonia” to “hospital-acquired pneumonia (HAP)” in this revised manuscript (page 6 line 2).

3. It is suggested to use same format for units throughout the manuscript, for example, use $p < 0.001$ or $p < .001$ consistently but not alternatively.

Answer: Thanks for your suggestion and to improve this aspect, we use $p < 0.001$ consistently in this revised manuscript.

4. Page 5, line 30: GI bleeding and UTI should be “gastrointestinal bleeding” and “urinary tract infection”.

Answer: Thanks for your suggestion and to improve this aspect, we change the words “GI bleeding and UTI” to “gastrointestinal bleeding and urinary tract infection” in this revised manuscript.

5. Page 11, line 8: “The patients who were not diagnosed with ICH were predominantly male (64.52%).” The word “not” could be deleted.

Answer: Thanks for your suggestion and to improve this aspect, we have deleted the word “not” in this revised manuscript.

6. The authors mentioned that the use of PPIs in nontraumatic ICH patients is associated with an increased risk of pneumonia. A related paper (Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *Am J Med.* 2010 Jan;123(1):47-53.) should be added to the References and Discussion.

Answer: Thanks for your suggestion and to improve this aspect, we add this article as reference 24 in discussion section of this revised manuscript. We hope that these changes and replies may meet your requirement for being published.

VERSION 2 – REVIEW

REVIEWER	Tang, Chih-Hsin China Medical University
REVIEW RETURNED	23-Oct-2014

GENERAL COMMENTS	The authors done a good job in revised. "Accept" to publish
-------------------------	---