

Review Article**Angiotensin-Converting Enzyme Inhibitors; Their Efficacy, Adverse effects, and the Genetic influence on Cough They May Cause**Arooj Fatima Sheikh*¹, Fatima Siraj Memon¹, Najam Ul Sahar²¹Shifa College of Pharmaceutical Sciences, Shifa Tamer-e-Millat University Islamabad, Pakistan²Shifa Plus Pharmacy, Bahria Town Rawalpindi, Pakistan*Correspondence: aroorfatimasheikh@gmail.com© The Author(s) 2022. This article is licensed under a Creative Commons Attribution 4.0 International License. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.**Abstract**

Hypertension is a significant health condition that increases the risk of several other diseases, including renal failure, myocardial infarction, stroke, and death. Angiotensin-converting enzyme inhibitors (ACE-Is) are part of most protocols used to manage hypertension and various other conditions, including congestive heart failure and myocardial infarction. Even though these therapies are well tolerated, one in every five individuals discontinues them due to adverse medication reactions, the most prevalent of which is a persistent dry cough. Heritability accounts for 30% to 50% of inter-individual variation in blood pressure. However, the genetic variation connected to ACE-I-induced cough remains contentious and requires additional investigation. In addition, genetic variation may affect the incidence of ACE-I-related cough. This article examines ACE-Is' efficacy, their adverse effects, and pharmacogenetic studies on ACE-I-induced cough.

Keywords: Hypertension, angiotensin-converting enzyme inhibitors, genetic polymorphisms, cough**Introduction**

Hypertension is a serious health condition that may lead to renal failure, stroke, coronary artery disease, myocardial infarction, heart failure, and death (James et al. 2014). As per World Health Organization (WHO) and Joint National Committee (JNC VI), hypertension (defined as a systolic blood pressure of 140 mm Hg and diastolic blood pressure of 90 mm Hg) affects a majority of the adult population globally (Chalmers et al. 1999, Lenfant et al. 2003). Unfortunately, high blood pressure has increased in developed and developing countries over the past two decades (Kingue et al. 2015). Globally, billions of people are estimated to live with hypertension, and the number of hypertensive cases is predicted to increase significantly in the future (Lim et al. 2012, Sarafidis et al. 2008). Furthermore, about 9 million deaths are associated with hypertension annually (Lim et al. 2012, Kingue et al. 2015).

Hypertension affects a significant fraction of the Pakistani adult population (Jafar et al. 2003). Results of

another survey show that hypertension is rapidly increasing in Pakistan and every 3rd hypertensive patient aged 40 years and above was comorbid with a range of diseases. Other findings of this survey revealed that only half of the hypertensive population were diagnosed, and of those, half were taking medical treatment. This suggests that controlled cases of high blood pressure were only 12.5 % (Saleem, Hassali, and Shafie 2010).

Given that hypertension is considered the major modifiable risk issue for cardiovascular disease (CVD); it may be addressed by taking proper lifestyle assessments and using antihypertensive drugs to manage blood pressure (Jiang et al. 2014). Different classes of antihypertensive agents are used to lower the chance of CV morbidity and mortality. Current guidelines and recent data show that angiotensin-converting enzyme inhibitors (ACE-Is) are the foremost usually advised drug to treat heart problems and other

similar conditions (Chobanian et al. 2003). They are used as first-line therapy in adults with primary hypertension, left ventricular dysfunction, chronic kidney disease, and heart failure (Yusuf et al. 2000, Swedberg, Kjeksus, and Group 1988, Brenner et al. 2001, Epstein 2015, Faisal et al. 2021). Unfortunately, despite their efficacy, many patients discontinue ACE-Is due to some adverse effects (Sica 2005).

Common adverse reactions of ACE-Is include angioedema, cough, hypotension, headache, and kidney impairment. However, dry cough, a frequent side effect of ACE-Is, may appear within a few hours after the initial dose of a drug. Cough has been reported to emerge in 5-20% of ACE-I-treated individuals, and it is more common in women, according to recent studies (Israili and Hall 1992, Os et al. 1994). There is a significant variation in the incidence of ACE-I-induced cough in distinct populations globally. For example, the incidence of chronic dry cough is frequently reported to be greater in Chinese patients treated with ACE-Is compared to other populations (Chan et al. 1993).

