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Acid-suppressive medications and risk of pneumonia in acute stroke patients: A systematic review and meta-analysis

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ABSTRACT

Goal: We performed a systematic review and meta-analysis aiming to clarify the relationship between acid-suppressive medication (ASM) and the risk of pneumonia in acute stroke.
Methods: The included studies examined patients with an acute ischemic and/or hemorrhagic stroke, assessed the relationship of one or both groups of ASM, histamine-2 receptor antagonist (H2RA) and proton-pump inhibitor (PPI), as a variable of interest, and used the occurrence of hospital-acquired pneumonia (HAP) as an outcome measure. The search was conducted in MEDLINE, Cochrane, Embase, and Google Scholar. Random-effects meta-analyses were used to obtain pooled estimates of the effect.
Results: 5 retrospective cohort-studies fulfilled study criteria. The results revealed a higher risk of pneumonia for both, patients receiving PPI (adjusted relative risk [RR] 2.37, 95% confidence interval [CI] 1.36–4.17, I^2 0%) and H2RAs (adjusted RR 1.73, 95% CI 0.74–4.25, I^2 68.3%), although the latter did not reach statistical significance. A comparison of the overall acid versus non-acid groups using unadjusted values yielded likewise an increased risk for pneumonia for patients receiving ASM (unadjusted RR 4.65, 95% CI 1.64–13.16, I^2 93.3%).
Conclusion: Results of this meta-analysis show an increased risk for HAP in acute stroke patients who receive ASM, particularly those exposed to PPIs. Larger, well-controlled studies in acute stroke populations are needed to establish a clearer association between ASM and HAP. These results, however, urge caution when prescribing ASM – especially to stroke patients considered to be at high risk for pneumonia.

1. Introduction

Pneumonia (PNA) is one of the most common and serious complications of a stroke [1]. It is a leading cause of death after a stroke and is associated with long-term disability [1,2]. Although the risk factors for stroke associated pneumonia are manifold, use of acid suppressive medication (ASM) has emerged as an important contributor to its development in stroke patients. These medications are used with the intent to prevent the occurrence of peptic ulcers related to antiplatelet or anticoagulant drugs, or stress-related mucosal damage by reducing the gastric acid secretion. However, their use may promote growth of pathogenic bacteria in the upper gastrointestinal tract, which, if aspirated especially by those patients who have poor swallowing control, may lead to the development of aspiration pneumonia. Recently an association between ASMs and pneumonia has been made in critical care [3,4] and in hospital-and community-based populations [3,5,6]. However, only a few studies have examined this association in the acute stroke population [7,8]. These investigations have been heterogeneous with respect to their inception cohorts, design, methodologies, and reporting of their associations in terms of proton pump inhibitors (PPI) versus histamine-2-receptor antagonists (H2RA). Stroke patients have several unique features that increase their risk for both gastrointestinal hemorrhage and pneumonia [2]. In this context, it is unclear whether there is a net benefit of routinely using these agents in stroke patients. In the absence of a randomized controlled trial to inform current practice, the risk of pneumonia posed by these agents can be best examined by summarizing the results of all existing studies via a meta-analysis.

We therefore undertook this study to examine the association of acid-suppressive medications (PPI and H2RA) and hospital-acquired pneumonia in stroke patients by conducting a comprehensive meta-analysis of all studies in existing literature on this subject.

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2. Methods

2.1. Search strategy and data sources

We looked for studies that reported an estimate of effect for a potential association between the use of ASM and the risk for pneumonia in the population of acute stroke patients. The search included observational studies as well as randomized clinical trials that were published as original articles.

The search was conducted in MEDLINE (pubmed), Cochrane, Embase, and Google Scholar. We also utilized the bibliographies of relevant articles to identify additional studies. We restricted the search to studies which were published in English.

