Angiotensin-Converting Enzyme Inhibitor Induced Cough in Chinese Patients: a Systematic Review and Meta-analysis

Ling Liang1,2, Janice Y. Kung3, Bradley Mitchelmore4, Jasmine Gill5, Andrew Cave6, and Hoan Linh Banh6

1Department of Cardiology, The First Affiliated Hospital of Xiamen University, Xiamen, China; 2Department of Cardiology, First Clinical Medical College of Fujian Medical University, Fuzhou, China; 3University of Alberta, John W. Scott Health Sciences Library; 4Public Health Agency of Canada; 5University of Alberta Hospital, Department of Pharmacy, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta; 6University of Alberta, Faculty of Medicine and Dentistry, Department of Family Medicine.

Corresponding authors: Ling Liang, M.D., Department of Cardiology, The First Affiliated Hospital of Xiamen University, No 55 Zhenhai Road, Xiamen, China, 361000; TEL.: (+86)13860129351; fax: +86(0)592-2181680; email: ravennaliang@sina.com; Hoan Linh Banh, Pharm.D., Faculty of Medicine and Dentistry/Department of Family Medicine, University of Alberta; 6-10 University Terrace, Edmonton, AB, T6G 2C8, Canada; email: hoan@ualberta.ca

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ABSTRACT -- Purpose: To determine the risk of angiotensin converting enzyme inhibitor (ACEI)-induced cough compared to non-ACEI cough among Chinese patients. Methods: A comprehensive search was conducted including randomized controlled trials, case-control studies and observational studies that compared ACEI treatment with control treatment in MEDLINE, EMBASE, CINAHL, Scopus, Google Scholar and ProQuest Dissertations & Theses Global. The studies which contained: Chinese population, ACEI, non-ACEI, and indications for the treatment of ACEI were included. The pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to compare the relative risk of cough between ACEIs and non-ACEI drugs based on the events of reported cough in each study. Results: Eleven randomized controlled trials were included with a total of 1815 patients. The total number of cough events in ACEI treatment was 101 in 930 patients (11%) and 20 in 885 patients (2%) in the Non-ACEI treatment. The pooled RR was 5.16 (95% CI: 3.39-7.85) under fixed model. The discontinuation number of single ACEI treatment due to coughing side effect was 21 and the withdrawal rate was 4.13%. Only two patients discontinued non-ACEIs treatment due to the intolerable cough and the withdrawal rate was 0.34%. The overall RR of withdrawal related to cough was 7.06 (95% CI: 2.49-20.04). Conclusions: The pooled risk of the incidence of ACEI-induced cough was about five times higher than that of non-ACEI-induced cough in Chinese population. The risk of withdrawal events related to cough in the single ACEI treatment was seven times of that in the non-ACEI treatment.

INTRODUCTION

According to the World Health Organization, almost 18 million (31%) of people who died in the world in 2008, died from cardiovascular diseases (CVD) and by 2030, approximately 24 million people will die from CVD (1). Angiotensin-converting enzyme inhibitors (ACEI) are cornerstones of treatment for CVD such as hypertension, heart failure and myocardial infarction. They have been shown to reduce mortality and morbidity in patients with cardiovascular diseases (2-7). ACEI-induced cough is one of the most commonly reported adverse effects of the treatment. However, the prevalence of ACEI-induced cough in Chinese patients is higher than that of the other populations. In one study the incidence of cough has been reported to be 5% to 35% (8). In North America (9) on the other hand, the reported incidence of ACEI-induced cough in Chinese patients varies from 5% to 29% (10). The primary objective of this systematic review and meta-analysis is to identify the incidence of ACEI-induced cough in Chinese patients. The secondary objective is to determine the risk of ACEI induced cough in Chinese patients.

METHOD

This systematic review was performed in accordance with the checklist of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement (11).

