A.A. El Solh
Division of Pulmonary, Critical Care and Sleep Medicine, Dept of Medicine, University at Buffalo School of Medicine and Biomedical Sciences, Buffalo, NY, USA.

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DOI: 10.1183/09031936.00111906

ACE inhibitors prevent aspiration pneumonia in Asian, but not Caucasian, elderly patients with stroke

To the Editors:

In a recent issue of the *European Respiratory Journal*, VAN DE GARDE *et al.* [1] demonstrated that the use of angiotensin-converting enzyme (ACE) inhibitors is not associated with a decreased risk of hospitalisation for community-acquired pneumonia (CAP) in a general, essentially white population. Their conclusion that the beneficial effect of ACE inhibitors on pneumonia risk is not observed in a general white population is in contrast with previous findings in Asian populations [1]. This was an excellent good study examining the association of ACE inhibitor treatment of cardiovascular disease with a risk reduction of CAP using a large sample size. The results are acceptable and not surprising; however, the discussion and conclusion are misleading.

As shown in table 1, there are controversies regarding the ACE inhibitor effects on the risk reduction of pneumonia even in Asian countries; furthermore, the study samples are very different among the studies. In a prospective study by SEKIZAWA *et al.* [2], ACE inhibitor use reduced pneumonia incidence for 2 yrs. They did not examine the general population; subjects were hypertensive elderly patients with a history of stroke or lacuna infarction, and a mean age 10 yrs older than that of the study by VAN DE GARDE *et al.* [1]. However, the study by ARAI *et al.* [3] examined the association of ACE inhibitors and the risk reduction of pneumonia in the general hypertensive elderly without stroke in Japan [3]. Surprisingly, they had an 8.3–8.9% incidence of pneumonia over 3 yrs, an incidence twenty times higher than the previous data [6, 7]. It is hard to believe that ~3% of hypertensive elderly outpatients without major complications suffered from pneumonia. We have previously presented data showing no association of ACE inhibitor use with pneumonia risk in elderly hypertensive subjects without stroke history [4]. Since ACE inhibitors, through the inactivation substance P, improve upper airway reflexes such as swallowing and cough, resulting in the reduction of aspiration pneumonia in elderly patients, they may not reduce the CAP in those patients without deglutition problems. Current evidence indicates that ACE inhibitors play a significant role in the prevention of aspiration pneumonia in the elderly, but not in common CAP in healthy adults. This was confirmed by the sub-analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). OHKUBO *et al.* [5] re-analysed the PROGRESS data concerning the incidence of pneumonia. ACE inhibitor-active treatment significantly reduced the risk of pneumonia among participants of Asian ethnicity (mean (95% confidence interval) 47% (14–67%), p=0.01), with no significant effect among non-Asian participants (5% (-27–29%), p=0.7; p for homogeneity=0.04). These findings add to the body of

TABLE 1 The association of angiotensin-converting enzyme (ACE) inhibitor use and the rate of pneumonia in different trials

	VAN DE GARDE [1]	SEKIZAWA [2]	ARAI [3]	TERAMOTO [4]	OHKUBO [5]	OHKUBO [5]
Race	Caucasian	Asian	Asian	Asian	Asian	Caucasian
Age yrs	67	76–77	75.3–76.5	>65	64	64
Subjects n	4925	440	576	358	2352	3753
Observation period yrs	6	2	3	3	3.9	3.9
History of stroke	No	Yes	No	No	Yes	Yes
Pneumonia incidence %						
Without ACE inhibitors		9	2.77–2.97	0.25	1.04	1.3
With ACE inhibitors		3.5	1.1	0.56	0.56	1.24
Pneumonia prevention by ACE inhibitors	No	Yes	Yes	No	Yes	No

evidence regarding the effects of these drugs on pneumonia. The randomised design of PROGRESS greatly reduced the likelihood of confounding of the analyses and provided an excellent opportunity to explore the validity of the associations reported in observational studies [2, 3]. Thus, the key issue is the selection of elderly subjects in terms of ethnicity, post-stroke state, performance status, type of ACE inhibitor and swallowing function.

The clinical epidemiology research group of ETMINAN *et al.* [8] recently reported that no association was found between the use of ACE inhibitors or angiotensin II receptor blockers (ARBs) and risk of hospitalisation secondary to CAP. The study further confirmed the limited efficacy of ACE inhibitors on the risk reduction of hospitalisation due to pneumonia in a white population. As we speculated, ARBs did not have any role in the prevention of aspiration pneumonia.

Stroke and post-stroke patients often exhibit a normal cough reflex, but not swallowing reflex, and the small volume of aspirated materials due to impaired swallowing during night is a key factor for the risk of pneumonia [9, 10]. Hence, a ten times higher rate of pneumonia in post-stroke patients without significant neurological deficit, compared with the rate of pneumonia in normal elderly [5]. Furthermore, the age-dependent impairment of upper airway reflexes should be carefully considered for the mechanism of CAP in the elderly irrespective of the history of stroke.

Finally, we emphasise that aspiration and silent aspiration are very important mechanisms of aspiration pneumonia. Silent aspiration is very common in patients with stroke and frail elderly patients, and nasogastric tube feeding without swallowing rehabilitation or oral care cannot reduce the pneumonia risk in patients with swallowing disorders [11].

We believe that angiotensin-converting enzyme inhibitors could prevent aspiration pneumonia in selected elderly patients. Post-stroke and the frail elderly are the best candidates for the pneumonia risk reduction by angiotensin-converting enzyme inhibitors [12]. However, these merits may not be consistently observed in Caucasian elderly patients with or without stroke.

S. Teramoto, H. Yamamoto, Y. Yamaguchi, Y. Hanaoka, M. Ishii, S. Hibi and Y. Ouchi

Dept of Geriatric Medicine, Dept of Urology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

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DOI: 10.1183/09031936.00115106

From the authors:

I would like to thank S. Teramoto and co-workers for their response to the study my co-workers and I performed on the effects of angiotensin-converting enzyme (ACE) inhibitors on the risk of acquiring pneumonia. Indeed, we could not confirm an association between the use of ACE inhibitors and the risk of pneumonia in a general population. This, however, does not exclude any beneficial effects of ACE inhibitors in specified patient subgroups.

As mentioned in our introduction and by S. Teramoto and co-workers, it is known that patients with a history of stroke do have a higher risk of acquiring pneumonia, which is particularly due to a reduced cough and swallowing reflex [1, 2]. That ACE inhibitors can be beneficial in these patients is already widely reported [3–5]. We aimed to study whether this protective effect can also be extended to the general population. Unfortunately, we were not able to test modification of the association through stroke, as data on stroke history were sparsely available in the database.

Concerning ethnicity, the reason why the association could not be confirmed in the non-Asian participants of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) is still subject to speculation. Genetic differences should certainly be considered. However, OHKUBO *et al.* [4] were unable to show an influence of the ACE I/D polymorphism on the protective