Pharmacogenetics is an essential part of precision medicine. It involves investigating the genetic variants that determine the response of the drug (Yip, Hawcutt, and Pirmohamed 2015). Various common single-nucleotide polymorphisms (SNPs) related to hypertension management have been investigated and reported by several pharmacogenetic and pharmacogenomic studies. Genetic variants have also been linked to the event of ACE-I-induced cough in many studies, indicating these variations may also play a predictive role. However, no individual genes have been identified as yet which could predict ACE-I-induced cough (Fan et al. 2007, Brugts et al. 2010).

Epidemiology of Hypertension

The incidence of hypertension is overgrowing, particularly in developing nations, despite the effective antihypertensive medications available (Kingue et al. 2015). More than 1.13 billion individuals are experiencing hypertension throughout the world and this number may rise to 1.56 billion by 2025 (Lim et al. 2012, Sarafidis et al. 2008). Furthermore, complications of hypertension account for 9 million deaths internationally (Kingue et al. 2015). Indeed, 45% of deaths from ischemic heart problems and 51% of deaths from cerebrovascular diseases are also attributable to hypertension (Lim et al. 2012).

As reported by the National Health Survey of Pakistan, high blood pressure influences 33% of the Pakistani population over the age of 45 years and, overall, 18% of the adult population of all ages. This survey also points out that only 50% of the hypertensive population was diagnosed, and only half of those who were diagnosed were managed with antihypertensive medications. This indicates that hardly 12.5% of hypertensive cases were managed annually in Pakistan (Saleem, Hassali, and Shafie 2010). Among the principal factors attributed to a greater risk of hypertension include an unhealthy diet, high sodium intake, obesity, physical inactivity, smoking, and alcohol consumption (Kingue et al. 2015).

ACE Inhibitors and Their Indications

As per Food and Drug Administration (FDA), ACE-Is are one of the most effective medications for managing hypertension (Chobanian et al. 2003). Globally, ACE-Is are the most commonly advised medications to treat various diseases (Messerli et al. 2018). ACE-Is produce relaxation of veins and arteries and suppress the formation of angiotensin II and kinin hydrolysis. As a result, they beneficially reduced the mean systolic and diastolic pressures in CV sufferers. In addition to their role in the reduction of hypertension, they have been demonstrated to treat sufferers who have a myocardial infarction, stroke, renal failure, heart failure, or a history of diabetes mellitus (Yusuf et al. 2000, Swedberg, Kjeksus, and Group 1988, Brenner et al. 2001, Epstein 2015, Faisal et al. 2021, Pfeffer et al. 2003).

ACE-Is in CV Risk Reduction

Renin-Angiotensin-Aldosterone System (RAAS), is a complex system accountable for controlling blood pressure and plays an essential part in the pathophysiology of CVD. Angiotensin II, the effector molecule of the renin-angiotensin-aldosterone system, is accountable for increasing blood pressure. The actions of angiotensin II are mediated when it binds to angiotensin II receptor type 1 or AT-1 receptors and causes it to activate. The activation of the AT-1 receptor results in vasoconstriction, the release of aldosterone and vasopressin, and sodium and water retention. Thus, an increased level of angiotensin II may cause hypertension (Benigni, Cassis, and Remuzzi 2010) (**Figure 1**).

ACE-Is, reduce the mortality of CVD by up to 18% during 3 years of follow-up (Khalil et al. 2001). Several

clinical guidelines including the American College of Cardiology and the American Heart Association, also suggested ACE-Is as the first-line therapy to cure hypertension, myocardial infarction, heart failure, and coronary artery disease due to their beneficial therapeutic effects (Fihn et al. 2014).

Over 30 years ago, ACE-Is were first used in clinical practice to treat high blood pressure and have been

indicated in the management of CVD for decades. Results of several clinical trials show consistent CV protection when treated with ACE-Is (Pfeffer et al. 1992). ACE-Is with cardio-protective activity produce their effects by suppressing the transformation of angiotensin I to angiotensin II. However, this also results in an unwanted consequence of bradykinin degeneration blockade and a decreased level of angiotensin II (Murphey, Vaughan, and Brown 2003).