Search strategy

The medical librarian conducted comprehensive searches which included all randomized controlled trials, case-control studies and observational studies available in English that compared active treatment with ACEI or control treatment (placebo, active control, or usual care) in MEDLINE (via
incidence of outcome measured which occurred in one article, while high risk or low risk of bias was judged based on the Cochrane Handbook (13).

Patient and public involvement
Patients and carers (and respective organizations) were involved in the design and development of the program development grant application. Patients and carers attended all the steering group meetings and were an integral part of the research team, commenting on and critiquing the inclusion and exclusion criteria, outcome selection, and the acceptability and likely value of interventions. As part of the steering group, they received and commented on study progression, emergent findings and reports. They are integral to the dissemination plans, including sharing the publication, but also helping craft lay summaries of the overall research project and key findings. A public -patient representative (EH) performed the data extraction together with research and clinical colleagues, and coauthored and edited this article. Public-patient representatives were also part of the steering group and informed the design and delivery of the article.

STATISTICAL ANALYSIS

The pooled estimates of risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to compare the relative risk of cough between ACEIs and non-ACEI drugs based on the events of reported cough in each study. \( I^2 \) statistic was applied to inspect heterogeneity. If \( I^2 < 50\% \) and \( p \) value is >0.1, heterogeneity is acceptable. If \( I^2 > 50\% \) and \( p \) value < 0.1, the random effect or a meta-regression method to find sources for the obvious heterogeneity was performed. The presence of small study effects was assessed by visually
interpreting funnel plot asymmetry and quantified by Egger test ($p < 0.05$). A two-tailed $p$-value $< 0.05$ was considered statistically significant. All the statistical analyses were performed in Stata 14.1 (Stata Corp, College Station, TX).

RESULTS

The Search Result
A total of 293 studies were identified from the search. One hundred and sixty-four studies were duplicates and were excluded. Eight studies were in Chinese language, but the studies were not relevant to the meta-analysis and were excluded. After screening the abstracts of the studies, 71 studies were excluded as they were not related to the topic. After screening the full text of the remaining 50 studies, six studies were not retrievable, five studies have no extractable data, and 28 studies with no comparators. As a result, eleven randomized controlled trials were included (Figure 1) with a total of 1815 patients in the studies. All observational studies were excluded because they did not have a comparator group.

Characteristics of the included trials
Totally, there were eleven randomized controlled trials included in this meta-analysis paper. Three studies were placebo-controlled trials, and eight studies were head-to-head comparisons between ACEI and other alternatives such as calcium channel blockers (CCB), angiotensin receptor blocker II (ARB) and diuretics. Three trials were completed in Hong Kong, three in mainland China and five in Taiwan. Participants with moderate hypertension were enrolled in six of the studies and five studies included patients with kidney disease. The subject age ranged from 18 to 75 years. The observation period of cough induced by treatments varied from four weeks to five years. Basic characteristics of the studies are listed in Table 1 and the quality of eligible studies is shown in Figure 2. Overall study quality has low risk of bias.

Cough events between ACEIs and Non-ACEIs
Cough events were reported in the eleven trials. The total number of cough events in ACEI treatment group was 101 in 930 patients (11%) and 20 in 885 patients (2%) in Non-ACEI treatment group. The overall pooled estimate of relative risk ratios (RRs) was 5.16 (95% CI: 3.39-7.85) under fixed model with no observed heterogeneity ($I^2=0\%$, $p=0.885$) (Figure 3). The risk ratio of cough with ACEI was 4.38 times (95% CI: 1.29-14.8) compared with Placebo treatment. Similarly, the risk ratio of cough between ACEI group and CCB group was 4.56 (95% CI: 2.18-9.56). The highest risk ratio was 5.61 (95% CI: 3.22-9.79) as the incidence of cough caused by ACEIs compared with ARB. The funnel plot was symmetric and Egger test $p$ value was 0.229, meaning there is no significant publication bias and no small sample size studies effect.