In order to identify observational studies we used the following combinations of search terms:

("acid suppressive therapy" OR "acid-suppressive drugs" OR "acid-suppressive medications" OR "gastric acid suppressants" OR "proton pump inhibitors" OR "proton pumps" OR omeprazole OR Nexium OR lansoprazole OR rabeprazole OR pantoprazole OR esomeprazole OR "H2 receptor antagonists" OR "histamine2 receptor antagonists" OR cimetidine OR ranitidine OR famotidine OR nizatidine) AND (pneumonia OR "community-acquired pneumonia" OR "nosocomial pneumonia" OR "hospital-acquired pneumonia") AND ("Stroke" OR "ischemic stroke" OR "acute stroke" OR "hemorrhage" or "hemorrhagic stroke" OR "cerebrovascular accident")

For identifying randomized controlled trials, the following combination of search terms was used: ("acid suppressive therapy" OR "acid-suppressive drugs" OR "acid-suppressive medications" OR "gastric acid suppressants" OR "proton pump inhibitors" OR "proton pumps" OR omeprazole OR Nexium OR lansoprazole OR rabeprazole OR pantoprazole OR esomeprazole OR "H2 receptor antagonists" OR "histamine2 receptor antagonists" OR cimetidine OR ranitidine OR famotidine OR nizatidine) AND ("Stroke" OR "ischemic stroke" OR "acute stroke" OR "hemorrhage" or "hemorrhagic stroke" OR "cerebrovascular accident").

Once we found our set of studies we contacted authors to gather more information about the published article. One of the authors kindly shared all our requested data with us.

2.2. Study selection

Studies which met all of the following criteria were included in the analysis: 1) The study was a case-control study, a cohort study or a randomized controlled trial 2) It investigated the association between use of ASM and risk of pneumonia in stroke populations 3) It quantified the outcome with adjusted odds ratios (OR), relative risk (RR) or number of events and corresponding 95% confidence intervals (CI) 4) It included ischemic stroke (IS) or spontaneous intracerebral hemorrhages (ICH) or both 5) traumatic hemorrhages were excluded.

Sub-criteria for inclusion were 1) hospital-acquired pneumonia (defined as any pneumonia occurring during hospitalization after stroke, in accordance with the definition of the Center of Disease Control (CDC) as well as the Infectious Diseases and American Thoracic Society of America) 2) only patients with a new diagnosis of stroke admitted to a hospital.

2.3. Data extraction and quality assessment

After narrowing the search to articles concerning themselves only with the relationship between stroke, ASM and pneumonia, four investigators (JM, JH, SK, SM) evaluated the full text of those articles for possible inclusion. All studies were assessed independently by all investigators in order to probe study eligibility. Disagreements were resolved by consensus.

This systematic review was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement [9].

The methodological quality of the observational studies was assessed using the Newcastle-Ottawa Scale for cohort studies [46], as well as the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from NIH [10]. All four investigators evaluated the study quality independently. A discussion cleaned up disagreements.

The Newcastle-Ottawa scale which asks 8 questions organized into 3 broad groups (Selection, Comparability and Outcome) with a maximum score of 9, revealed a score in a range of 7–9 for all the selected studies. The average was 8.3. The NIH quality assessment tool consists of 14 questions which are to be answered with yes, no, or other (such as *not reported* or *not applicable*). We used yes = 1 and no = 0 in order to quantify the score and compare its outcome to the above mentioned tool. 3 questions in this particular tool were not applicable for our evaluation. From the 11 remaining questions between 6 and 10 received a yes with an average of 8.0. The questions with the most problematic judgments across the studies were the different levels of exposure and the blinding of outcome assessors.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.4. Statistical analysis

