

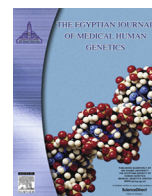
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Original article

Angiotensin-converting enzyme (ACE) I/D and bradykinin B2 receptor T/C genes polymorphism in patients with ACE inhibitors-related coughMohammad Saifur Rohman^{a,b,*}, Jonny Karunia Fajar^{c,*}, Bagus Hery Kuncahyo^{a,b}, Lowry Yunita^{a,b}, Erdo Puncak Sidarta^b, Putu Nina Belinda Saka^b, Teuku Heriansyah^{d,*}, Nashi Widodo^e^a Department of Cardiology and Vascular Medicine, Faculty of Medicine, Brawijaya University/Saiful Anwar General Hospital, Malang 65117, Indonesia^b Brawijaya Cardiovascular Research Center, Faculty of Medicine, Brawijaya University, Malang 65117, Indonesia^c Medical Research Unit, School of Medicine, Syiah Kuala University, Banda Aceh 23111, Indonesia^d Department of Cardiology and Vascular Medicine, School of Medicine, Syiah Kuala University/Zainoel Abidin General Hospital, Banda Aceh 23111, Indonesia^e Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang, 65145, Indonesia; Aging Research Institute, Brawijaya University, Indonesia

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ABSTRACT

Background: Angiotensin-converting enzyme (ACE) inhibitors-related cough had been reported to contribute for discontinuation of ACE inhibitors therapy. The role of ACE I/D and bradykinin B2 receptor T/C genes in ACE inhibitors-related cough is still unclear.**Objectives:** To determine ACE I/D and bradykinin B2 receptor T/C genes polymorphisms in patients with ACE-inhibitors-related cough.**Subjects and methods:** An analytical study with cross-sectional design was conducted at Saiful Anwar General Hospital from June 2013 to September 2014. We used the polymerase chain reaction to genotype ACE I/D and bradykinin B2 receptor T/C genes. Data on both ACE I/D and bradykinin B2 receptor T/C genes polymorphisms in cough and non cough group of hypertensive patients treated with ACE inhibitors in our Hospital during the period were analyzed using multiple logistic regression. Moreover, a meta-analysis was performed to summarize findings from other regions.**Results:** A total of 18 patients with cough (21%) and 67 patients without cough (79%) of hypertensive patients treated with ACE inhibitors from our Hospital during the period were analyzed for this study. In our population, no correlation was observed between ACE inhibitors-related cough and both ACE I/D ($p = 0.560$) and bradykinin B2 receptor T/C ($p = 0.475$) genes polymorphism. However, our meta-analysis of five studies consisting of 267 patients with cough and 346 patients without cough revealed that higher risk of ACE inhibitors-related cough was 1.82-fold associated with T allele of bradykinin B2 receptor T/C gene polymorphism ($p = 0.0310$).**Conclusions:** While the evidence in our meta-analysis suggests strong role for bradykinin gene polymorphism in ACE inhibitors-related cough, however, in our population, we did not find any association.© 2018 Ain Shams University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).**1. Introduction**

Angiotensin-converting enzyme (ACE) inhibitors have been widely used as gold standard and established as corner-stones for the management of hypertension [1,2]. However, it has been reported that ACE inhibitors therapy are accompanied by several side-effects [3], and the most often reported ACE inhibitors side-effect is ACE inhibitors-related cough [4]. First reported in 1985 [5], until now, the incidence of ACE inhibitors-related cough is vari-

able, ranging from 0.7 to 35% [4,6–10], and has been associated with the reasons for patients to discontinue the treatment of hypertension. The incidence of ACE inhibitors discontinuation due to cough is about 4–50% of all patients with ACE inhibitors-related cough [4,11–13]. It has been known that hypertension is the most crucial risk factor for stroke [14], coronary heart disease (CHD) [15], heart failure (HF) [16], and end-stage renal disease (ESRD) [17,18]. Therefore, the cessation of hypertensive treatment is very detrimental for the patients.

The incidence data [4,6–10] suggested that ACE inhibitors-related cough only occurred in some patients. This means that genetic factors may play an important role for the development of ACE inhibitors-related cough. Although the etiology of ACE inhibitors-related cough remains unclear [9], however, theoretically,

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ACE and bradykinin are thought to have a crucial role in the pathogenesis of ACE inhibitors-related cough [4] and these levels are proven to be influenced by genes polymorphism. Abbas et al. [19] reported that DD genotypes of *ACE insertion/deletion (I/D) gene* polymorphism on chromosome 17q23 were associated with higher ACE serum levels, and higher bradykinin activity was observed in T allele of *bradykinin B2 receptor – 58 T/C gene* polymorphism [20]. Since 1990 s, some studies had reported the correlation between genes [*ACE I/D* and *bradykinin B 2 receptor T/C*] polymorphism and ACE inhibitors-related cough in different populations [20–29]. However, in Indonesia, until now, no study has been conducted to evaluate these associations.