![Figure 2. Bias risk assessment for the studies (yellow color: unclear risk, green color: low risk, red color: high risk.)](image)

Withdrawal events related to cough between ACEIs and Non-ACEIs
Five trials were extracted to analyse the withdrawal events related to cough. 21 patients in 509 (4.13%) discontinued the single ACEI treatment due to the intolerable cough, while only 2 patients developed cough in 594 patients under non-ACEIs treatment (0.34%). The pooled risk ratio of withdrawal events due to the intolerable cough was 7.06 (95% CI: 2.49-20.04) under fixed model. I square was 0% and the heterogeneity was undetectable ($p=0.946$) (see Figure 4). No publication bias was observed from the symmetric funnel plot. Egger test result ($p = 0.914$) indicated no small sample size studies effect.
| Study, year | Journal | Patients characteristics, sample size | ACEI drugs | Comparator drugs | Maximal dosage of ACEIs | Follow-up |
|-------------|---------|--------------------------------------|------------|-----------------|------------------------|-----------|
| Brian Tomlinson et al 2004 | Clinical Therapeutics | Population: hypertension  
Mean age (range): 60.5y  
80 patients (G1=40,G2=40) | G1: Enalapril | G2: Amlodipine | 20mg | 14 weeks |
| Chien-Hsun Hsia et al 2005 | Acta Cardiologica Sinica | Population: hypertension  
Mean age (range): 18-75y  
50 patients (G1=26,G2=24) | G1: Perindopril+ indapamide | G2: Losartan | 4/1.25mg | 12 weeks |
| Fan Fan Hou et al 2006 | New England Journal of Medicine | Population: chronic kidney disease  
Mean age (range): 18-70y  
328 patients (G1=216,G2=112) | G1: Benazepril | G2: Placebo | 20mg | 4 weeks |
| Gary T. C. Ko et al 2005 | Advances in Therapy | Population: type 2 diabetes and normal renal function or early-stage nephropathy  
Mean age (range): 61y  
42 patients (G1=20,G2=22) | G1: Enalapril | G2: Valsartan | 10mg | 52 weeks |
| I-Te Lee et al 2012 | Clinical Therapeutics | Population: hypertension patients with microalbuminuria  
Mean age (range): 59.7y  
167 patients (G1=83,G2=84) | G1: Amlodipine/Benazepril | G2: Valsartan/hydrochlorothiazide | 5/10mg | 16 weeks |
| Kuan-Rau Chiou et al 2000 | Chinese Medical Journal | Population: hypertension  
Mean age (range): 53.2y  
68 patients (G1=34,G2=34) | G1: Enalapril | G2: Irbesartan | 20mg | 8 weeks |
| Paul Chan et al 1997 | American journal of hypertension | Population: hypertension  
Mean age (range): 65y  
156 patients (G1=52,G2=26,G3=51,G4=27) | G1: Lisinopril + Diltiazem  
G2: Lisinopril + Placebo  
G3: Diltiazem + placebo  
G4: Placebo + placebo | | 10mg | 12 weeks |
| Paul Chan et al 1997 | Journal of Clinical Pharmacology | Population: hypertension  
Mean age (range): 73y  
84 patients (G1=28,G2=28,G3=28) | G1: Lisinopril | G2: Metolazone  
G3: Losartan | 10mg | 10 weeks |
| Philip Kam-Tao Li et al 2003 | Annals of internal medicine | Population: peritoneal dialysis  
Mean age (range): 59y  
60 patients (G1=30,G2=30) | G1: Ramipril | G2: Placebo | 5mg | 12 months |
| X Chen et al 2006 | Journal of International Medical Research | Population: renal parenchymal hypertension  
Mean age (range): 18-70y  
85 patients (G1=42,G2=43) | G1: Benazepril | G2: Barnidipine | 20mg | 4 weeks |
| YU Li-tian et al 2011 | Chinese Medical Journal | Population: hypertension with high risk of cardiovascular event  
Mean age (range): 65.6y  
1159 patients (G1=385,G2=390,G3=384) | G1: Ramipril | G2: Telmisartan  
G3: Ramipril + Telmisartan | 10mg | 5 years |
Figure 3. Relative risks of coughing between ACEI and non-ACEI

