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Review Article

Pathophysiology of cough with angiotensin-converting enzyme inhibitors: How to explain within-class differences?

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ABSTRACT

Angiotensin converting enzyme inhibitors (ACEi) have consistently demonstrated improved survival and reduced risk of major cardiovascular events, across the spectrum of cardiovascular disease, including hypertension, coronary artery disease, myocardial infarction, and heart failure. The cardioprotective effects of ACEi result from inhibiting the conversion of angiotensin I to angiotensin II, and inhibition of bradykinin degradation. They are generally well tolerated but may cause the onset of a dry cough in some patients. This review presents current evidence on the incidence and mechanisms of cough associated with ACEi use, and then considers how to manage ACEi-related cough in clinical practice. The incidence of ACEi-induced cough in the published literature varies widely due to heterogeneity in the source data and lack of adequate controls. Incidence also varies among individual ACEi with agents such as perindopril, which has a high tissue ACE affinity, associated with a lower rate of cough. Evidence from real-world studies shows that the incidence of ACEi-associated cough is lower than rates reported in clinical trials. Patients who experience any dry cough are often switched to angiotensin- receptor blockers or other classes of antihypertensive drugs, regardless of cough severity. To avoid inappropriate discontinuation of ACEi in clinical practice, an alternative approach in patients with persistent cough is to perform a challenge/re-challenge to determine if re-introduction of ACEi is associated with recurrence of symptoms. Incidence of cough should not be considered a class effect for ACEi, and the patient may benefit by a switch from one ACEi to another. Every effort should be made to enable patients to continue ACEi therapy to reduce adverse cardiovascular outcomes and improve survival.

1. Introduction

Angiotensin-converting enzyme inhibitors (ACEi) are largely used for the prevention and treatment of cardiovascular and renal diseases [1]. The rationale supporting the use of ACEi is based on evidence of extensive activation of the renin-angiotensin-aldosterone system (RAAS) in the pathophysiology of these diseases. The mechanism of action of ACEi (Fig. 1) is based on blockade of ACE, the enzyme responsible for the conversion of angiotensin-I into angiotensin-II, as well as for the degradation of several hemodynamically active peptides including bradykinin (BK). The latter contributes to the overall benefit associated with ACEi treatment [1]. This mechanism of action differs from that or angiotensin-II receptor antagonists (ARB's) that directly inhibit the angiotensin-II receptors type-1 while the clinical relevance of type-2 stimulation has never been confirmed in humans [1,2].

The effectiveness of ACEi in reducing cardiovascular disease (CVD) risk has been demonstrated in many randomized clinical trials, involving a broad variety of patients with or without manifest CVD [3–10]. ACEi are recommended by all guidelines addressing the treatment of CVD and renal disease both in the general population [11–13] and in patients with diabetes [14,15]. They can be effectively combined with almost all other classes of cardiovascular drugs with a significant improvement in blood pressure control, vascular and renal function, and long-term cardiovascular prognosis [16,17]. The use of ACEi is part of daily clinical practice in the management of patients with cardiovascular and renal diseases [3–6]. The safety and tolerability profile of ACEi ranks highly among the large family of cardiovascular drugs. Side effects include dry cough, hypotension, hyperkalemia, headache, dizziness, and renal impairment, which occur more often in patients with more severe medical conditions or treated with multiple classes of drugs [18]. The aim of this review was to summarize the available information about the relevance of cough in patients treated with ACEi, with a special focus on pathophysiology and its interaction with the pharmacological profile of the different ACEi.