The primary outcome of this meta-analysis was hospital-acquired pneumonia after a stroke. We computed a pooled Relative Risk and 95% CI from the adjusted ORs and 95% CIs reported in the observational studies. We examined heterogeneity in results across the studies using both, Cochrane's Q and Higgins I^2. The former assesses whether the individual studies' treatment effects are farther away from the common effect, beyond what is expected by chance while the latter measures the percentage of total variance in the summary estimate due to between-study heterogeneity [11]. Values of $I^2 < 25\%$, 25–50%, and > 50% suggest-low, moderate, and high degree of heterogeneity, respectively. In light of the expected heterogeneity between the study designs and population characteristics, we calculated the summary effect by means of random-effects models. In particular, we used a Bayesian hierarchical model to estimate the random effects model. We assumed a Gaussian distribution for random effects. Normal (0,1000) and Inverse-Gamma (0.001, 0.001) were assumed on the mean and variance of the random effects, respectively. The freely available, open-source program OpenBUGS 3.2.3 [12] was used to fit the model. One study omitted sensitivity analyses were conducted by removing one study at a time to assess whether any of the included studies had a large influence on the results.

3. Results

3.1. Search results

The search across all used databases retrieved 1566 references. Among those 508 duplicates were identified. Of the remaining 1058 articles (150 observational, 908 RCT), 1042 were excluded based on title and abstract. Full text articles were obtained for all the remaining 13 articles. Of these 1 did not include acid suppressive drugs, 2 were letters to editors and did not provide enough information. This left 10 articles which were relevant to this investigation. However, during the extensive quality assessment the 4 reviewers excluded 5 more articles (1 pertained to only ventilator associated pneumonia (VAP)), 1 study assessed patients during their rehabilitation, 2 were outside the acute phase and 1 study compared H2RA directly to PPI without the use of a control group). This resulted in 5 articles which were included in the statistical analysis (see Fig. 1).

While extracting the statistical values from the remaining 5 papers it became obvious that one study had looked only at H2RAs, another had