Our present study aimed to evaluate the association between ACE inhibitors-related cough and the polymorphisms of both *ACE I/D* and *bradykinin B2 receptor T/C genes* in our Hospital. Moreover, due to the reports concerning the association between both *ACE I/D* and *bradykinin B2 receptor T/C genes* polymorphism and the risk of ACE inhibitor-related cough remained conflicting [20–29], we also performed a meta-analysis to conclude the association.

2. Subjects and methods

2.1. Study designs and patients

During the period (June 2013–September 2014), an analytical study with cross-sectional design was conducted in Saiful Anwar General Hospital, Malang, Indonesia to assess the association between ACE inhibitors-related cough and [*ACE I/D* and *bradykinin B2 receptor T/C*] genes polymorphisms in hypertensive patients treated with ACE inhibitors. The target population was all hypertensive patients treated with ACE inhibitors in our Hospital during June 2013–September 2014. We used total sampling method. The inclusion criteria were all essential hypertensive subjects for more than two years who had been given ACE inhibitors at a daily dose for eight weeks or more. Subjects with the following condition were excluded, i.e.: (1) patients with any secondary cause of hypertension; (2) patients with a history of recent respiratory infection, other respiratory diseases, or pulmonary congestion; (3) patients with productive coughing or with chest X-ray problems; (4) patients who disagree to give blood for the study. The diagnosis of patients with ACE inhibitors-related cough was adapted from previous studies [20,24,28–30]. Subjects who complained of dry cough, and their symptoms had disappeared soon after withdrawal of the ACE inhibitors [24,28,29] and or after taking medicine were categorized [20,30] as cough group. While, patients with no complaint of cough were classified as non cough group. We collected blood samples from the peripheral vein. Then, they were put in EDTA-coated tubes and kept cold. Within 72 h, QIAamp kit (QiaGen, Tokyo, Japan) was used to extract the DNA from leukocytes according to the standard protocol [28,29]. This study was approved by Ethical Committee of Brawijaya University, Malang, Indonesia, and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments in humans. All patients had signed written informed consent prior to the study.

2.2. ACE I/D genotype determination

The *ACE I/D gene* polymorphism was identified by polymerase chain reaction (PCR) as described by previous studies [20,24,28,29] with some modifications. A set of primers (forward 5'-GCC CTGCAGGTCTCTGCAGCATGT-3' and reverse 5'-GGATGGCTCTCCCC GCCTTGCTTC-3') was designed to cover the polymorphic region in intron of the ACE gene. A 20 µL of total reaction volume contained 2 µL of genomic DNA, 2 µL of each primer, 4 µL of ddH₂O,

and 10 µL PCR mixture. Amplification was performed using a thermal cycler (Perkin Elmer 2400, Boston, USA). DNA was amplified for 34 cycles and each cycle consisted of pre-denaturation at 95 °C for five minutes, denaturation at 96 °C for 45 s, annealing at 60.3 °C for 45 s, extension at 72 °C for 45 s, and post-extension at 72 °C for 10 min. We used electrophoresis on a 2% agarose gel (Hoeffer, Holliston, USA) to separate PCR products.

2.3. Bradykinin B2 receptor T/C genotype determination

A 20 µL of total reaction volume contained 1 µL of genomic DNA, 0.5 µL of each primer (forward 5-GCAGAGCTCAGCTGGAGGCG-3 and reverse 5-CCTCCTCGGAGCCAGAAG-3), 8 µL of ddH₂O, and 10 µL PCR mixture with each primer concentration was 10 pmol. DNA was amplified for 35 cycles, each cycle consisted of pre-denaturation at 95 °C for five minutes, denaturation at 95 °C for one minute, annealing at 63 °C for 30 s, extension at 72 °C for one minute, and post-extension at 72 °C for 10 min. The PCR products were separated by electrophoresis on a 1% agarose gel. To determine bradykinin B2 receptor gene polymorphism, the PCR products were electrophoresed using single-strand conformation polymorphism (SSCP) method. A 5 µL of the PCR product was diluted with 5 µL formamide, denatured at 95 °C for 10 min, and subjected to SSCP analysis in a 18.5% polyacrylamide (2× TBE) gel. Electrophoresis was conducted in 2× TBE buffer at room temperature and 150 V for 210 min, and the gels were then silver-stained. Some samples representative of each genotype detected by SSCP were sequenced by fluorescent cycle sequencing to confirm the presence of T or C at nucleotide position-58 upstream of the putative transcription start site. The method was adapted from the previous studies [20,24,28,29].