Figure 4. The forest plot of withdrawal related to cough between ACEI and non-ACEI
DISCUSSION

The eleven randomized controlled studies included in this meta-analysis provide a unique perspective on ACEI-induced cough in the Chinese population. Although there were many differences in the included trials, such as the participants’ age and comparators used, the overall statistical heterogeneity of combined relative risk ratio was not observed. As a result, we did not analyze data based on the different comparators stratification. Previous studies indicated that different ethnic groups have different risks for developing adverse drug reactions, in particular to the cardiovascular drugs such as ACEI (14). In the present study, the incidence of ACEI induced cough in Chinese patients compared to non-ACEI cough was 11% and 2% respectively. A Cochrane review on ACEI compared to angiotensin enzyme receptor II blockers (ARB) in the treatment of primary hypertension showed that when compared with ACEI, ARB had about 2% lower incidence in the discontinuation of drug due to cough (15). The relative risk inhibitor induced cough was 2.7 (1.6 – 4.5) in East Asian compared to white patient. This meta-analysis included Chinese, Koreans, and Japanese as East Asians. No sub-analysis of Chinese population was included in the study. Vukadinovic et. al. completed a meta-analysis on the general population, and they found the relative risk for cough in patients treated with ACEI was 2.19 (95% confidence interval (CI) 1.78–2.70, P < 0.0001) vs. placebo (16). The ONTARGET study showed the ramipril group (an ACEI) had a higher treatment discontinuation due to cough as compared to telmisartan (an ARB) (4.2% vs 1.1%, P<0.001)(17) This current meta-analysis showed that Chinese patients treated with an ACEI were about five times more likely to develop cough compared to a non-ACEI. The dropout rate due to the cough in single ACEI treatment group was seven times the rate of the comparators treatment group.

The generally accepted mechanism of cough is that it is caused by bradykinin and substance P which are degraded by ACE As a result, they are accumulated in the lungs when the ACE is inhibited (18). Both bradykinin and substance P sensitize the airway sensory nerves which induce cough (19-20). Evidence suggests that bradykinin receptor gene polymorphism is associated with ACEI-induced cough (21).

Only one study examined the difference in discontinuation rates in ACEI induce cough in Chinese compared with the general population (9). The results showed that Chinese are more than twice as likely to discontinue lisinopril (an ACEI) due to cough as the general population. Factors such as age, sex, co-morbidity and genetic polymorphisms, affect drug metabolism and drug responses including adverse effects.

A possible explanation for the increased incidence of cough in the Chinese is the presence of a genetic polymorphism predisposing to cough. Cytochrome P450 (CYP450) is the most common drug metabolism pathway. The CYP450 genotype is expressed differently in different ethnic groups (22). There are three groups of ACEI: captopril, prodrugs (Ramipril, enalapril), and lisinopril. With the exception of lisinopril, all ACEI molecules have a carboxyl functional group that requires carboxylase enzyme activation. Lisinopril is the only water-soluble ACEI that does not undergo hepatic metabolism. The SLCO1B1 gene is responsible in the hepatic metabolism of drugs including ACEI such as enalapril (23). An observational study with 450 Chinese patients conducted by Luo, et al., examined the association between SLCO1B1 genetic polymorphisms and enalapril induced cough in a Chinese population (24). The results showed that patients with SLCO1B1 521C allele and SLCO1B1*15/*15 carriers are twice and seven times more likely to develop enalapril induced cough, respectively. Using the same patients from the previous observational study, Lou also showed there is an association between rs495828 polymorphism and enalapril induced cough (25). The role of genetic polymorphism in cough susceptible individuals warrants further exploration.

Limitations
All the included studies did not use a consistent tool to assess cough and the definition of cough related ACEI varied from one study to another. The observation periods were different in the included trials, which could lead to the different results of cough outcome since the cough occurrence rate increases in a longer observation time. Because none of the randomized control studies have been designed to directly compare the incidence of cough induced by ACEI between Chinese patients and other races, it is hard to draw a conclusion that the occurrence of cough side effect from ACEI in Chinese is higher and the discontinuation rate is higher than other races.