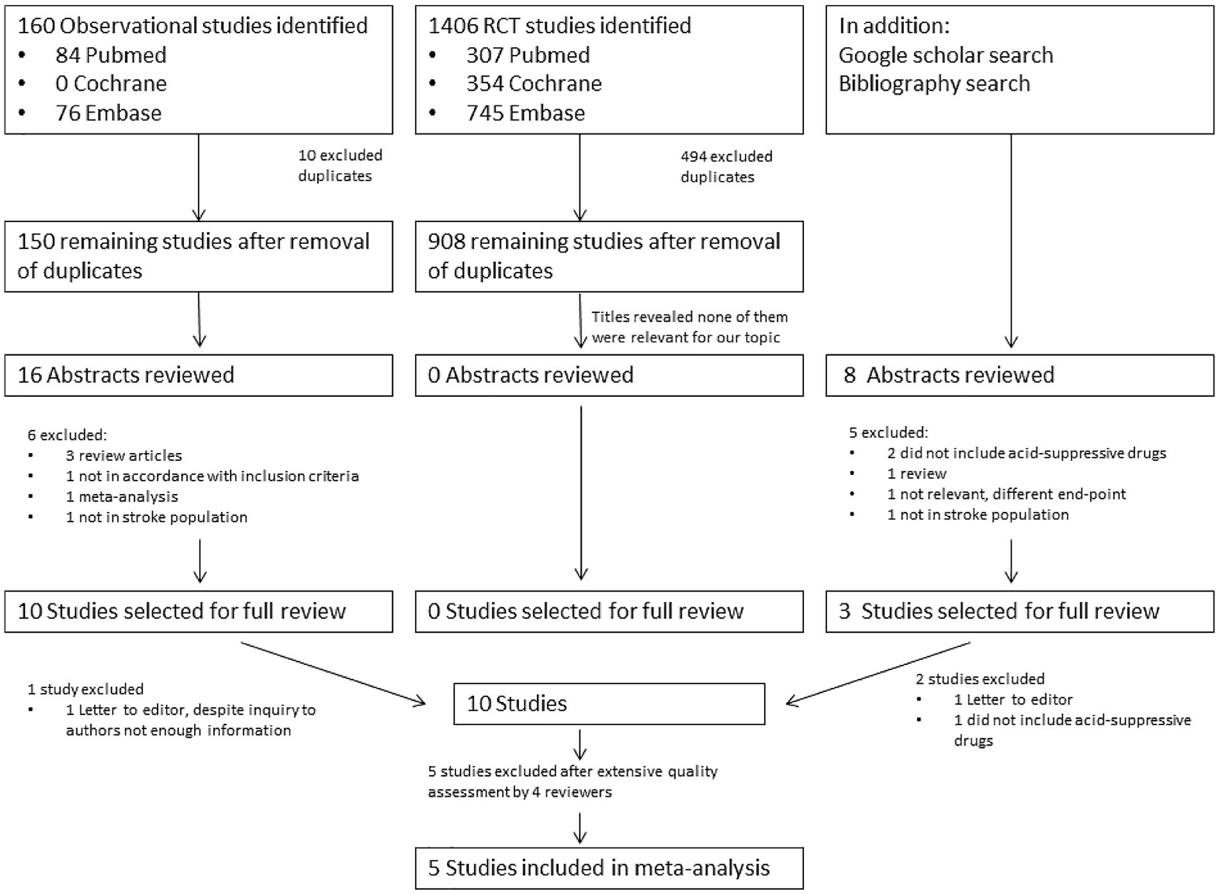

Fig. 1. Flow chart for study selection.

reported exclusively PPIs and due to a difference in design, a third article had not reported adjusted ORs. Thus, we were only able to include 3 articles in the analyses comparing PPI versus non-acid medication, and 3 for the H2RA versus non-acid medication comparison. Furthermore, not all of the included papers reported adjusted results for both, H2RA and PPI separately, therefore were not able to calculate an overall comparison between acid and non-acid groups with adjusted values. We did, however, conduct a random effects analysis with unadjusted values for all 5 of the papers included.

3.2. Systematical review

A descriptive summary of the 5 studies meeting our criteria can be found in Table 1. The association between ASM and pneumonia after stroke was the primary outcome in 3 of these studies and a secondary endpoint in the other two. All of them were retrospective cohort studies with 2 being conducted in the US, 2 in China and 1 in Japan, between the years 2000 to 2016.

3 studies included both classes of medication (i.e., H2RA and PPI), while 2 other studies focused exclusively on either H2RA [13] or PPI [14]. Data of PPI and H2RA exposure was extracted from the patient's medical records or pharmacy charges during the hospitalization (PPI $n = 909$, 23.1%); H2RA $n = 1386$, 35.2%) and diagnostic codes were used to identify pneumonia cases ($n = 1038$, 26.4%).

Overall, a total of 3936 study subjects were included. The PPI analysis used 2211 and the H2RA analysis 3446 participants. 3 studies included both, IS and ICH, while 2 included only ICH patients.

3.3. Meta-analysis

For the PPI group compared to the non-acid suppressors, the meta-analytic adjusted relative risk (RR) of pneumonia was 2.37 (95% CI 1.36, 4.17). The estimated Cochrane's Q and the I^2 showed a high homogeneity across the selected 3 studies (Q = 0.56, $p = .7463$, $I^2 = 0\%$). (Fig. 2a).

The comparison between H2RA and non-acid suppressive medication revealed a much larger heterogeneity across the studies with a Cochrane's Q of 6.31 which was significant at $p = .036$ and an I^2 of 68.3%. The estimated meta-analytic adjusted RR for pneumonia was 1.73 (95% CI 0.74, 4.25). (Fig. 2b).

Comparing the ASM group with the non-ASM group using unadjusted values yields a meta-analytic RR for pneumonia of 4.65 (95% CI 1.64, 13.16) and very high heterogeneity between studies with a Cochrane's Q of 59.92 ($p = .001$) and an I^2 of 93.3%. (Fig. 2c).