2.4. Statistical analysis

The association between ACE inhibitors-related cough and [*ACE I/D* and *bradykinin B2 receptor T/C*] genes polymorphisms was analyzed using multiple logistic regression. All significance tests were two tailed and P-value of <0.05 was considered statistically significant. All analysis was performed using the Statistical Package of Social Sciences 17.0 software (SPSS Inc., Chicago, IL).

2.5. Meta-analysis

A meta-analysis was also employed to assess the association between ACE inhibitors-related cough and [*ACE I/D* and *bradykinin B2 receptor T/C*] genes polymorphisms. The method of meta-analysis was adapted from our previous studies [31–37]. The inclusion criteria for meta-analysis were: (1) retrospective studies; (2) prospective studies; (3) cross-sectional studies; (4) randomized-controlled trials (RCTs); (5) controlled before-and-after studies; (6) cross-over studies; (7) investigating the association between ACE inhibitors-related cough and [*ACE I/D* and *bradykinin B2 receptor T/C*] genes polymorphisms; and (8) providing sufficient data for calculating odd ratio (OR) and 95% confidence interval (CI). Briefly, articles concerning the association between ACE inhibitors-related cough and [*ACE I/D* and *bradykinin B2 receptor T/C*] genes polymorphisms were comprehensively searched on PubMed and Embase up to January 15th, 2018. For searching strategy, the combination of the following key words was used: (ACE inhibitors-related cough OR angiotensin-converting enzyme inhibitors-related cough) AND (*ACE I/D gene* polymorphism or *angiotensin-converting enzyme I/D gene* polymorphism) OR (*bradykinin B2 receptor T/C gene* polymorphism). For each study, information regarding: (1) first author name; (2) publication year; (3) country of origin; (4) ethnicity; and (5) sample sizes of cough and non cough group were extracted. The association between ACE inhibitors-related

cough and [ACE I/D and bradykinin B2 receptor T/C] genes polymorphisms was determined by calculating pooled OR 95% CIs. The significance of pooled ORs was estimated by Z-tests ($p < 0.05$ was considered statistically significant). A Q-test was employed to evaluate whether heterogeneity existed. A random effects model was used to calculate the OR 95% CI if heterogeneity existed ($p < 0.10$), otherwise a fixed effects model was used. To assess publication bias, an Egger's test was used ($p < 0.05$ was considered statistically significant). We used a Comprehensive Meta-analysis 2.0 software (CMA, New Jersey, USA) to analyze the data.

3. Results

During this period, a total of 1327 patients were selected for the study. Of these, 648 patients (48.8%) were excluded because of secondary hypertension, 251 patients (18.91%) were excluded because of pneumonia, 67 patients (5.05%) were excluded because of pulmonary congestion, 13 patients (0.98%) were excluded because of lung tumor, and 263 patients (19.82%) were excluded because they disagreed to join the study. Finally, 85 patients were included in the study. A flowchart of the study is shown in Fig. 1.

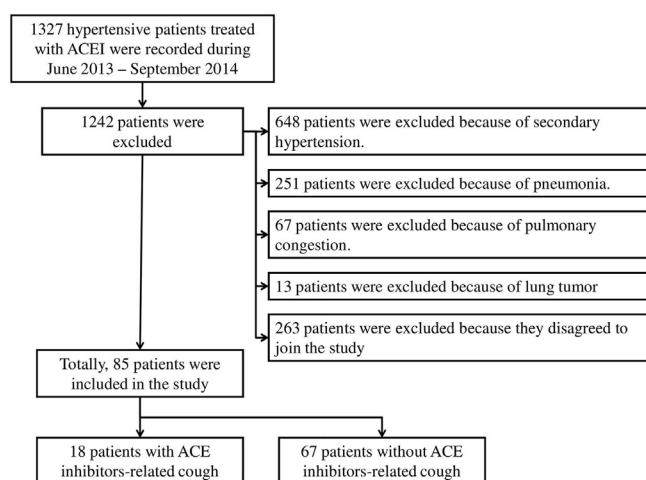


Fig. 1. Flowchart of the study. ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor.

The incidence of cough and non cough groups in our study were 21% (18 cases) and 79% (67 cases), respectively. The average age of the cough group was 62.0 (± 10.25) years old with the average systolic blood pressure was 150.0 (± 17.80 mmHg). Other parameters of the patients such as duration of hypertension, type of ACE inhibitors, and laboratory findings are presented in Table 1. Of those baseline characteristics and laboratory findings, only duration of hypertension and diastolic blood pressure were associated with ACE inhibitors-related cough.