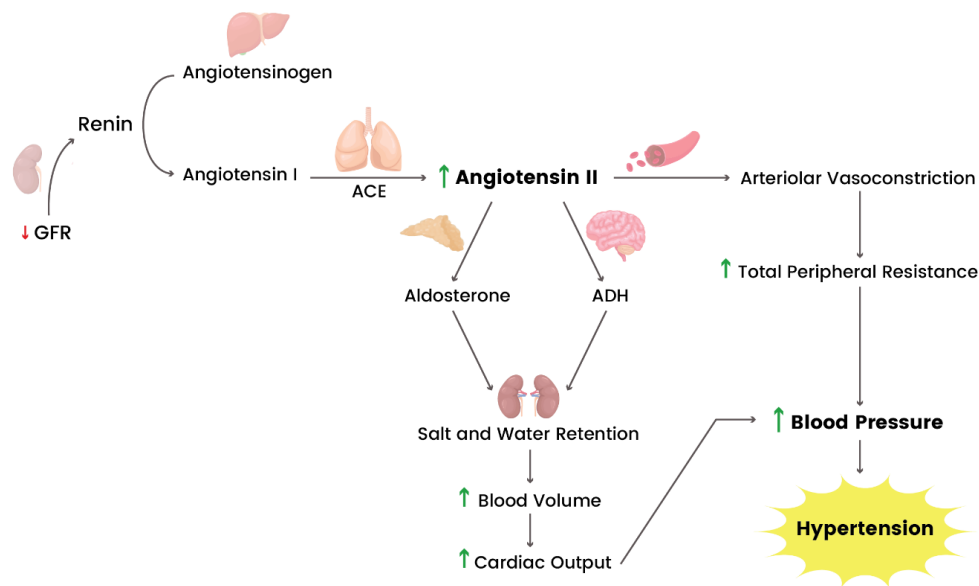


Figure 1. Proposed pathophysiology of hypertension.

GFR, glomerular filtration rate; JGA, juxtaglomerular apparatus; ADH, antidiuretic hormone.

Adverse Effects of ACE-Is

ACE-Is contribute beneficial therapeutic and detrimental effects, including hypotension, particularly in patients with malignant hypertension, renin-dependent vasoconstriction, sufferers with congestive heart failure and hyponatremia, or those individuals who are on diuretics (Frohlich, Cooper, and Lewis 1984). Another adverse event of ACE-Is is hyperkalemia, attributable to a decrease in aldosterone secretion following ACE-Is administration. Hyperkalemia could be extremely harmful in patients who have renal insufficiency, are diabetic, and in those

using nonsteroidal anti-inflammatory drugs and salt substitutes (Ben Salem et al. 2014).

Renal impairment is another possible side effect of ACE-Is, induced by reduced renal perfusion due to inhibition of angiotensin II (Hollenberg 1985). Other common side effects include headache, dizziness, rash, and fever. Dry cough and angioedema are two other potential adverse reactions of ACE-Is. Sometimes the cough is accompanied by wheezing. Due to persistent dry cough, patients may discontinue ACE-Is treatment (Sica 2005).

Mechanism of ACE-I-Induced Cough

Multiple mechanisms that could be at play in originating dry cough due to ACE-Is have been proposed. Speculation on bradykinin levels is one of the frequently presented hypotheses. Kininogen (precursor protein for kinins) via kallikrein releases bradykinin, and it is rapidly degraded by ACE (Packard, Wurdeman, and Arouni 2002). This degeneration is silenced by ACE-Is, resulting in an accumulation of bradykinin (Packard, Wurdeman, and Arouni 2002, Dykewicz 2004). This accumulation of bradykinin and substance P in respiratory tracts because of ACE-Is is the possible mechanism that has been postulated in the initiation of cough (Israili and Hall 1992, Fox et al. 1996). Some investigations propose that bradykinin receptors are triggered by ACE-Is, and

the bradykinin receptors with specific gene polymorphisms elicit persistent cough (Hallberg et al. 2017).

Furthermore, phospholipase A2 is stimulated by bradykinin, which prompts the production of arachidonic acid derivatives i.e., histamine, leukotrienes, and prostaglandins mainly (I-2 and E-2), which may also give rise to cough and bronchoconstriction (Packard, Wurdeman, and Arouni 2002, Dykewicz 2004, Trifilieff, Da Silva, and Gies 1993). Other mechanisms implicate the substance P pathway, produced from afferent sensory nerves, especially the C- fibers induced by capsaicin (an irritant that causes cough). Substance P (major neurotransmitter of C-fibers) plays a key part in the etiology of ACE-I-related cough. Substance P is degenerated by ACE, and their actions are amplified by ACE-Is (Figure 2), ultimately becoming a cough stimulus in susceptible sufferers (Sekizawa, Ebihara, and Sasaki 1995, Ujiie et al. 1993).