4. Discussion

This meta-analysis investigated the association of ASM with HAP in acute stroke. Our search of the existing literature on this subject revealed a handful of studies which have systematically investigated this relationship in the acute-subacute stroke phase. The methods and analysis employed in this investigation allows us to combine the results from these studies to improve statistical power, provide more reliable estimates of this association and resolve some of the uncertainties on this topic. An advantage of a meta-analysis is that it allows statistical control for aggregate data since there are usually differences in the methodologies and analytical approaches between individual studies. Towards this end, we have utilized a random-effects model which is an established method for addressing these variabilities and are known to produce more conservative estimates than the traditional fixed effect models typically used in a multivariable regression analysis [15]. We have furthermore conducted a sensitivity analysis to identify and

Table 1
Characteristics of studies included in the final analysis.

Study	Country	Study design	Study period	Adjustment	No of patients	Stroke type	ASM type	PNA risk
Alsumrain et al. 2012	USA	Cohort	2006–2009	Site and type of pneumonia, length of stay, use of PPI, H2 blockers, use of ACE inhibitor and use of smoking and alcohol	290	ICH	PPI H2RA	na
Arai et al. 2016	Japan	Cohort	2006–2016	Age, sex, NIHSS, GCS, COPD, DM, congestive heart failure, alcohol, smoking	335	ICH IS	PPI H2RA	aRR 2.00 CI = 1.12–3.57 (PPI) aRR 1.24 CI = 0.85–1.81 (H2RA)
Herzig et al. 2014	USA	Cohort	2000–2010	Ag, sex, race, length of hospitalization, ICU stay, inn-hospital medications, comorbidities, gastrointestinal hemorrhage, alcohol and drug use	1676	ICH IS	PPI H2RA	aOR 2.7 CI = 1.4–5.4 (PPI) aOR 1.6 CI = 0.8–3.4 (H2RA)
Ran et al. 2011	China	Cohort	2008–2009	Sex, age, tobacco use, history of heart failure, COPD, diabetes mellitus, history of stroke, level of consciousness, location and size of hematoma, intraventricular extension, use of mechanical ventilation, use of nasogastric tube, hospitalization time, antibiotic therapy	200	ICH	PPI	aOR 2.7 CI = 1.2–6.7
Sui & Zhang 2011	China	Cohort	2000–2009	Age, gender, history of smoking diabetes, heart diseases, days of hospitalization, location and nature of stroke, GCS, MMSE, intubation, tracheal incision, nasal feeding, H2-receptor blocking agents and antimicrobials	1435	ICH IS	H2RA	aOR 2.837 CI = 1.994–5.689

account for any single study results which may have had an unduly large influence on the summary estimates. Results of this meta-analysis show a significantly increased risk for HAP in acute stroke patients exposed to acid-suppressive medications, especially PPIs. The relationship between H2RA and HAP remains unclear due to significant heterogeneity between studies and requires further clarification in future investigations. These results, however, urge caution when prescribing PPI – especially to those stroke patients who are considered to be at high risk for pneumonia.

ASM are widely prescribed in hospitalized stroke patients. Overall 66.1% patients included in this meta-analysis received an ASM (43.0% were prescribed H2RA and 30.9% PPI). These figures parallel findings of other studies on hospitalized inpatients, which show that an estimated 40 to 70% of medical inpatients receive some form of ASM, of which approximately 50% are new initiations [16,17]. Their widespread use in the stroke population is difficult to reconcile with the low risk of upper gastrointestinal bleeding in this patient population [18–20].

Numerous studies which investigated the association between ASMs and pneumonia in different patient populations have found an increased risk for pneumonia in patients receiving acid-suppressive drugs [3,21–23]. This association seems in general stronger for PPI than for H2RAs.