Table 2 shows the distributions of the genotypes frequencies of the polymorphisms of ACE I/D and bradykinin B2 receptor T/C genes in cough and non cough groups. Results of PCR product electrophoresis for ACE I/D gene and results of SSCP for bradykinin B2 receptor gene are described in Fig. 2. For ACE I/D, the genotype frequencies were 38.9% for II, 44.4% for ID, 16.7% for DD in patients with ACE inhibitors-related cough and 50.7% for II, 22.4% for ID, and 26.9% for DD in subjects without cough. For bradykinin B2 receptor T/C, the genotype frequencies in patients with ACE inhibitors-related cough were 44.4% for TT, 0% for TC, 55.6% for CC, while in subjects without cough were 25.4% for TT, 9% for TC, and 65.7% for CC. In our population, we found that both ACE I/D ($p = 0.560$) and bradykinin B2 receptor T/C ($p = 0.475$) genes polymorphism were not associated with the risk of ACE inhibitors-related cough.

In the meta-analysis; for ACE I/D gene polymorphism, a total of 546 patients with cough and 1232 patients without cough of ten studies [21–29] including our study were analyzed. For bradykinin B2 receptor T/C gene polymorphism, we included five studies [20,24,28,29] including our study consisting of 267 patients with cough and 346 patients without cough for meta-analysis. A flowchart concerning studies included in meta-analysis is described in Fig. 3. Overall, the results showed no significant association between ACE I/D gene polymorphism and ACE inhibitors-related cough (Fig. 4). However, pooled data suggested that T allele of bradykinin B2 receptor T/C gene polymorphism was associated with increase the risk of ACE inhibitors-related cough (OR95%CI = 1.82 [1.06–3.13], $p = 0.0310$). A forest plot regarding the correlation between ACE inhibitors-related cough and ACE I/D gene polymorphism is displayed in Fig. 4, while bradykinin B2 receptor T/C is described in Fig. 5. A summary of the ORs and 95% CIs regarding the correlation between ACE inhibitors-related cough and these genes is shown in Table 3.

Table 1

Baseline characteristics and laboratory findings of the study.

No.	Covariates	Cough (n = 18)	Not cough (n = 67)	p	OR	95%CI
1	Age (years; mean \pm SD)	62.0 \pm 10.25	61.0 \pm 9.57	0.268	1.06	0.96–1.17
2	Male (n[%])	7 (38.9)	22 (32.8)	0.419	0.41	0.05–3.55
3	Hypertension duration (months; mean \pm SD)	97.0 \pm 79.00	70.0 \pm 54.59	0.031	1.01	1.00–1.03
4	Systolic pressure (mmHg; mean \pm SD)	150.0 \pm 17.80	150.0 \pm 16.46	0.063	0.93	0.87–1.00
5	Diastolic pressure (mmHg; mean \pm SD)	93.0 \pm 9.66	87.0 \pm 10.85	0.025	1.13	1.02–1.25
6	Type of ACEi			0.133	0.40	0.12–1.32
	Captopril (n[%])	8(44.4)	27 (40.3)			
	Lisinopril (n[%])	8(44.4)	33 (49.3)			
	Ramipril (n[%])	2(11.1)	7 (10.4)			
7	Urea (mg/dl; mean \pm SD)	29.0 \pm 8.75	29.0 \pm 11.63	0.252	1.07	0.96–1.19
8	Creatinine (mg/dl; mean \pm SD)	\pm 0.26	0.35	0.116	0.03	0.01–2.40
9	Uric acid (mg/dl; mean \pm SD)	6.0 \pm 1.61	6.0 \pm 2.31	0.654	0.88	0.52–1.51
10	Total cholesterol (mg/dl; mean \pm SD)	211.0 \pm 47.28	175.0 \pm 45.55	0.073	1.07	1.01–1.13
11	LDL (mg/dl; mean \pm SD)	126.0 \pm 38.55	111.0 \pm 33.12	0.054	0.94	0.89–1.00
12	HDL (mg/dl; mean \pm SD)	51.0 \pm 11.29	47.0 \pm 10.92	0.354	0.96	0.87–1.05
13	Triglyceride (mg/dl; mean \pm SD)	178.0 \pm 113.20	126.0 \pm 57.50	0.756	1.00	0.99–1.01
14	Fasting blood glucose (mg/dl; mean \pm SD)	104.0 \pm 24.98	96.0 \pm 31.37	0.224	1.03	0.98–1.09
15	Two-hour postprandial blood glucose (mg/dl; mean \pm SD)	122.0 \pm 32.63	122.0 \pm 43.29	0.345	0.98	0.94–1.02

Notes: ACE, angiotensin-converting enzyme; ACEi, angiotensin-converting enzyme inhibitor; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OR, odds ratio; CI, confidence interval.

Table 2
Distributions of the genotypes and alleles frequencies in our study.