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1.1. ACEi and cough

A persistent dry cough is the most common adverse effect of ACEi and has been reported to occur in a variable proportion of patients depending on the source of the data (observational, spontaneous report, controlled clinical trial), age, race and the gender of the population [19]. ACEi-induced cough is usually described as a scratching sensation in the throat that generally disappears a few days after discontinuation of treatment. Dry cough usually develops in the first week or month after starting the drug and is reported to be more frequent in Asian people and in female patients probably because of some differences in the metabolism of bradykinin peptides [20]. The overall incidence of cough in patients treated with ACEi is reported between 1% and over 30% depending on data set and patient population. It is less common in patients with hypertension, and more common in patients with coronary artery disease, in particular in those with heart failure bearing disease-related causes of cough, such as pulmonary congestion and bronchiolar edema [21–23]. In addition the incidence of dry cough has been reported as more frequent among diabetics than non-diabetic patients [24]. This large difference in the reported incidence of cough is mainly due to heterogeneity in the source of the clinical data. Only a minority of ACEi trials have included cough as a formal endpoint, and these studies were limited by small sample sizes and lack of long-term follow-up with a low number of events. This, in turn, has resulted in marked differences in reported incidences [25–28]. Moreover, the incidence of cough varies among individual ACEis, and only a few drugs from this class have real-world data to support findings from randomized trials in clinical practice. The paucity of evidence providing a link between controlled studies and real-life data has largely limited analysis of the actual incidence of cough in patients treated with ACEi and led to an increase in the "narrative" interpretation of symptoms of cough.

The consequence is that patients who experience any dry cough are often directly switched to ARBs, or other classes of antihypertensive drugs, in agreement with recommendations from most of the guidelines [11–13]. This could significantly modify the overall preventive impact of RAAS inhibition, particularly in terms of total and cardiovascular mortality.

1.2. Mechanism of ACEi-induced cough

Although the exact mechanism of ACEi-induced cough remains incompletely understood, several possible mechanisms have been hypothesized for cough development. The most widely accepted theory is based on the capacity of ACEis to prevent the ACE-dependent degradation of BK and substance P, with a subsequent accumulation of these substances in the upper and lower respiratory tracts [18]. BK acts through rapidly adapting stretch receptors and C-fiber receptors of airway sensory nerves that promote the release of neurokinin A and substance P. This causes airway smooth muscle to constrict, leading to bronchoconstriction and cough [29].

However, the most challenging point in terms of mechanism of cough is: why does cough not occur in all patients receiving ACEis? Many different mechanisms have been proposed including differences in individual bronchial reactivity or subclinical history of asthma [30,31], underlying lung congestion (e.g. patients with chronic heart failure), increased sensitivity of BK-dependent airway sensory nerve fibers, decreased capacity of BK degradation (aminopeptidase P-APP enzyme deficiency), and BK receptor gene polymorphism leading to differences in cough reflex sensitivity. Conversely, other studies have reported that previous asthma or history of bronchial hyper-reactivity does not pose a risk for developing ACEi-induced cough [32,33].

Genetic polymorphisms may influence the incidence of ACEi-induced cough. A recent meta-analysis including 26 studies showed a significant association between ACE I/D I carriers (ACE gene insertion) and ACEi-induced cough, with some racial (Asian) and age (elderly) differences [34]. Another study investigated the polymorphisms of BK receptors as a genetic marker of ACEi-related cough in a Japanese hypertensive population [35]. The TT genotype and T allele of BK B2 receptors were identified at a significantly higher frequency in patients with cough than in those without, with a more evident effect in women. No relationship was observed for the polymorphisms of ACE (I/D) and angiotensin II receptors. These genetic findings appear to be involved in the occurrence of cough and may provide a valuable tool to detect patients at risk of developing this side effect of ACEi before drug administration. In general, a summary review of the evidence provided by studies evaluating these pathogenetic hypotheses suggests the involvement of two or more genetic mechanisms in the development of ACEi-induced cough [27].