While the majority of studies investigated this relationship in various patient and healthy populations, only a handful explored it in acute stroke patients [7,8,24]. More than half of those looked at both, PPI and H2RA, while the rest only assessed one or the other acid suppressor. Each study had its own set of limitations, but a small sample size was a common problem for many – a fact which puts the external validity of their results somewhat in question. A too small subject sample may have rendered the multivariate level testing underpowered to detect real differences, despite being significant on univariate analysis [25,26]. Another study [27] found an increased unadjusted risk only when combining PPI and H2RAs into a single group; however, separately they both did not reach statistical significance. On the other hand, in one study a very large sample size was used by investigators [24] to compare the risks of pneumonia from PPI directly with H2RA; however, since there was no comparison with a non-medication control group an estimate about the overall risk of either medication is difficult to infer. In the acute phase of stroke there are to date only a couple of studies [7,8] which are reporting not only a significantly increased risk for pneumonia for ASM users, but also a stronger link for PPIs compared to H2RAs. It should be noted though, that the sample size is only satisfactory for one of the studies [7] and still small in the other one [8]. With this meta-analysis we hope to increase the reliability of the results by boosting the overall sample size.

Our analysis not only showed a clear overall trend to a higher risk of pneumonia for acid-suppressive medication compared to controls, but the results for both, PPI and H2RA, went in a similar direction. The three studies included in the PPI versus non-acid medication analysis found that use of PPI more than doubled the risk of HAP in this population [7,8,14]. Despite the small number of studies used for this comparison, the heterogeneity was very low [7,8,14]. The pooled result of H2RA on the other hand showed a lower risk for pneumonia. Within that group, interestingly one study [13] showed risk estimates of pneumonia from H2RA to be similar to that from exposure to PPI in individual studies; however, the overall pooled risk for pneumonia after H2RA was still lower than for the PPI group. It needs to be noted that this comparison was not significant and also revealed a relatively high heterogeneity and therefore requires caution in interpreting these results.

The explanation for a different risk posed by these two classes of ASM is not entirely clear. Potential mechanisms include a stronger degree of acid suppression by PPIs [22,23,28,29]. Greater acid suppression may promote an increase in gastric colonization [23]. Impairment of immune cell function by PPI might be another mechanism

