

Effects of an angiotensin converting enzyme inhibitor-based regimen on pneumonia risk

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ABSTRACT

Observational studies conducted among Asian populations suggest that the risk of pneumonia is substantially reduced among users of angiotensin converting enzyme (ACE) inhibitors but not other blood pressure lowering agents. We conducted analyses of the effects of ACE inhibitor therapy on pneumonia in 6105 patients with a history of stroke or transient ischaemic attack enrolled in a randomised trial conducted in Australasia, Europe and Asia. Patients were randomly assigned perindopril-based active treatment or placebo. The effects of ACE inhibitors on pneumonia (fatal or non-fatal) were determined from Cox models fitted according to the principle of intention-to-treat. During a median follow-up of 3.9 years, 261 patients developed pneumonia. Overall, active treatment was associated with a non-significant 19% lower risk of pneumonia (95% CI -3 to 37; p=0.09) compared to placebo. Active treatment significantly reduced the risk of pneumonia among participants of Asian ethnicity [47% (14 to 67%; p=0.01)], with no significant effect among non-Asian participants [5% (-27 to 29%; p=0.7)] (p for homogeneity=0.04). These findings substantially add to the body of evidence about the effects of these drugs on pneumonia but do not provide the definitive information required to inform clinical decisions about the prevention of pneumonia with ACE inhibitors.

(199 words)

Key Words: Pneumonia, Angiotensin-Converting Enzyme Inhibitor, Angiotensin Converting Enzyme Insertion/Deletion polymorphism, Stroke, Randomized Controlled Trial

INTRODUCTION

Pneumonia is a major cause of mortality and morbidity, particularly among the elderly and debilitated (1-4). In a number of observational studies conducted among elderly Japanese populations, use of angiotensin converting enzyme (ACE) inhibitors, but not other blood pressure lowering drugs, has been associated with a reduced risk of pneumonia (5-11). Among elderly and debilitated populations, in whom silent aspiration of oropharyngeal pathogens (12) is believed to be a leading cause of pneumonia (1-4), it is possible that established effects of ACE inhibitors on cough (13) and swallowing (14) may provide protection against infection. Furthermore, any such benefit may be particularly marked among individuals of Asian ethnicity, in whom ACE inhibitor-related cough has been reported to be more prevalent (15,16) and among whom ACE insertion/deletion (I/D) polymorphisms may influence the risk of pneumonia (17). However, the non-randomised studies on which the observed effects of ACE inhibitors on pneumonia are based are subject to bias even after adjustment for known confounding factors, and the findings may thus be unreliable (18).

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a large-scale randomised trial conducted among individuals with a history of stroke or transient ischaemic attack, including participants from both Asian and non-Asian regions (19-23). The main objective of this secondary analysis of the trial was to determine the effects of the ACE inhibitor-based blood pressure lowering regimen on the risk of pneumonia overall and among subgroups defined on the basis of Asian and non-Asian ethnicity.

METHODS

Study design

The design and principal results of PROGRESS have been reported previously (19-21). In brief, 6105 patients with a history of stroke and/or transient ischaemic attack were enrolled from 172 collaborating centres in ten countries (Australia, New Zealand, France, Belgium, Italy, Japan, People's Republic of China, Sweden, UK and Ireland). The ethics committee of each collaborating centre approved the study and all participants provided written, informed consent.

Individuals with a history of cerebrovascular disease (stroke, transient ischaemic attack or amaurosis fugax) within the previous five years, and no definite indication for, or contraindication to, treatment with an ACE inhibitor were eligible for the study. There were no blood pressure entry criteria, although it was recommended that individuals with uncontrolled hypertension receive antihypertensive therapy with agents other than angiotensin converting enzyme inhibitors before entry to the trial. It was also recommended that participants should be clinically stable for at least two weeks after their most recent vascular event before entry to the study.

All potential participants entered a 4-6 week run-in period on perindopril 2-4 mg daily to check for tolerability and adherence. Patients that successfully completed the run-in period were randomly assigned either to continued active blood pressure lowering treatment or to matching placebo therapy in a double-blind manner. Study treatment allocation was provided by a central computer-based randomisation service accessed by telephone or facsimile. Active treatment comprised a flexible regimen

based on perindopril (4 mg daily) with the addition of indapamide (2.5 mg daily, or 2mg daily in Japan) in patients for whom the responsible physician judged there to be no specific indication for, or contraindication to, treatment with a diuretic. Participants were instructed to take study tablets daily. All other aspects of medical and surgical care were left to the discretion of the responsible physician.