CONCLUSION
The incidence of medication induced cough in the Chinese population was 11% with ACEI medications and 2% for non-ACEI medications. The risk of developing ACEI induced cough was 5.16 (95% CI: 3.39-7.85) times that of non-ACEI
induced cough in this population. The dropout rate due to the intolerable cough in the single ACEI treatment group was 7.06 (95% CI: 2.49-20.04) times that in the non-ACEI treatment.

CONTRIBUTORS
L.L. and H.L.B. conceived and conceptualized the research idea. J.K. conducted comprehensive searches. J.G., L.L. and H.L.B. reviewed the search, performed the screening, full text assessment. L.L. and H.L.B. did the quality assessment and data extraction. L.L. did data analyses, B.M. contributed and H.L.B. supervised the analysis. L.L. and H.L.B. framed the results and drafted the manuscript. A.C. and B.M. made revisions on the draft and approved the final version. L.L. supervised the whole study process and is guarantor.

COMPETING INTERESTS
The authors have no competing interests to declare.

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DATA SHARING STATEMENT
No additional data are available.

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**Supplementary Table.**

| Database                        | Search Strategy                                                                 |
|--------------------------------|---------------------------------------------------------------------------------|
| **MEDLINE**                     | 1. exp Angiotensin-Converting Enzyme Inhibitors/                               |
| Ovid                            | 2. (ACE inhibitor* or angiotensin converting enzyme inhibitor*).mp.            |
| MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to February 14, 2019 | 3. angiotensin converting enzyme antagonist*.mp.                             |
|                                | 4. angiotensin converting enzyme blocker*.mp.                                  |
|                                | 5. dipeptidyl carboxypeptidase inhibitor*.mp.                                  |
|                                | 6. benazepril*.mp.                                                            |
|                                | 7. Captopril/ or captopril.mp.                                                |
|                                | 8. cilazapril*.mp. or exp CILAZAPRIL/                                        |
|                                | 9. exp Enalapril/ or enalapril*.mp.                                           |
|                                | 10. enalaprilat.mp. or exp ENALAPRILAT/                                       |
|                                | 11. fosinopril*.mp. or exp FOSINOPRIL/                                       |
|                                | 12. imidapril*.mp.                                                            |
|                                | 13. exp LISINOPRIL/ or lisinopril.mp.                                         |
|                                | 14. moexipril*.mp.                                                            |
|                                | 15. perindopril*.mp. or exp PERINDOPRIL/                                      |
|                                | 16. quinapril*.mp.                                                            |
|                                | 17. Ramipril/ or ramipril*.mp.                                                |
|                                | 18. saralasin.mp. or exp SARALASIN/                                           |
|                                | 19. Teprotide.mp. or exp TEPROTIDE/                                           |
|                                | 20. trandolapril*.mp.                                                         |
|                                | 21. (alacepril or altiopril or ancovenin or ceranapril or ceronapril or deacetylalacepril or delapril or epicaptopril or fasidotril* or foroxymithine or gemopatrilat or idrapril or indolapril or libenzapril or moveltipril or omapatrilat or pentopril* or pivopril or rentiapril or s nitrosocaptopril or spirapril* or temocapril* or utibapril* or zabicapril* or zofenopril*).mp. |
|                                | 22. or/1-21                                                                   |
|                                | 23. Cough/                                                                     |
|                                | 24. cough*.mp.                                                                |
|                                | 25. exp Bronchial Spasm/ or (bronchospasm* or bronchial spasm*).mp.           |
|                                | 26. 23 or 24 or 25                                                            |
|                                | 27. Chinese.ti,ab,kf.                                                         |
|                                | 28. China.ti,ab,kf. or exp CHINA/                                             |
|                                | 29. Taiwan*.ti,ab,kf. or Taiwan/                                              |
|                                | 30. (Hong Kong or Macao or Macau or Macanese).ti,ab,kf.                       |
|                                | 31. Singapore*.ti,ab,kf. or Singapore/                                        |
|                                | 32. or/27-31                                                                  |
|                                | 33. 22 and 26 and 32                                                          |
|                                | 34. limit 33 to chinese                                                       |
|                                | 35. limit 33 to english language                                               |
|                                | 36. 34 or 35                                                                  |
| Embase                         | 1. exp dipeptidyl carboxypeptidase inhibitor/                                  |
| Embase 1974 to 2019 February 14 | 2. (ACE inhibitor* or angiotensin converting enzyme inhibitor*).mp.          |
|                                | 3. angiotensin converting enzyme antagonist*.mp.                             |
|                                | 4. angiotensin converting enzyme blocker*.mp.                                 |
|                                | 5. dipeptidyl carboxypeptidase inhibitor*.mp.                                 |
|                                | 6. benazepril*.mp.                                                            |
|                                | 7. captopril.mp.                                                              |
|                                | 8. cilazapril*.mp.                                                            |
|                                | 9. enalapril*.mp.                                                             |
|                                | 10. enalaprilat.mp.                                                           |
|                                | 11. fosinopril*.mp.                                                           |
|                                | 12. imidapril*.mp.                                                            |
|                                | 13. lisinopril.mp.                                                            |
|                                | 14. moexipril*.mp.                                                            |
|                                | 15. perindopril*.mp.                                                          |