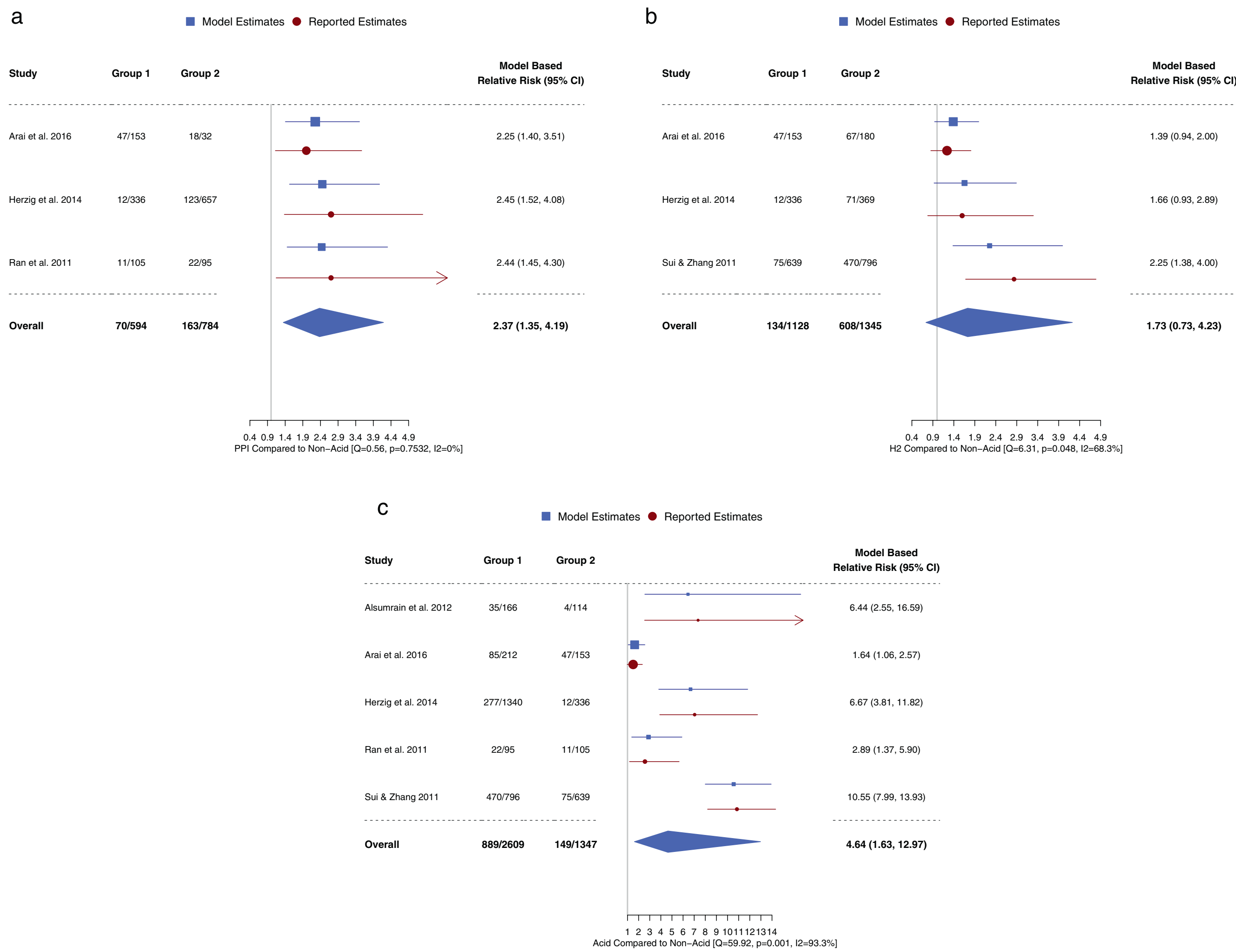

Fig. 2. (a) Meta-analysis evaluating the risk of PNA after receiving PPI based on random-effects model. (b) Meta-analysis evaluating the risk of PNA after receiving H2RA based on random-effects model. (c) Meta-analysis evaluating the risk of PNA after receiving ASM based on random-effects model.

to explain the observed differential risk [30,31]. It has been speculated that the immunosuppressive effects of these medications may further exacerbate the immunosuppression induced by an acute stroke [32,33].

With the exception of one [24], all stroke related studies which included both, PPIs and H2RAs [7,13,14,27,34], show a higher risk for pneumonia with PPI compared to H2RA. However, this association has not been consistently observed in other patient populations and healthy cohorts [24,35–38].

A potential bias increasing pneumonia risk in patients who receive acid-suppressors might be that critically ill patients are more likely to receive acid-suppression prophylaxis on hospital admission than their more stable counterparts, i.e. there is confounding by indication [39,40]. Ran et al. [14] found that patients who were placed on mechanical ventilation, had a nasogastric tube or presented with a worse level of consciousness were more likely to be on acid suppressive therapy. It is important to note though that the logistic regression analysis of this study revealed a clear association between ASMs and pneumonia after controlling for all factors significant on a univariate level. A stroke study looking at ventilator-associated pneumonia (VAP) [26] identified stroke severity, COPD, hemorrhagic conversion and duration of ventilation are significant risk factors for developing VAP, but the variable ASM did not survive the multivariate stepwise logistic regression analysis. In addition, because only ventilated patients at risk for VAP (which carries a different pathogenesis) were examined, its inherent selection bias precluded its use in the meta-analysis. Altogether, in the few observational studies in our stroke cohort, most of them controlled their analyses to a greater or lesser degree by including relevant and important covariates such as level of consciousness, stroke severity and intubation [7,13] in their multivariate regression analysis. Arai et al. [8] did not control for intubation or feeding tube which might have confounded the result to some degree.

In this context it is worth mentioning though that there are stroke studies which do not show an association between ASM and pneumonia in multivariate analyses – they were, however, significantly associated on a univariate level [26,27]. This lack of significance on a multivariate level testing could be due to the relatively small sample size in both these groups rather than a confounding problem. Marciniak et al. [27] did note that the reason for the significant effect on the unilateral level might be that these medications were used in more impaired patients, and that the small sample size may not have allowed the detection of independent effects.