Randomised participants had visits scheduled for five occasions in the first year after randomisation and 6-monthly intervals thereafter. Wherever possible, clinic visits were continued for the entire scheduled duration of follow-up for all surviving randomised patients, including those who discontinued study drug treatment for any reason. At each visit, inquiry was made about the occurrence of major non-fatal events, including pneumonia. An endpoint adjudication committee reviewed source documentation about the cause of death for all participants that died during the scheduled period of follow-up. This committee assigned one or both of a proximate and an underlying cause of death. In this analysis, pneumonia was taken as the cause of death whether it was proximate or underlying. Pneumonia was defined according to the ninth revision of the International Classification of Diseases (pneumonia = 480-487, 507 or 514) (24) and was deemed fatal if the individual died within 28 days of the diagnosis. Samples of venous blood were collected in EDTA for extraction of DNA from buffy coat using a salting out procedure. Genotyping of the ACE insertion/deletion polymorphism was performed after polymerase chain reaction amplification of the region encompassing the polymorphism with 3 primers by hybridisation with allele specific oligonucleotides (23).

Statistical power

For the primary analysis of the overall effects of randomised treatment on pneumonia (n=6,105, 261 cases of pneumonia), there was 90% power to detect a 34% or greater difference in the relative risk of pneumonia between randomised groups (with p=0.05). For the Asian (n=2,352, 74 cases of pneumonia) and non-Asian (n=3,753, 187 cases of pneumonia) subgroups there was similar power to detect 56% or greater and 40% or greater differences in relative risk, respectively.

Statistical analysis

Analyses were conducted according to the principle of intention-to-treat. Cumulative event curves were estimated using the Kaplan-Meier procedure, and the effects of treatment on the outcome of pneumonia were estimated from Cox proportional hazards models. Similar models were fitted to determine the effects of the ACE I/D polymorphisms on risk of pneumonia with adjustment for age, gender, Asian ethnicity, cardiovascular disease history, current smoking, diabetes and Barthel Index. For those patients who experienced more than one pneumonia event during follow-up, the time since randomisation to the first event was used. Participants who died from other causes were treated as censored. Relative risk reductions are described in the text as percentage reductions ($[1 - \text{hazard ratio}] \times 100$). The effect of treatment on discontinuation due to cough was estimated using a logistic regression model since the exact date of discontinuation was not recorded. All p-values were calculated from 2-sided tests of statistical significance. The effects of treatment on pneumonia were estimated for subgroups defined by self-reported ethnicity (Asian or not), ACE I/D polymorphism (DD vs. ID vs. II), study treatment planned at randomisation (single drug therapy vs. combination therapy), sex and age (<65 vs. ≥65). Homogeneity of

treatment effects between subgroups was tested by adding an interaction term to the relevant statistical model.

RESULTS

Participant enrolment and baseline characteristics

7,121 potential participants were registered and 6,105 were randomised. Of the 1016 (14%) registered participants that were not randomised, 192 (2.7%) withdrew during the 4-week active run-in period due to cough. There was no difference in the rate of withdrawal due to cough in the run-in period between Asian and non-Asian participants (63 [2.4%] vs. 129 [2.9%] respectively; p=0.2). Of those randomised, 3,051 were assigned active treatment and 3,054 were assigned placebo. Overall, 58% were treated with combination therapy or double placebo and 42% with perindopril alone or single placebo. The characteristics of the participants have previously been published in detail (20,21) and are only summarised here (Table 1). Overall, 39% were Asian and 61% were non-Asian. There was good balance between active treatment and placebo groups for all recorded participant characteristics, including those that might possibly be expected to influence the incidence and outcome of pneumonia such as age, dependency (measured by the Barthel Index), smoking status, diabetes and ACE I/D polymorphisms. ACE I/D genotyping was successful among the 5688 randomised participants: of these, 2828 were in the active treatment group and 2860 were in the placebo group (23).

Follow-up and discontinuation of the treatment

Median follow-up was 3.9 years and vital status at the scheduled end of follow-up was ascertained for all but three randomised participants (0.05%). By the end of scheduled follow-up, or prior death, 1,350 (22%) participants had prematurely discontinued all study treatments (active 23%, placebo 21%; $p=0.02$) (21). In addition, by the end of scheduled follow-up a further 134 participants had prematurely discontinued perindopril/placebo (active 87, placebo 47) but continued with indapamide/placebo. Among the 1,484 participants that prematurely discontinued both study treatments or perindopril/placebo alone, cough was the reason cited for discontinuation in 127 (4.2%) actively treated participants and in 25 (0.8%) placebo treated participants ($p<0.001$). Overall, treatment with the ACE inhibitor was associated with a 5.3 [95% confidence interval (CI) 3.4 to 8.1] increase in the odds of treatment discontinuation due to cough. This increased risk was of similar magnitude in both Asian (odds ratio 5.8 [95% CI; 2.4 to 13.9]) and non-Asian participants (5.1 [95% CI; 3.1 to 8.4]) (p for homogeneity=0.8).