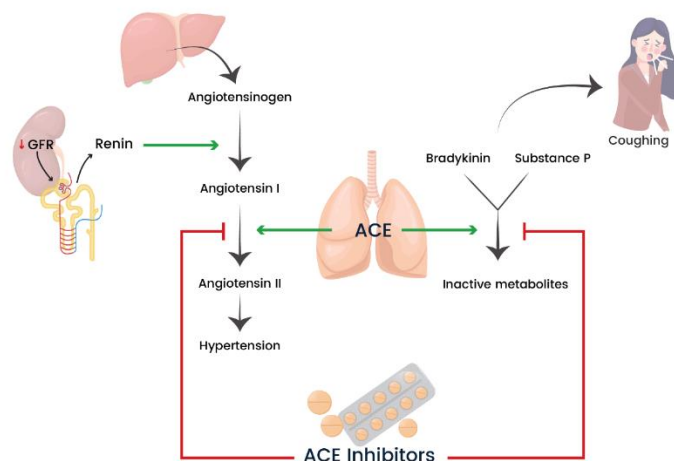


Figure 2. Sites of action and suggested mechanism of angiotensin-converting enzyme (ACE) inhibitors-related cough.

Prevalence and Severity of Cough

Dry cough affects 5 to 20 percent of populations treated with ACE-Is (Bangalore, Kumar, and Messerli 2010, Brugts et al. 2014). In a cohort study, 19% of individuals taking ACE-Is have been shown to terminate their therapy because of side effects, mostly persisting cough (Morimoto et al. 2004). Cough was shown to be unrelated to age, gender, medicine dose, or smoking status in a few studies (Woo and Nicholls 1995).

However, the cough was shown to be more common in females than in men in other studies and associated with age, East Asian ethnicity, genetic variations, and smoking status (Sadanaga et al. 2009). Cough is observed to be more common among Chinese patients using ACE-Is than in the general population (Chan et al. 1993).

Furthermore, the frequency and severity of cough differ amongst ACE-Is, and different ACE-Is have real-world

clinical data from various clinical trials to back up their claims. The reported incidence of cough was 28% with enalapril in the Japanese cohort (Sadanaga et al. 2009). In the Pakistani cohort, the incidence of cough with enalapril was 20%, 16.6% with captopril, 10% with lisinopril and ramipril, and, 15% with perindopril (Saboor et al. 2012). In another clinical study conducted in India, the percentage of dry cough with perindopril

was 3.6% (Bansal et al. 2014). The data from the Greek population demonstrated the cough prevalence to be very low (ranges 0.001%) even with a maximum dose of perindopril (Tsioufis et al. 2019). In the Chinese community, the rate of cough was 46% of the patients' taking captopril and 41% of patients taking enalapril (Woo and Nicholls 1995) (Table 1).

Table 1. Summary of the prevalence of cough with ACE-Is in different clinical studies.

Study type	ACE-I & sample size	Cough (%)	Country	Reference
Randomized	Captopril, N=191	46	China	(Woo and Nicholls 1995)
Randomized	Enalapril, N=191	41	China	(Woo and Nicholls 1995)
Consecutive screening	Enalapril, N=199	28	Japan	(Sadanaga et al. 2009)
Prospective open-labeled	Enalapril, N=100	20	Pakistan	(Saboor et al. 2012)
Prospective open-labeled	Captopril, N=30	16.6	Pakistan	(Saboor et al. 2012)
Prospective open-labeled	Lisinopril, N=10	10	Pakistan	(Saboor et al. 2012)
Prospective open-labeled	Ramipril, N=20	10	Pakistan	(Saboor et al. 2012)
Prospective open-labeled	Perindopril, N=20	15	Pakistan	(Saboor et al. 2012)
Multicenter prospective observational	Perindopril, N=426	3.6	India	(Bansal et al. 2014)
Multicenter, non-interventional prospective	Perindopril, N=2285	0.001	Greek cohort	(Tsioufis et al. 2019)

Genetic Polymorphism Associated with ACE-I-Initiated Cough

Effect of ACE I/D polymorphism

The ACE gene is found on chromosome 17 (17q23.3 locus), and encodes ACE protein. It converts angiotensin I to active peptide angiotensin II, which provokes the proliferation of hematopoietic stem cells (Hubert et al. 1991). An insertion/deletion (I/D) polymorphism in this gene (rs4343) has been connected with serum ACE activity. The majority of the

investigations showed that carriers of allele I had a minor activity of ACE than carriers of allele D. Therefore, due to a larger accumulation of bradykinin, carriers of allele I would have a higher emergence of ACE I-related cough (Mukae et al. 2002).