Despite all this sound evidence, the BK hypothesis has some drawbacks generated from studies of direct head-to-head comparisons between various ACEi with recognized differences in the level of interaction with BK metabolism. First, in a randomized double-blind study that used a de-challenge and re-challenge method, a twofold higher incidence of cough was seen in patients undergoing enalapril therapy (22%) compared with perindopril treatment (11%) [36]. Furthermore, a retrospective study reached the same conclusions with a

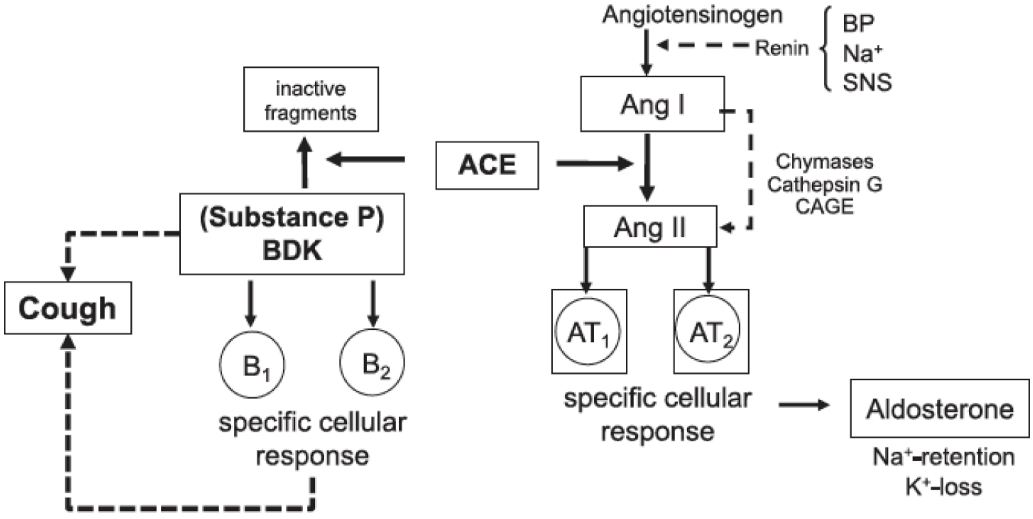

Fig. 1. Physiological interactions between ACE, angiotensin-II and bradykinin . Ang = angiotensin, BP = blood pressure, Na+ = sodium, SNS = sympathetic nervous system, ACE = angiotensin-converting enzyme, BDK = bradykinin.

threefold increase in the incidence of cough in patients with hypertension treated with enalapril (7%) vs. perindopril (2.2%) [36]. This observation is crucial as the lower incidence of cough with perindopril has been observed even though this ACEi exhibits the highest BK/angiotensin selectivity, but also the strongest interaction with the vascular RAAS (Fig. 2) [38].

These findings support the importance of the tissue binding of ACEi over their circulating effects, even in terms of adverse events (Fig. 2). Treatment with perindopril can be expected to reduce ANG II and to increase BK levels, particularly at the level of cardiac and vascular tissues. This helps maintain vascular homeostasis, probably with minor interactions with the extravascular system (e.g. respiratory system). As explained earlier, among ACEi, tissue potentiation of BK is particularly pronounced for perindopril and may underlie the cardiovascular benefits offered by the drug with a low rate of extravascular adverse events. This evidence suggests that the incidence of cough cannot be considered a class effect for ACEi, supporting the idea that it may be reasonable to switch from one ACEi to another in case of cough leading to discontinuation of drug.

1.3. How to manage ACEi-related cough in clinical practice?

1.3.1. Clinical approach

The decision on what is the best therapeutic strategy for patients who present with cough during ACEi treatment is dependent on the intensity of the symptom and the presence or not of concomitant CVD with a specific recommendation for ACEi treatment. Cough intensity is usually mild to moderate in most patients, and only occasionally is it severe enough to require drug discontinuation. Before deciding to remove an effective drug with well-established cardiovascular protection from the treatment plan, it is mandatory to discuss with the patient the actual cough severity, which must be weighed against the potential loss of cardiovascular protection. As far as the problem of concomitant diseases, the efficacy of ACEi has been proven in many patients, with significant reductions in cardiovascular mortality and morbidity. The decision about whether or not to remove the ACEi must be discounted against the expected clinical benefit, as prevention of cardiovascular events holding greater importance than any slight improvement in quality of life. Furthermore, Reisin and Schneeweiss reported in two different studies that cough spontaneously disappeared in 25% to 50% of hypertensive patients treated with ACEi (follow-up 2–8 months), despite continued and unchanged treatment [39,40]. More recently, a Japanese study reported a reduced incidence of cough with continuous use of ACEi [41]. The risk of inappropriate ACEi removal can be reduced by performing a challenge and re-challenge of to test if the re-introduction of the ACEi induces cough after remission of symptoms [42]. In practical terms the current protocol is based on 4 weeks of withdrawal and if the cough disappear the drugs can be re-introduced in daily therapy.