Effects of treatment on pneumonia in all participants

A total of 261 study participants suffered 270 episodes (115 fatal and 155 non-fatal) of pneumonia during follow-up. Pneumonia occurred in 117 individuals assigned active treatment (3.8%) and 144 individuals assigned placebo (4.7%). The cumulative event curves for pneumonia in the active and placebo groups diverged early and remained separate throughout follow-up (Figure 1), but the difference between the treatment groups did not reach standard levels of statistical significance (log-rank test, $p=0.09$). The relative risk reduction associated with active treatment was 19% (95% CI -3 to 37%, $p=0.09$) (Figure 2) equating to 96 individuals treated for 5 years to avert one such event. There was no evidence of any difference in the

effects of treatment on fatal or nonfatal pneumonia, or in pneumonia preceded by, or not preceded by, a recurrent stroke (Figure 2).

Effects of treatment on pneumonia in participant subgroups

There was a significant reduction in the risk of pneumonia in the subgroup of participants of Asian origin (relative risk reduction 47% [95%CI 14 to 67%, $p=0.009$]) equating to 45 individuals treated for 5 years to avert one such event (95%CI 27 to 146), but no clear reduction in participants recruited outside of Asia [relative risk reduction 5% (95%CI -27 to 29%, $p=0.7$)] (p for homogeneity between Asians and the other origins = 0.04) (Figure 3). There was no independently significant reduction in the risk of pneumonia in either of the participant subgroups defined on the basis of intended study treatment regimen (single drug therapy or combination therapy) with no statistical evidence of heterogeneity between the subgroups (p for homogeneity = 0.9) (Figure 3). Neither was there any evidence of heterogeneity between the effects of treatment in subgroups defined by sex (p for homogeneity = 0.2) or age (p for homogeneity = 0.9).

Effects of ACE I/D polymorphism on pneumonia

The distribution of the ACE I/D polymorphisms in the PROGRESS population is shown (Table 1). There was a greater prevalence of the II polymorphisms in the Asian (II=41%, ID=44%, DD=15%) compared to non-Asian populations (II=21%, ID=47%, DD=32%) ($p<0.001$). There was no clear effect of ACE I/D polymorphisms on the risk of pneumonia (Table 2). Neither did the ACE I/D polymorphism interact with the effect of randomised treatment on pneumonia (Table 3).

DISCUSSION

This randomised controlled trial conducted among patients with cerebrovascular disease substantially adds to the body of evidence about the effects of ACE inhibitors on pneumonia. The study results suggest that ACE inhibitors might confer protection against pneumonia but do not provide the conclusive information required to consider these agents a new therapeutic option for pneumonia prevention. In particular, the *post hoc* nature of the analyses and their rather limited statistical power provide for persisting uncertainty about this possible new role of ACE inhibitors. The main reason that PROGRESS does not fully resolve the uncertainty surrounding the effects of ACE inhibitors on pneumonia is that the trial was not specifically designed to address this question. The rather few pneumonia events recorded in PROGRESS (n=261) limit the statistical power and the multiple comparisons and post hoc nature of the analyses increase the chance of spurious positive or negative findings (18,25). So, the apparent difference in protection against pneumonia afforded to Asian participants and non-Asian participants could easily be a consequence of the play of chance. Likewise the failure to detect anticipated different rates of cough between these population subgroups (15,16).

However, while statistical power may not have been high, the randomised design of PROGRESS did greatly reduce the likelihood of confounding of the analyses (18,25) and provided an excellent opportunity to explore the validity of the associations reported from observational studies (5-11). In PROGRESS, the overall direction of effect of treatment was similar to that reported in the observational studies and the size of the protective effect in the Asian population subgroup was broadly similar to the size of benefit reported previously (5-11). While the comparability of the findings

could still be coincidental the PROGRESS results somewhat decrease the likelihood that the previously reported protective effects of ACE inhibitors on pneumonia were entirely the result of biased analyses.