One aspect which remained unaddressed in all of the studies, but might contribute to a better understanding of the relationship between ASMs and pneumonia, is the effect of timing and doses of these medications, which may modulate the risk of ASMs. However, this meta-analysis was unable to explore these themes due to lack of data points. Another potential issue which cannot be explored for the same reason is whether pneumonia rates are different in ischemic and hemorrhagic stroke populations. Some previous studies have shown that ICH may independently increase risk of pneumonia [9], however, this has not been replicated in other investigations [41–44].

The most obvious limitation of this meta-analysis is the small sample size of the studies. Despite a relatively large pool of studies looking at the effects and risks of acid-suppressive medication, the vast majority of them was conducted in a non-acute stroke population and was therefore not suited for our analysis. Overall there were only 10 papers which were within our target terms. After an intensive quality assessment – in accordance with the MOOSE statement [9]– 5 studies were selected for our meta-analysis, of whom one looked exclusively at H2RAs [13] and one only at PPIs versus controls [14]. This variability unfortunately bears another limitation. Not all 5 of the studies could be used for each of the comparisons we were interested in. Only the overall pooled analysis looking at acid versus non-acid users comprises all 5 studies. For the other 2 comparisons, PPI and H2RA versus non-acid, however, only 3 studies could be utilized for each of the analyses. Two references were in both, the PPI and the H2RA group, while one of the references was different for both of them. Despite both of these analyses showing a higher risk for pneumonia it is difficult to draw a direct comparison as there is a large variability in variables such as number of subjects as well as the count of affected patients.

Another obstacle was the fact that the final set of studies had different designs and for this reason some did not report adjusted but merely unadjusted ORs. This made the comparison of patients who received both classes of ASM or one or the other with those who did not get any acid suppressors rather challenging. Those differences are the reason why we reported the random effects comparison using only unadjusted ORs. The resulting RR of 4.65 (1.64, 13.16) is pointing into the expected direction and in alignment with other studies reporting a higher risk for pneumonia for patients who receive acid-suppressive medication. The heterogeneity in this comparison was high and in addition there is a wide confidence interval which might be expected with this small sample size. One has to interpret this result with caution and it is of importance to replicate our findings with a larger sample size in the future.

The heterogeneity was moderately high in the group receiving the H2RA compared to a non-acid control group. All analyses were thus based on the random-effects model for meta-analysis as this includes consideration of heterogeneity in the effect estimate. Another method to countering heterogeneity would be to pool studies that are sufficiently similar. In our case, however, the small sample size did not allow us to use this approach. Some degrees of heterogeneity in the results of meta-analyses is to be expected since systematic reviews bring together studies that are diverse both clinically and methodologically [45]. It has been suggested that there seems little point in simply testing for heterogeneity when what matters is the extent to which it affects the conclusions of the meta-analysis [11]. An analysis of > 500 Cochrane Database meta-analyses shows that about a quarter of meta-analyses have I^2 values over 50% and that quantification of heterogeneity is only one component of a wider investigation of variability across studies - the most important being diversity in clinical and methodological aspects [11].

5. Conclusion

ASM are commonly prescribed in hospitalized stroke patients and this investigation synthesizes the most current evidence on the relationship between ASM and hospital-acquired pneumonia in this patient population. Results of this meta-analysis demonstrate an increased risk for pneumonia in acute stroke patients exposed to acid-suppressive medications. The risk is higher for those exposed to PPIs versus H2RAs. Further studies with larger sample sizes that incorporate important variables influencing this relationship in acute stroke populations are needed to establish a clearer association between ASM and pneumonia, and better inform clinical practices involving these medications in acute stroke patients. For now, clinicians should avoid unrestricted administration of ASM in acute stroke patients.

Conflict of interest

The authors declare that that research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflict of interest.

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