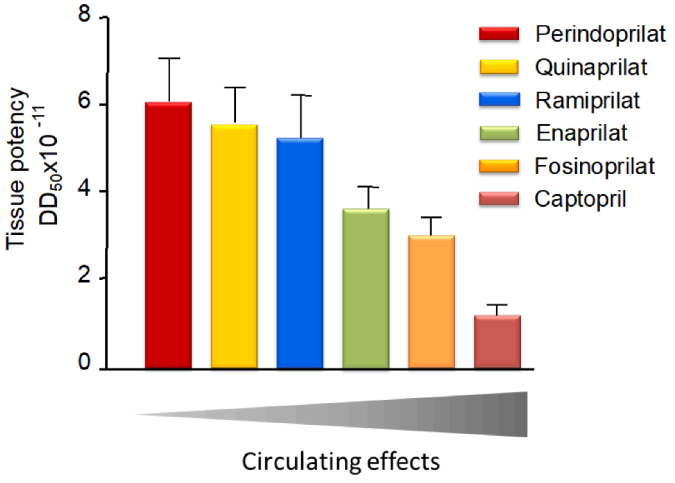

Fig. 2. ACEi and affinity for tissue ACE (adapted from [37]) and circulating effects.

This strategy has been shown to effectively reduce the cumulative incidence of cough [43], and to preserve the preventive efficacy of ACE-inhibition. In the presence of cough, the current strategy suggested by most guidelines is to switch from an ACEi to an ARB. However, this strategy does not entirely abolish the risk of cough (about 3% of ARB-treated patients complain of cough) [44], and it also reduces the extent of cardiovascular protection. A reduction in the rate of cough can be also achieved by shifting from average ACE-inhibitors to those drugs bearing lesser incidence of cough in clinical practice (perindopril and zofenopril). Additional studies/surveys focused on continuation of ACEi while monitoring the development of cough in patients belonging to different cardiovascular risk categories are warranted to reduce the rate of unjustified discontinuation of effective disease-modifying drugs.

1.3.2. Role of concomitant medications to reduce incidence of cough

ACEi are often combined with other classes of first-line cardiovascular drugs, particularly in the treatment of hypertension. Clinical studies have suggested that the incidence of cough can be significantly reduced by combination treatment, with the double benefit of improving blood pressure control and treatment adherence. In particular, some studies have reported that the addition of calcium channel blockers to ACEi can reduce cough acting through two possible mechanisms. First, by inhibiting prostaglandin synthesis, and second by inhibiting Ca-dependent release of glutamate, which plays an important role in the central transmission of the cough reflex [45]. This finding is further supported by other studies that reported a lower incidence of cough with concomitant calcium channel blockers or diuretics compared to ACEi monotherapy (Fig. 3) [42,46,47].

Several other treatments may also reduce the rate of cough in patients treated with ACEi including sodium cromoglycate, theophylline, sulindac, indomethacin, ferrous sulfate, and picotamide [47]. The administration of these agents may be complicated by the onset of drug-specific adverse events, and should not be considered in routine practice, but as a rescue treatment for those patients who cannot tolerate any other RAAS inhibitor.