The means by which ACE inhibitors affect the respiratory system is thought to be through elevation of substance P, a neurotransmitter for primary sensory afferent nerves that is normally degraded by ACE. Elevated levels of substance P are associated with ACE inhibitor cough (5, 26) and may also produce the enhanced swallowing reflex observed among patients treated with ACE inhibitors (14, 27). In combination, an increased cough reflex cough and improved swallowing provide a reasonable basis for a decreased risk of aspiration pneumonia among ACE inhibitor treated patients. A recent report in which the ACE D allele (of the ACE I/D polymorphism) was identified as an independent risk factor for pneumonia (17) provided a possible explanation for differences in the response of Asian and non-Asian population groups to ACE inhibitor therapy with regard to respiratory disease. However, while there was the anticipated differential distribution of the ACE I/D polymorphisms between Asian and non-Asian participants in PROGRESS (23), there was no effect of the D allele on pneumonia risk and there was no interaction of the ACE I/D polymorphism with the effects of treatment on pneumonia. Furthermore, this was true not only for pneumonia but also for many other serious outcomes recorded in the study (21, 22).

The absence of differences between the rates of cough in Asian and non-Asian participants in PROGRESS during either the run-in phase or the randomized treatment phase contrasts with previous reports documenting higher rates in Asian

populations (15, 16). It is difficult to be certain whether the comparability in the rates of cough in these two population groups in PROGRESS is real, raising uncertainty about the previous reports of differences, or a consequence of a study design that was not specifically intended to address such questions (19). In particular, the PROGRESS study only recorded information about cough when serious enough to cause treatment discontinuation and did not gather detailed information about cough severity. Furthermore, the rather few discontinuations of therapy due to cough limited statistical power for comparisons between patient subgroups. While the trial design makes it is very unlikely that other factors influencing decisions about discontinuation would have varied between treatment groups, it is possible that factors such as cultural attitudes could have resulted in systematic differences between population subgroups with regard to the termination of ACE inhibitor therapy because of side effects. For example, it is possible that a real difference in the effect of the ACE inhibitor on cough between Asian and non-Asian populations could have been obscured by a greater determination to continue with study treatment among one group compared to another.

Misclassification of pneumonia as heart failure, the other leading cause of acute respiratory symptoms in this patient population, does not appear to have been an important problem in PROGRESS. Fatal cases of pneumonia were centrally verified and diagnosis was likely very reliable. Non-fatal cases were diagnosed by clinicians at the many collaborating centres and it is possible that some errors in diagnosis may have occurred. However, there was no evidence of any difference in the effects of randomised treatment on pneumonia between the patients treated with combination (ACE inhibitor and diuretic vs. placebos) compared to those treated with single drug

therapy (ACE inhibitor vs. placebo). If a large proportion of the cases of pneumonia were actually mis-diagnosed cases of heart failure, a greater beneficial effect of combination treatment compared to single drug treatment would have been expected. In PROGRESS, combination treatment resulted in twice the proportional benefit of single drug therapy for heart failure (22) but only a 2% additional benefit for pneumonia. Similarly, the absence of heterogeneity of treatment effects by the presence or absence during follow-up of prior recurrent stroke, suggests that prevention of stroke-related pneumonia was not a strong determinant of the treatment effects observed.

In conclusion, these data from PROGRESS provide some additional support for beneficial effects of ACE inhibitors on the risk of pneumonia. However, this report does not fully resolve all the outstanding uncertainties about the effects of ACE inhibitors on this outcome for either Asian or non-Asian individuals. Furthermore, these findings introduce important new questions about the putative role of the ACE I/D polymorphism in any such effects. Overviews of the present results in conjunction with other completed and ongoing large-scale randomised trials of ACE inhibitors would provide one means of further elucidating the effects of ACE inhibitors on respiratory outcomes. In the meantime, ACE inhibitor-based blood pressure lowering therapy remains a highly effective treatment for the prevention of serious cardiac and cerebral complications among patients with a history of vascular disease.

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A complete list of the PROGRESS Collaborative group has been previously published (21). Management Committee: J. Chalmers, S. MacMahon, C. Anderson, M.G. Bousser, J. Cutler, S. Davis, G. Donnan, L.Hansson (deceased), S. Harrap, K. Lees, L. Liu, G. Mancina, B. Neal, T. Omae, J. Reid, A. Rodgers, R. Sega, A. Terent, C.Tzourio, M. Woodward. Endpoint Adjudication Committee: G. Donnan (chair), N. Anderson, C. Bladin, B. Chambers, G. Gordon, N. Sharpe. Statistical Analysis: S. Colman, A. Lee, M. Woodward.