Genes polymorphism		Cough (n = 18)	Non cough (n = 67)	p	OR	95%CI
ACE I/D polymorphism	II (n[%])	7(38.9)	34 (50.7)	0.560	1.33	0.51–3.52
	ID (n[%])	8 (44.4)	15 (22.4)			
	DD (n[%])	3 (16.7)	18 (26.9)			
	I (n[%])	22 (61.1)	83 (61.9)			
	D (n[%])	14 (38.9)	51 (38.1)			
Bradykinin β 2 receptor T/C polymorphism	TT (n[%])	8 (44.4)	17 (25.4)	0.475	0.74	0.32–1.71
	TC (n[%])	0 (0)	6 (9.0)			
	CC (n[%])	10 (55.6)	44 (65.7)			
	T (n[%])	16 (44.4)	40 (29.9)			
	C (n[%])	20 (55.6)	94 (70.1)			

Notes: ACE, angiotensin-converting enzyme; OR, odds ratio; CI, confidence interval.

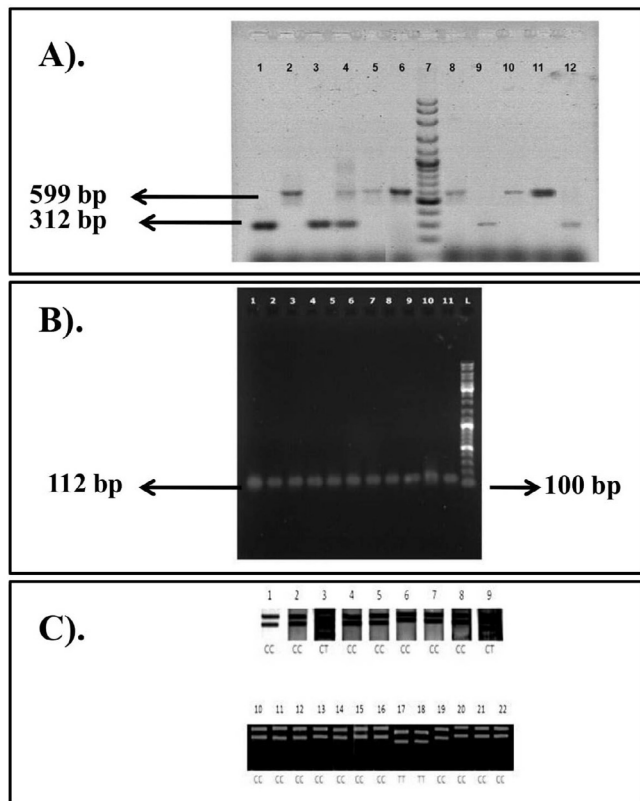


Fig. 2. A). Results of PCR product electrophoresis for *ACE I/D* gene. The 599 bp band shows the II genotypes (2, 5, 6, 8, 10, 11), 312 bp indicates DD genotypes (1,3,9,12), two bands of 312 bp and 599 bp indicate ID genotype (4). The seventh row is a 1000 bp marker. B). Results of amplification of *bradykinin B2 receptor T/C* gene. C). Results of SSCP for *bradykinin B2 receptor T/C* gene.

4. Discussion

ACE inhibitors have been widely used for the management of hypertension [2]. Dry cough is the most frequent reported ACE inhibitors side-effects, and has been the most frequent reason for patients to discontinue ACE inhibitors therapy [4,38]. The mechanism of ACE inhibitors-related cough may involve several genes such as *ACE I/D* and *bradykinin B2 receptor T/C* [4,39]. Our study reported ACE I/D and bradykinin B2 receptor T/C genes polymorphism in subjects with ACE inhibitors-related cough.

In Indonesia, *ACE I/D* gene polymorphism studies had been reported by Rasyid et al. [40] and Bawazier et al. [41]. However, they did not correlate the gene with ACE inhibitors-related cough. This is the first study in Indonesia regarding the correlation

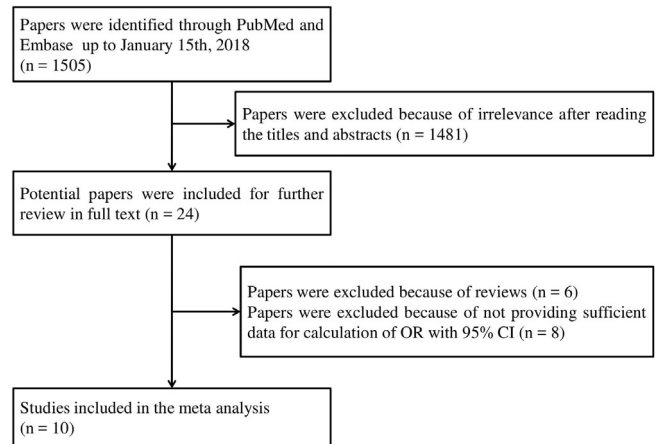


Fig. 3. Flowchart of studies selection in meta-analysis, with specification of reasons.