1.3.3. Importance of underlying disease

ACEi are widely used for the treatment of patients with CVD ranging from uncomplicated hypertension to late stages of heart failure. The rate of cough in treated patients is significantly higher in those with coronary artery disease and heart failure, while the percentage is proportionally smaller in patients with hypertension. Vukadinovic et al. [21] published a comprehensive review of more than 20 clinical trials reporting the placebo-adjusted rate of cough in different populations of patients treated with ACEi, and reported that cough cannot be related to active ACEi in over 60% of treated patients. They also identified a remarkable proportion of unreliable “ACEi related” coughers, particularly among patients treated for coronary artery disease and heart failure in whom the prevalence of non-drug related cough during ACEi treatment was 58% and 71%, respectively. These data suggest that the true proportion of patients in whom discontinuation of an ACEi is appropriate because of cough is smaller than expected. This is particularly true in the uncomplicated hypertensive population, where the absolute rate of cough is probably less than 5% [21,22] when assessed by an accurate methodology excluding the narrative approach.

1.3.4. Selection of type of ACEi and incidence of cough

The incidence of cough varies based on the individual ACEi used. ACEi are categorized into three groups based on the presence of a sulfhydryl, carboxyl, or phosphoryl group, but the relevance of this structural difference in terms of cough remains unclear [48]. A previous study based on the incidence of adverse drug reactions showed that

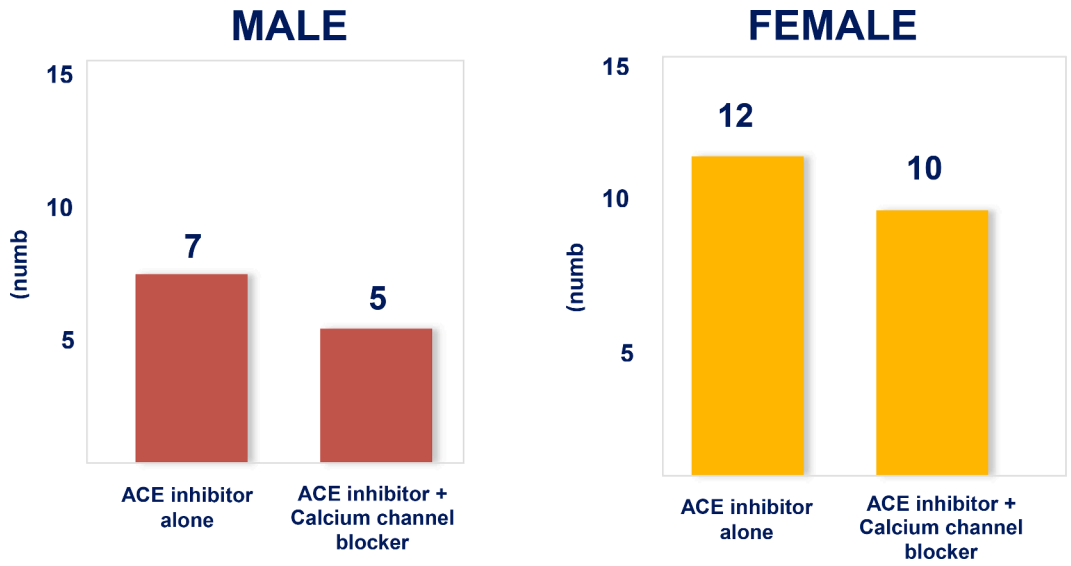

Fig. 3. Incidence of cough in patients with mono- or dual-therapy including an ACEi (Reproduced with permission from [40]).

phosphoryl group-containing ACEi (fosinopril) were associated with a higher incidence of cough compared with carboxyl group-containing ACEi (enalapril, lisinopril, and ramipril) [49]. These results are in agreement with experimental data comparing the rate of cough induced by two structurally different ACEi with a sulphydryl (zofenopril) or a carboxyl moiety (ramipril). An increase in the cough response to both mechanical and chemical stimulation was significantly enhanced in animals (rabbits) treated with ramiprilat without differences in the hemodynamic response. The frequency of coughs also increased in ramipril-treated animals from 21.1 + 2.6 to 34.9 + 3.5; $P < 0.01$) [50]. Similar data have been published in another animal model (guinea pig) with an increase in the rate of cough in response to citric acid that was observed only in ramipril-treated animals when compared to zofenopril or vehicle control groups [51]. These findings confirm that there are differences in the cough potentiation effect induced by different ACEi. The mechanism of the low rate of cough observed with zofenopril appears to be different from that proposed for perindopril and may be related to its ability to induce a lower accumulation of BK and prostaglandins in the lung. All this evidence supports a role for pharmacological heterogeneity within the ACEi class and suggests a lower rate of cough for those molecules more extensively bound to vascular tissue ACE, even though the mechanism of cough limitation does not seem to be unique across the different drugs.