*Supplementary Table continues...*
16. quinapril*.mp.
17. ramipril*.mp.
18. saralasin.mp. or exp saralasin/
19. Teprotide.mp.
20. trandolapril*.mp.
21. (alacepril or altiopril or ancovenin or ceranapril or ceronaprıl or deacetyllaceprıl or delapril or epicaptopril or fasidotril* or foroxymithine or genopratril or idrapril or indolapril or libenzapril or moveltipril or omapatrilat or pentopril* or pivopril or rentiapril or s nitrosocaptopril or spirapril* or temocapril* or utibapril* or zabicipril* or zofenopril*).mp.
22. or/1-21
23. exp coughing/
24. cough*.mp.
25. exp bronchospasm/ or (bronchospasm* or bronchial spasm*).mp.
26. 23 or 24 or 25
27. Chinese.ti,ab,kw. or Chinese/
28. China.ti,ab,kw. or exp China/
29. Taiwan*.ti,ab,kw. or Taiwan/ or Taiwanese/
30. (Hong Kong or Macao or Macau or Macanese).ti,ab,kw.
31. Singapore*.ti,ab,kw. or Singapore/ or Singaporean/
32. or/27-31
33. 22 and 26 and 32
34. limit 33 to chinese
35. limit 33 to english language
36. 34 or 35

| CINAHL     | S1           | (MH "Angiotensin-Converting Enzyme Inhibitors") |
|------------|--------------|-------------------------------------------------|
|            | S2           | "ACE inhibitor*" or "angiotensin converting enzyme inhibitor"* |
|            | S3           | "angiotensin converting enzyme antagonist*" |
|            | S4           | "angiotensin converting enzyme blocker*" |
|            | S5           | "dipeptidyl carboxypeptidase inhibitor*" |
|            | S6           | "benazepril*" |
|            | S7           | (MH "Captopril") OR "captopril" |
|            | S8           | "cilazapril*" |
|            | S9           | (MH "Enalapril") OR "enalapril*" |
|            | S10          | (MH "Enalaprilat") OR enalaprilat |
|            | S11          | (MH "Fosinopril") OR "fosinopril*" |
|            | S12          | "imidapril*" |
|            | S13          | (MH "Lisinopril") OR "lisinopril" |
|            | S14          | "moexipril*" |
|            | S15          | (MH "Perindopril") OR "perindopril*" |
|            | S16          | "quinapril*" |
|            | S17          | "ramipril*" |
|            | S18          | "saralasin" |
|            | S19          | "Teprotide" |
|            | S20          | (MH "Trandolapril") |
|            | S21          | alacepril or altiopril or ancovenin or ceranapril or ceronapril or deacetyllaceprıl or delapril or epicaptopril or fasidotril* or foroxymithine or genopratril or idrapril or indolapril or libenzapril or moveltipril or omapatrilat or pentopril* or pivopril or rentiapril or s nitrosocaptopril or spirapril* or temocapril* or utibapril* or zabicipril* or zofenopril* |
|            | S22          | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 |
|            | S23          | (MH "Cough") |
|            | S24          | cough* |
|            | S25          | (MH "Bronchial Spasm") |
|            | S26          | bronchospasm* or "bronchial spasm*" |
|            | S27          | S23 OR S24 OR S25 OR S26 |
|            | S28          | (MH "Chinese") OR "Chinese" |