between *ACE I/D* and *bradykinin B2 receptor T/C* genes polymorphism with the risk of ACE inhibitor-related cough. The first study regarding this association was conducted by Furuya et al. [21] in Japan population. Basically, the concept of this study had similarities with several studies regarding the correlation between the genes and the risk of ACE inhibitors-related cough. In our population, the incidence of ACE inhibitors-related cough was 21% of all hypertensive patients treated with ACE inhibitors. This incidence was in range as reported by several studies [4,6–10]. Moreover, of the exclusion process, interestingly, our findings showed that the incidence of secondary hypertension in our Hospital (48.8%) was higher than that reported by several studies, ranging from 5 to 30% of all hypertensive patients [42–46]. This may be due to that our Hospital is the referral center. Therefore, most patients in our hospital have complicated clinical conditions, including secondary hypertension-associated conditions. Perhaps, if this study was conducted at all Hospitals in our area, the incidence of secondary hypertension would not be as high as we reported.

The correlation between ACE inhibitors-related cough and *ACE I/D* gene polymorphism has been widely reported in some countries. In our population, no correlation was observed between *ACE I/D* gene polymorphism and ACE inhibitors-related cough. Theoretically, ACE level is associated with ACE inhibitors-related cough and this level is linked to *ACE I/D* gene polymorphism [19,47]. However, our study failed to support this theory. Several factors need to be evaluated to elucidate this correlation. Totally, nine previous studies [21–29] had been conducted concerning the association between *ACE I/D* gene polymorphism and the risk of ACE inhibitors-related cough. However, of these studies, some limitations were noted, such as no specific method to determine