Whatever the impact of drug-specific characteristics, the use of ACEi in clinical practice should be based on medications that induce cough less frequently. In this context, perindopril has been associated with a relatively low incidence of cough combined with extensive evidence supporting its cardiovascular benefits and tolerability. Nevertheless, the lack of head-to-head comparison of data in humans does not allow a definite conclusion about the differences across ACE-inhibitors and we must rely on indirect comparison integrated by more convincing animal reports. On the other side, the paper of co-workers [52] based on a large administrative data base, suggests a lower rate of discontinuation for patients treated with perindopril and zofenopril in the Italian population and this indirectly support a better tolerability for these two drugs probably due to the lesser incidence of dry cough, the most common adverse event of ACE-inhibitors.

The incidence of cough in patients treated with perindopril has been estimated both from randomized trials (RCT's) and real-world data. Data from three, large, landmark randomized clinical trials based primarily on the ACEi perindopril (ADVANCE, EUROPA, and PROGRESS) have been investigated as a single database. This has enabled useful subgroup analyses focused on selected populations of patients with a common background of vascular disease or high risk of vascular disease, and a clinical indication for ACEi use according to guidelines [53]. The final analysis included about 28,000 patients with CVD and revealed a cough discontinuation rate of 3.9% over a mean follow-up of 4 years (3.5% EUROPA with perindopril 8 mg, 4.3% ADVANCE with perindopril 4–8 mg, and 4.4% PROGRESS with perindopril 4 mg). A clinical risk score that was defined by the three strongest predictors of cough (advanced age, female gender and use of lipid-lowering drugs) was associated with an odds ratio of 4.4 (95% CI 3.1–5.4) in the subjects with the highest score. Interestingly, racial background was not related to a differential incidence of cough in patients of Caucasian or Asian origin (OR 1.11 95% CI 0.92–1.39), and this has clinical relevance for decisions about the use of ACEi or ARBs in Asian patients. The relationship between the use of lipid-lowering drugs and cough in ACEi -treated patients might be explained by the potential effects of statins on the expression of BK receptors [54], which could be responsible for an increased sensitivity to tissue BK accumulation at the level of airways. In view of the large prevalence of patients with a specific clinical indication for ACEi in the general population, these data can be used to reduce the probability of cough and to increase the clinical impact of ACEi considering the lower-than-expected incidence of cough.

In a series of perindopril-based studies performed in real clinical practice, including PAINT, PIANIST, PROOF, and PETRA [55–58], the incidence of cough was reported to be very low (ranging from <0.001% to 0.8%), even with the use of maximum dose perindopril (Table 1). Similarly, data from three Indian studies (STRONG, MONOCOMB, and PROTECT) demonstrated a cough incidence of 1.5% to 4%, in agreement with the incidence reported in global perindopril studies [59,26,61]. The difference between real life data and RCT's are probably dependent on the different approach to adverse events in real life studies in comparison to RCT that can be regarded as the golden standard. In particular, the real-life data mainly identify the patients stopping from treatment based on their personal perception of adverse events and this contribute to the proportion of poor adherence. Conversely, patients enroled in RCT are "pushed" to report any adverse event and to stay on treatment up to the end of the follow-up period. The clinical relevance of real-life data is supported by the pare of co-workers [52] supporting a relevant difference in the rate of discontinuation among patients treated with different drugs belonging to the same drug class.

The lower-than-expected rate of cough in patients treated with perindopril has been confirmed with other drugs with a high level of ACE tissue binding. In 23 studies conducted in hypertensive and post-myocardial infarction patients exposed for a median follow-up time of

Table 1
Summary of incidence of cough with perindopril in clinical studies.