The influence of ACE I/D variants on cough was significant in East Asians, however, not in many other individuals. In the South African population, no powerful connection was found (Moholisa et al. 2013). The ethnic distinction can be attributed to distinct

genotype distribution among ethnicities. As mentioned earlier, several investigations revealed that allele I was more common in East Asian communities (Lee and Tsai 2001, Kreft-Jais et al. 1994). In contrast, allele D was predominant in Caucasians (Kreft-Jais et al. 1994) and Africans (Moholisa et al. 2013). This could describe the feasibility of variants of *ACE I/D* as a pharmacogenetic predictor only in the East Asian cohort.

Effect of *BDKRB2-581T/C* polymorphism

We stated earlier in the review that triggering vagal afferent nerves within the airway produced via agglomeration of bradykinin is likely a possible process for ACE-I-initiated cough. Bradykinin's effects on irritating the cough reflex are mainly mediated by stimulating the B2 receptors on bronchopulmonary C fiber (Hewitt et al. 2016). Bradykinin receptor B2, encoded by the *BDKRB2* gene in humans, is a G-protein coupled receptor (Leeb-Lundberg et al. 2005, Fernandes et al. 2001). The polymorphic elements of human bradykinin B2 receptors have been recognized as being located in the promoter region (Mukae et al. 2000) and three exons (Braun et al. 1995).

Many studies explored the connection between *BDKRB2-58T/C* (rs1799722) variants and cough among East Asian populations. However, only Mukae's investigation (Mukae et al. 2000, Mukae et al. 2002) found significant frequencies of ACE-I-related cough in sufferers with T allele and TT/TC genotype ($p < 0.05$). Although, their investigations exhibit no notable distinction in genotype frequencies of *BDKRB2-58T/C* or allele distribution between coughing and non-coughing individuals. Therefore, it was hard to make a judgment on the influence of variants of *BDKRB2-58T/C* in East Asians because of an absence of extra evidence.

Effect of *SLCO1B1* polymorphism

The majority of ACE-Is are prodrugs that are metabolized within the liver to produce the active substance. The expression of human organic anion-transporting polypeptide 1B1, OATP1B1 (encoded by gene *SLCO1B1*) in the basolateral membrane of hepatocytes was shown to impact this metabolic transformation (Liu et al. 2006). Therefore, the *SLCO1B1* polymorphism might play a key role in ACE-Is pharmacokinetic variability and adverse effects induced by the accumulation of their active products.

Several studies found a connection between *SLCO1B1* variants and ACE-I-initiated cough. The differential distribution of *SLCO1B1* 521T>C variants (Val174Ala, rs4149056), including East Asians (Luo et al. 2015) and Caucasians (Pasanen et al. 2006), could describe why ACE-I-initiated cough is higher in East Asians. Luo's investigations showed the association between *SLCO1B1* polymorphism and a higher incidence of ACE I-initiated cough. In their analysis, *SLCO1B1* variants indicate a strong correlation with a higher risk of enalapril-initiated cough (Luo et al. 2015). His other investigations (Luo et al. 2014, Luo et al. 2015) revealed that *SLCO1B1* 521T>C (Val174Ala, rs4149056) C allele carriers had a greater chance of having enalapril-related cough than T-allele carriers. However, there was no such connection found between cough and *SLCO1B1* variants 388A>G (Asn130Asp, rs2306283) ($p > 0.05$).

Effect of *BDKRB2 +9/-9* polymorphism

The *BDKRB2 +9/-9* (rs5810761) variants have been linked to reflex muscle vasodilation, pulmonary vascular tone, and activity of ACE (Olson et al. 2009). It was hypothesized that the *BDKRB2 +9/-9* polymorphism might be linked to coughing reflex throughout ACE-Is therapy. One study conducted in South Africa, found a significant link. It showed that *BDKRB2 +9/-9* genetic variation was linked with ACE-I-induced cough in Africans (Moholisa et al. 2013).

Effect of *ABO* polymorphism

ABO gene encodes glycosyltransferase, found on chromosome 9, which transports the monosaccharides to the cell-surface H antigens. As the ACE molecules are carriers of ABO antigens, oligosaccharide moieties on ABO antigens, bound covalently to the ACE molecules might influence the aqueous solubility of ACE and its susceptibility to proteases, resulting in the release of varying amounts of the active enzyme (Cídl et al. 1996). A greater chance of ACE-I-initiated cough in individuals with minor allele T of *ABO* (rs495828) was found, which might be owing to its impact on lowering plasma ACE activity (Cídl et al. 1996)-(Chung et al. 2010). Both Mas's study (Mas et al. 2011) in Caucasians and Luo's study (Luo et al. 2014) in East Asians yielded similar outcomes. This demonstrated that *ABO* (rs495828) variants might be used as a good predictor of ACE-I-initiated cough (Table 2).