Supplementary Table continues...
| S29 | (MH "China") OR "China" |
| S30 | (MH "Taiwan") or Taiwan* |
| S31 | (MH "Hong Kong") or "Hong Kong" |
| S32 | (MH "Macao") or Macao or Macau or Macanese |
| S33 | "Singapore*" |
| S34 | S28 OR S29 OR S30 OR S31 OR S32 OR S33 |
| S35 | S22 AND S27 AND S34 |

**Scopus**

TITLE-ABS-KEY("ACE inhibitor*" OR "angiotensin converting enzyme inhibitor*" OR "angiotensin converting enzyme antagonist*" OR "angiotensin converting enzyme blocker*" OR "dipeptidyl carboxypeptidase inhibitor*" OR benazepril* OR captopril OR cilazapril* OR enalapril* OR enalaprilat OR fosinopril* OR imidapril* OR lisinopril OR moexipril* OR perindopril* OR quinapril* OR ramipril* OR saralasin OR Teprotide OR trandolapril* OR alacepril or altiopril or ancocvenin or ceranapril or ceronapril or deacetylalacepril or delapril or epicaptopril or fasidotril* or foroxymithine or gomopatrilat or idrapril or indolapril or libenzapril or moveltipril or omapatrilat or pentopril* or pivopril or rentiapril or "s nitrosocaptopril" or spirapril* or temocapril* or utibapril* or zabicipril* or zofenopril*) AND TITLE-ABS-KEY(cough* OR bronchospasm* OR "bronchial spasm") AND TITLE-ABS-KEY(Chinese OR China OR Taiwan* OR "Hong Kong" OR Macao or Macau or Macanese OR Singapore*)

Limit to English, Chinese

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noft("ACE inhibitor*" OR "angiotensin converting enzyme inhibitor*" OR "angiotensin converting enzyme antagonist*" OR "angiotensin converting enzyme blocker*" OR "dipeptidyl carboxypeptidase inhibitor*" OR benazepril* OR captopril OR cilazapril* OR enalapril* OR enalaprilat OR fosinopril* OR imidapril* OR lisinopril OR moexipril* OR perindopril* OR quinapril* OR ramipril* OR saralasin OR Teprotide OR trandolapril* OR alacepril or altiopril or ancocvenin or ceranapril or ceronapril or deacetylalacepril or delapril or epicaptopril or fasidotril* or foroxymithine or gomopatrilat or idrapril or indolapril or libenzapril or moveltipril or omapatrilat or pentopril* or pivopril or rentiapril or "s nitrosocaptopril" or spirapril* or temocapril* or utibapril* or zabicipril* or zofenopril*) AND noft(cough* OR bronchospasm* OR "bronchial spasm") AND noft(Chinese OR China OR Taiwan* OR "Hong Kong" OR Macao or Macau or Macanese OR Singapore*)

**Google Scholar**

(ACE inhibitors OR "angiotensin converting enzyme") AND cough AND (Chinese OR China OR "Hong Kong" OR Macao OR Macau OR Taiwan OR Singapore)