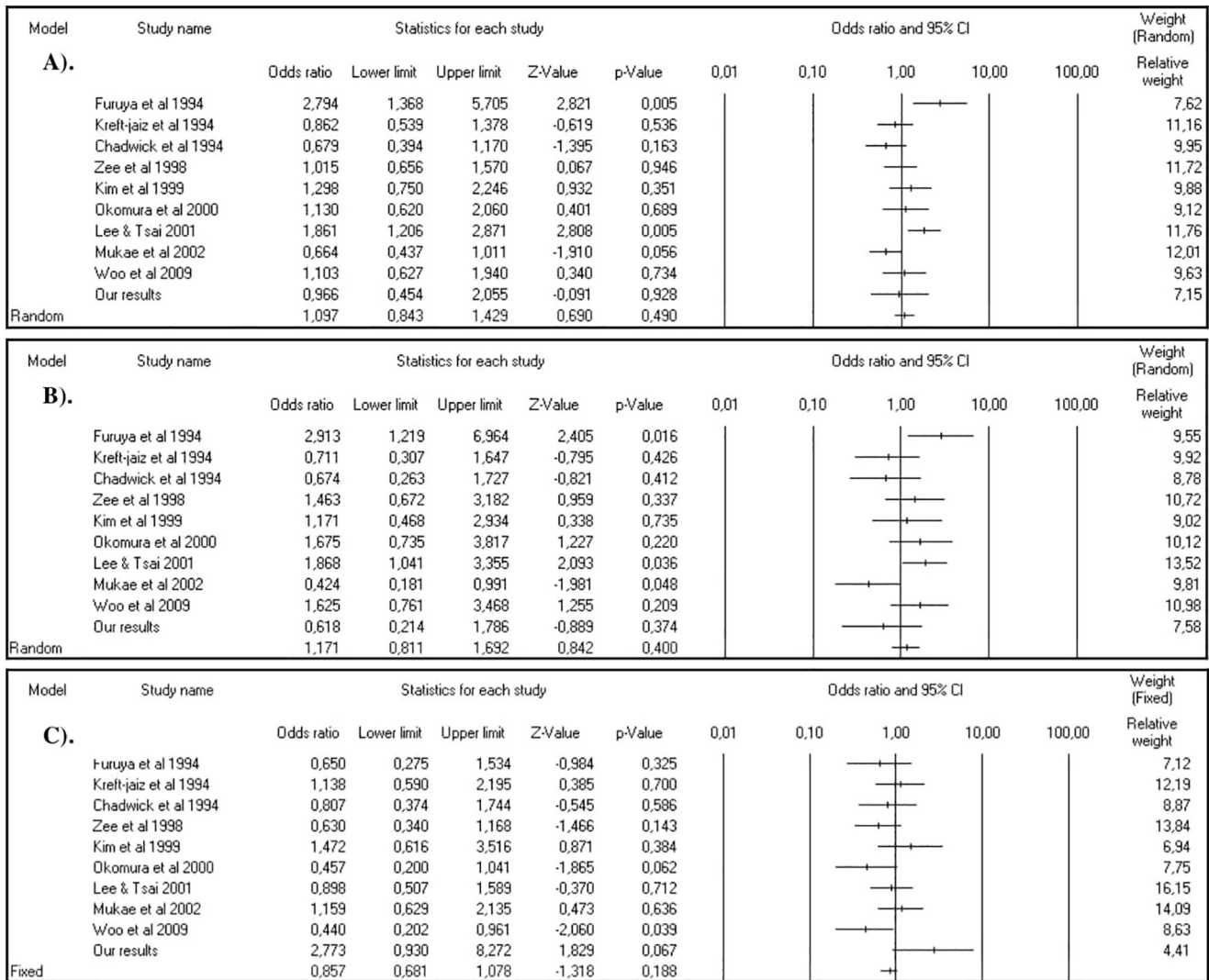


Fig. 4. Forestplot the association between ACE I/D gene polymorphism and ACE inhibitors-related cough. A). I vs D; B). II vs ID + DD; C). ID vs II + DD.

cough group and several factors that might have the impact in ACE inhibitors-related cough were not included. In our study, these limitations were eliminated. Furthermore, our meta-analysis found that ACE I/D gene polymorphism was not associated with the risk of ACE inhibitors-related cough. See Fig. 4. Our meta-analysis extended the previous studies [48,49] revealed that, overall, ACE I/D gene polymorphism was not correlated with the risk of ACE inhibitors-related cough, although association was found in subjects with age over 60 years old [50] and Asian population [48]. However, several studies included in their meta-analysis were not found. In our meta-analysis, all studies were available, and therefore our meta-analysis was more reliable than theirs.

Our results showed that bradykinin B2 receptor T/C gene polymorphism was not associated with the risk of ACE inhibitors-related cough. Our results were consistent with Woo et al. [29] and Zee et al. [24], but contrast with Mukae et al. [20] and Mukae et al. [28]. Because of these differences, we performed a meta-analysis to determine the actual association. Of five studies including our study, the pooled data suggested that T allele of bradykinin B2 receptor T/C gene polymorphism was correlated with 1.82-fold increased risk of ACE inhibitors-related cough. The mechanism of ACE inhibitors-related cough is still unclear. However, some literatures reveal that the mechanism involves prostaglandins, bradykinins, and tachykinins that accumulate in the upper respiratory

tract and lung. Furthermore, they may activate kininase II activity and stimulate unmyelinated afferent C sensory nerve which is responsible for producing the dry cough. Normally, these substances are degraded by ACE and cause suppression of kininase II activity. Therefore, ACE inhibition is thought to cause decreased metabolism of these substances and play a crucial role for the development of ACE inhibitors-related cough [4,9,27,50]. This mechanism might be a benchmark for our meta-analysis found that bradykinin B2 receptor T/C gene polymorphism had a significant association with the risk of ACE inhibitors-related cough.

Although our meta-analysis showed that bradykinin B2 receptor T/C gene polymorphism was associated with the risk of ACE inhibitors-related cough, however, because of small sample size, it is not possible to use this covariate as the predictor for ACE inhibitors-related cough. Nevertheless, since the genes were theoretically assumed to correlate with ACE inhibitor-related cough and the reports remained inconclusive, further studies are required to find the better outcome involving a larger sample size with multiple ethnicities. Moreover, this study has the potency to contribute in the development of better understanding about drugs pharmacogenetic, and it is expected that, in the near future, this study may help to improve the drugs design.

There were several limitations in the study. First, in this study was not included data regarding the factors associated with ACE