Table 2. Association of pharmacogenetic markers with ACE-I-related cough.

SNP	Gene	Drug	Sample size	Country	Findings	Reference
rs4149056	<i>SLCO1B1</i> 521T>C	Enalapril	450	China	C allele is associated with cough	(Luo et al. 2015)
rs2306283	<i>SLCO1B1</i> 388A>G	Enalapril	450	China	Weak association with cough	(Luo et al. 2015)
rs4343	<i>ACE I/D</i>	Enalapril, lisinopril or imidapril	190	Japan	Associated with cough	(Mukae et al. 2002)
rs1799722	<i>BDKRB2</i> - 581T/C	ACE-Is	30	Japan	Associated with cough	(Mukae et al. 2000)
rs5810761	<i>BDKRB2</i> +9/-9	Enalapril	36	South Africa	Associated with cough	(Moholisa et al. 2013)
rs495828	<i>ABO</i>	ACE-Is	281	Spain	Associated with variation in ACE-I drug concentrations	(Mas et al. 2011)
rs495828	<i>ABO</i>	Enalapril	450	China	Associated with cough	(Luo et al. 2014)

Management of ACE-I-Induced Cough

Even though ACE-I-related cough is usually mild to moderate, it may sometimes become severe, necessitating therapy. In one study by Reisin and Schneeweiss, the cough dissipated after a few months of therapy for a significant fraction of patients (27.4%), despite continuous ACE-Is medication and with no management strategy for its suppression (Reisin and Schneeweiss 1992b). After the cough disappeared, all patients were followed for another 13 months to ensure no recurrence. In a separate investigation by the same research group, more than half of the patients experienced complete relief (Reisin and Schneeweiss 1992a). In a different case-control study, the likelihood of developing cough (ratio) was found to be 1.6 for long-term users (>6 months), 2.0 for patients on ACE-Is medication for 2–6 months, and 4.8 for those just starting treatment (less than two months). Another proposed strategy, although slightly controversial, is transiently tapering ACE-Is therapy when a cough is reported and re-starting with therapy when a visible reduction in signs and symptoms of cough is observed. In a relatively recent investigation, this approach was revealed to lessen the onset of cough (Sato and Fukuda 2015).

Since the severity of cough also varies based on the use of ACE-Is by individuals, the selection of ACE-Is should be made carefully. It has been shown that phosphoryl group-containing ACE-I (fosinopril) was connected with a greater risk of cough compared to carboxyl group-containing ACE-Is (ramipril, lisinopril, and enalapril) (Sangole and Dadkar 2010). Similarly, perindopril has been linked with a comparatively lesser prevalence of cough and has vast evidence supporting its CV benefits and tolerability.

Concluding Remarks

ACE-Is are essential in the management of hypertension, but the cough they induce is exhausting and may decrease compliance. Bradykinin and substance P, both of which are degenerated by ACE, may have a part in the development of cough. As a result of the blocking of an ACE, bradykinin and substance P accumulate in the body. Prostaglandins are also stimulated by bradykinin which might lead to cough. Several studies have shown the correlation of genetic variations in *ACE*, *SLCO1B1*, *ABO*, and *BDKRB2* genes with cough in patients using ACE-Is. These studies highlight the significance of genetic determinants of ACE-I-induced cough. Significantly,

the variant of *ACE I/D* was found to be a predictor of ACE-I-related cough, notably among East Asians. Genetic polymorphisms in *ABO*, *BDKRB 2+9/-9*, and *SLCO1B1* are also good candidates as predictors of ACE-I-related cough.

On the other hand, *BDKRB2-58T/C* exhibited no clear link with ACE-Is-induced cough. With more work being done, it is hoped that new pharmacogenetic indicators with ample evidence will be discovered. Our review also highlights the consequence of bradykinin in the pathophysiology of this adverse event. Additional analyses are required to confirm this connection. If confirmed, it could be included in clinical practice as a plausible risk issue for ACE-I-related cough.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Ethics approval

Not applicable.

Consent forms

Not applicable.

Authors contribution

AF conceptualized the review. AF, FS, and NS did the literature search, collected relevant studies, and wrote the final manuscript. All the authors have read and approved the final version of the manuscript.

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