Name of study/ author	Type of study	Perindopril dose	Cough Incidence (%)
PIANIST [55]	Observational	Perindopril 10 mg	0.8
PAINT [56]	Observational	Perindopril 5 and 10 mg	<0.1
PETRA [57]	Observational	Perindopril 5 and 10 mg	0.04
GREEK cohort [63]	Observational	Perindopril 5 and 10 mg	0.001
PROOF [54]	Observational	Perindopril 5 and 10 mg	
Nedogoda SV et al. [64]	Randomized	Perindopril 5 mg	No cough (0)
Mourad JJ et al. [65]	Randomized	Perindopril 5 and 10 mg	1.1
PROTECT I [66]	Observational	Perindopril 4 and 8 mg	4.3
Bansai S et al. [60]	Observational	Perindopril, N 1250	Monotherapy: 3.6 Combination:1.8 and 4.3
STRONG [58]	Observational	Perindopril, N 427	3.2
Padma MV et al. [59]	Observational	Perindopril, N 298	4.0

PIANIST, Perindopril-Indapamide plus AmlodipiNe in high rISk hyperTensive patients; PAINT, Perindopril-Amlodipine plus Indapamide combination for controlled hypertension Non-intervention Trial; PETRA, The Antihypertensive Efficacy of the Triple Fixed Combination of Perindopril, Indapamide, and Amlodipine; PROOF, Combined Therapy of Arterial Hypertension With a Triple Fixed-Dose Combination of Amlodipine/Indapamide/ Perindopril Arginine in Real Clinical Practice; PROTECT, Effectiveness of PeRindOpril in the management of hyperTension: idEntification of patient and physiCian determinants of response to Treatment; STRONG, SafeTy & efficacy analysis of coveRsyl amlodipine in uncOntrolled and Newly diaGnosed hypertension.

3 months to treatment with zofenopril, doses of 7.5–60 mg once-daily were associated with an incidence of cough of 2.6% (range 0%–4.2%). The rate of cough was 2.4% in the hypertension trials (2.4% in the double-blind randomized studies and 2.4% in the open-label post-marketing studies) and 3.6% in the double-blind randomized post-myocardial infarction trials. The incidence of cough was dose dependent and more common in the first 3–6 months of treatment (3.0%) vs 0.2% at 9–12 months [62].

A paper summarizing the incidence of cough with other ACE-inhibitors, reports the results of several randomized clinical trials involving ramipril (12%), benazepril (2.2%), Enalapril (2.2%) Lisinopril (3.5%), Trandolapril (1.9) [59] whose incidence of cough was already discounted by placebo [63].

These properties are based on its individual pharmacological profile as well as its favorable plasma/tissue ratio of ACE-inhibition that is probably responsible for the extensive cardiovascular protection and low rate of adverse events including cough.

2. Conclusions

ACEi are probably the most popular and extensively studied drugs for the prevention and treatment of CVD. Their efficacy has been proven in patients with hypertension, coronary artery disease, and heart failure with and without concomitant diabetes and/or chronic kidney disease. They have a favorable tolerability profile with cough as the only relevant adverse event that occurs in a variable proportion of the treated population, and which is dependent on the underlying disease and pharmacological profile of the ACEi concerned. The incidence of cough has been reported to be less than expected in real life and in placebo-controlled studies, while the presence of gender and racial differences is still a matter of debate and not unanimously confirmed by available data. The pathophysiological mechanism of cough is complex and closely related to the activity of circulating BK, with a lesser contribution of tissue BK levels. This may explain the reduced rate of cough in patients treated with drugs that strongly inhibit tissue ACE, such as perindopril and zofenopril. In clinical terms, cough intensity is often minimal or mild and does not support the automatic removal or modification of treatment. Such a decision should be carefully considered and generally discouraged in patients responding to treatment with only minimal and tolerable symptoms of cough. To avoid inappropriate discontinuation of ACEi in clinical practice, a challenge/re-challenge should be performed in patients with incident cough to determine if re-introduction of ACEi is associated with recurrence of symptoms.

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