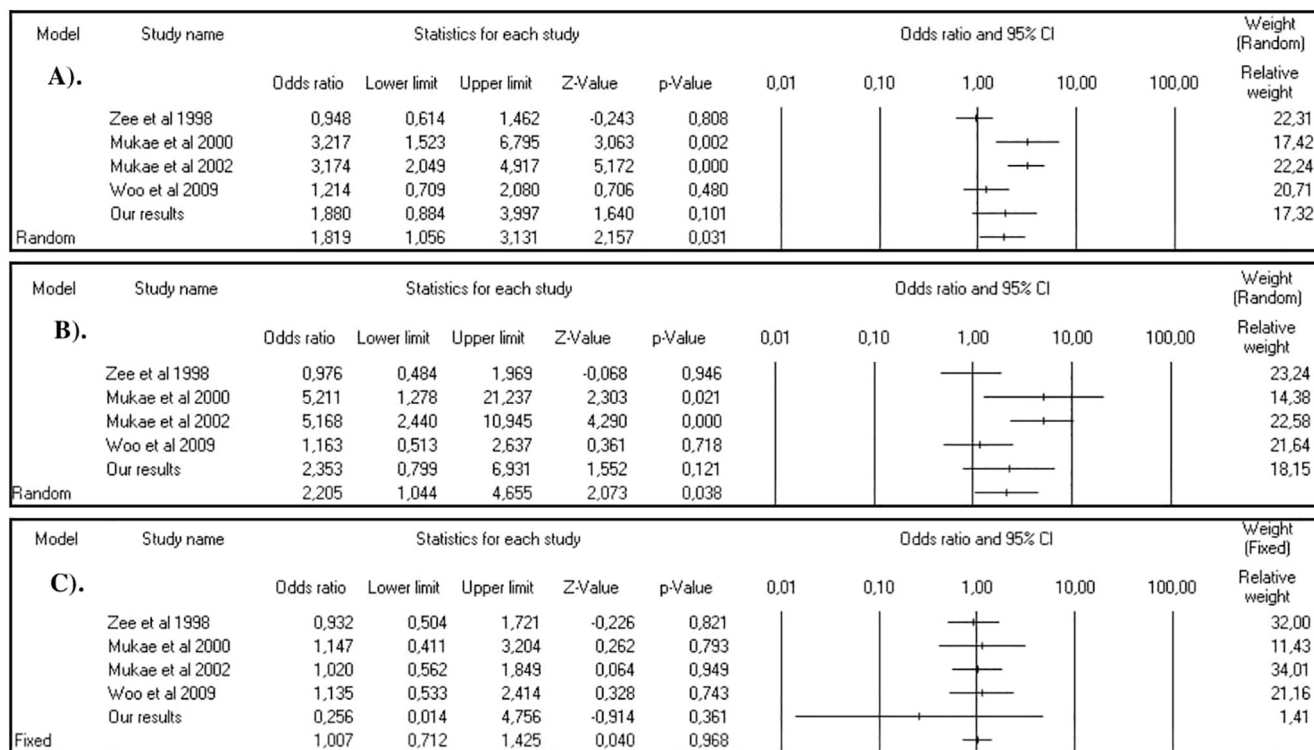


Fig. 5. Forestplot the association between *bradykinin B2 receptor T/C gene* polymorphism and ACE inhibitors-related cough. A). T vs C; B). TT vs TC + CC; C). TC vs TT + CC.

Table 3

Summary of meta-analysis concerning the association between *ACE I/D* and *bradykinin B2 receptor T/C genes* polymorphism with ACE inhibitor-related cough.

Gene polymorphisms	Alleles/genotypes	Model	OR	95%CI	pE	pH	p
<i>ACE I/D</i>	I vs D	Random	1.10	0.84–1.43	0.3240	0.0080	0.4900
	II vs ID + DD	Random	1.17	0.81–1.69	0.4140	0.0370	0.4000
	ID vs II + DD	Random	0.86	0.68–1.08	0.2780	0.1220	0.1880
<i>Bradykinin B2 receptor T/C</i>	T vs C	Random	1.82	1.06–3.13	0.5440	0.0010	0.0310
	TT vs TC + CC	Random	2.21	1.04–4.66	0.7050	0.0080	0.0380
	TC vs TT + CC	Fixed	1.01	0.71–1.43	<0.0001	0.9000	0.9680

Notes: ACE, angiotensin-converting enzyme; OR, odds ratio; CI, confidence interval; pE, p Egger; pH, p Heterogeneity.

inhibitors-related cough, i.e.: duration of ACE inhibitors therapy and history of drug use. Second, false negative results could be occurred in this study due to the small sample size. Third, our results did not fully reflect the Indonesian population because samples were recruited only from Saiful Anwar General Hospital. Fourth, all of the studies included in our meta-analysis were cross-sectional. Further meta-analysis including only RCT studies are needed to get a better level of evidence.

5. Conclusion

Our population data revealed that both *ACE I/D* and *bradykinin B2 receptor T/C genes* polymorphism were not associated with the risk of ACE inhibitors-related cough. However, our meta-analysis found that T allele of *bradykinin B2 receptor T/C gene* was associated with increased the risk of ACE inhibitors-related cough. Our results may develop better understanding concerning the correlation between these genes and the risk of ACE inhibitor-related cough.

Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

Designed the experiments = MSR, JKF, BHK, LY, TH. Performed the experiments = BHK, LY. Analyzed the data = MSR, JKF, EPS, PNBS. Contributed reagents/material/analysis tools = MSR, JKF, EPS, PNBS. Wrote the manuscript = MSR, JKF, EPS, PNBS, TH. Reference collection and data management = MSR, JKF, EPS, PNBS, TH. Statistical analyses and paper writing = MSR, JKF, EPS, PNBS, TH. Revised manuscript = MSR, JKF, TH, NW.

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