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Figure legends

Figure 1: Cumulative incidence of pneumonia

Figure 2: Effects of study treatment on pneumonia. Boxes are centred on the point estimates of effect in the relevant subset of outcomes and are sized in proportion to the number of events recorded. The diamond represents the overall result for the trial and is centred on the overall point estimate of effect. The horizontal lines and the tips of the diamond represent 95% confidence intervals.

Figure 3: Effects of study treatment on pneumonia in participant subgroups. Boxes are centred on the point estimates of effect in the relevant participant subgroup and are sized in proportion to the number of events recorded. Other conventions as for Figure 2.

Table 1. Baseline characteristics of randomised participants

	Randomised treatment	
	Active n=3,051	Placebo n=3,054
Mean age, years (SD)	64 (10)	64 (10)
Female (%)	923 (30)	929 (30)
Asian (%)	1176 (39)	1176 (39)
Cerebrovascular disease history*		
Ischaemic stroke (%)	2160 (71)	2153 (71)
Cerebral haemorrhage (%)	332 (11)	329 (11)
TIA or amaurosis fugax (%)	682 (22)	682 (22)
Current smoker (%)	606 (20)	614 (20)
Diabetes (%)	394 (13)	366 (12)
Barthel Index, score (SD)	97 (10)	97 (10)
ACE I/D polymorphisms †		
II	799 (28)	832 (29)
ID	1328 (47)	1279 (45)
DD	701 (25)	749 (26)

*Some participants had experienced more than one type of event at baseline

† Genotyping of ACE *I/D* (insertion/deletion) polymorphisms was successful among the 5688 randomised participants.

Table 2. Effects of ACE I/D polymorphism on pneumonia

Genotype	No of events/patients	Hazard ratio (95% CI)*
DD	72 / 1450	1.29 (0.91 - 1.84)
ID	115 / 2607	1.24 (0.90 - 1.71)
II	58 / 1631	1 (reference)
DD or ID	187 / 4057	1.24 (0.94 - 1.63)
II	58 / 1631	1 (reference)

CI: confidence interval

*adjusted for age, gender, ethnicity, cardiovascular disease history, current smoking, diabetes, Barthel Index

Table 3 Effects of ACE inhibitors vs. placebo on pneumonia by ACE I/D polymorphism

Genotype	Active		Placebo		Active v Placebo Hazard ratio (95% CI)	Homogeneity P-value
	Event counts	Rates per 100 person years	Event counts	Rates per 100 person years		
DD	35	1.3	37	1.3	1.00 (0.63-1.58)	0.5
DI	49	1	66	1.3	0.71(0.49-1.03)	
II	28	0.9	30	0.9	0.97(0.58-1.62)	

CI: confidence interval

Figure 1

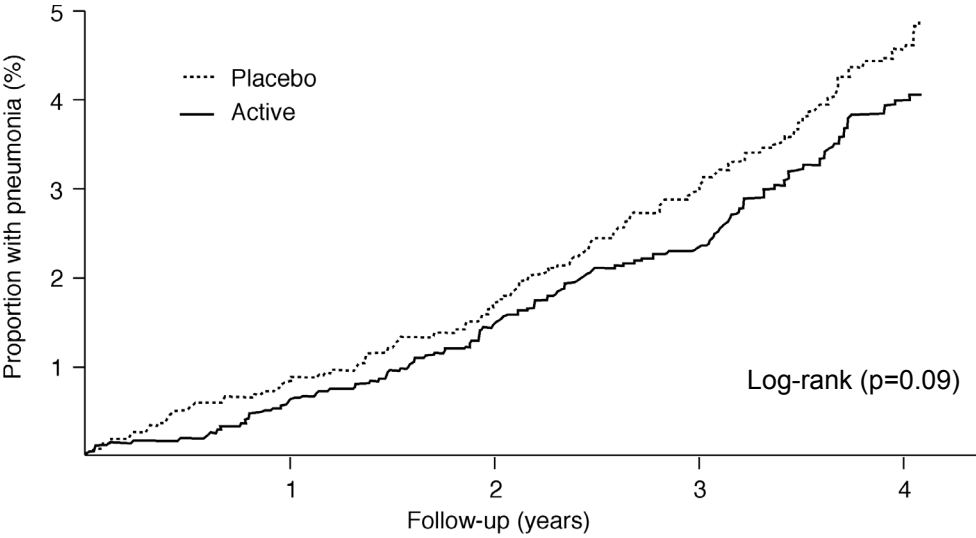


Figure 3

