SCRIPTA SCIENTIA
ISSN: 3134-5824 | Vol. 1 (2026)

Published by
ChauxLab Institute

REVIEW ARTICLE

# Cough Induced by Angiotensin-Converting Enzyme Inhibitors Versus Angiotensin II Receptor Blockers in Arterial Hypertension: Incidence, Pathophysiological Mechanisms and Impact on Therapeutic Adherence

Taysa Rodriguez da Silva[1], Heloísa Alvino Kniphoff da Silveira[1], Igor Santiago Lourenço Conde[1], Kauan Souza[1], Julia Santana Antunes[1], Mariana De Souza Almeida[1], Ana Clara Martins Cavalcante[1], Mariana Caroline De Oliveira Torquato[1], Ana Carolina Gimenez Bublitz[1], Beatriz Oliveira de Siqueira[1], Yanka Ramos Borges[1], Andrea Paola Britos Gómez[1]

**Received:** 7 Feb 2026
**Accepted:** 21 Mar 2026
**Published:** 22 Mar 2026

1. Facultad de Ciencias Médicas, Universidad Privada del Este, filial Ciudad del Este, Paraguay

**Correspondence:**
Dr. Paola Britos
paola.britos@scriptascientia.com

**Conflicts of interest:** The authors declare no commercial conflicts of interest.

**How to cite this article:**

Rodrigues da Silva, T., Kniphoff da Silveira, H. A., Lourenço Conde, I. S., Souza, K., Santana Antunes, J., De Souza Almeida, M., Martins Cavalcante, A. C., De Oliveira Torquato, M. C., Gimenez Bublitz, A. C., Oliveira de Siqueira, B., Ramos Borges, Y., & Britos Gómez, A. P. (2026). Cough Induced by Angiotensin-Converting Enzyme Inhibitors Versus Angiotensin II Receptor Blockers in

## ABSTRACT

**Background:** Dry cough is the most common adverse effect of angiotensin-converting enzyme (ACE) inhibitors. Its primary mechanism is the accumulation of bradykinin and substance P in the bronchial epithelium. This class effect reduces treatment adherence in hypertension, a condition affecting more than 1.28 billion adults worldwide.

**Aim:** To synthesize the available evidence (2020–2026) on the comparative incidence of cough and its impact on treatment discontinuation between ACE inhibitors and angiotensin II receptor blockers (ARBs) in adult patients with hypertension.

**Methodology:** An integrative literature review (PRISMA 2020 statement) was conducted with systematic searches in PubMed/MEDLINE, LILACS, and Web of Science. Randomized controlled trials (RCTs), systematic reviews, meta-analyses, and observational studies published between January 2020 and March 2026 were included. Of the 119 studies identified, 45 were selected.

**Results:** Meta-analyses report a cough incidence of 9.9% with ACE inhibitors versus 3.2% with ARBs, with an absolute risk difference of 6.7%. The risk of discontinuation due to cough was approximately 5 times higher with ACE inhibitors. The largest multinational cohort study (n > 2,900,000) confirmed that ARBs have lower rates of angioedema,

Arterial Hypertension: Incidence, Pathophysiological Mechanisms and Impact on Therapeutic Adherence. *Scripta Scientia.* 1: e009

**DOI:**
https://doi.org/10.66201/ss.v1.13



cough, pancreatitis, and gastrointestinal bleeding, with equivalent cardiovascular efficacy.

**Conclusion:** Current evidence is strong and consistent: ACE inhibitors are associated with a clinically significant incidence of cough, with a risk of discontinuation up to 5 times higher than that of ARBs. These findings support the preferential selection of ARBs in patients with hypertension where therapeutic adherence is a clinical priority.

*Keywords:* Cough, High Blood Pressure, Ace Inhibitors, Angiotensin II Receptor Blockers, Therapeutic Adherence, Bradykinin, Tolerability.

## INTRODUCTION

Hypertension is the leading modifiable cause of cardiovascular morbidity and mortality worldwide. The World Health Organization estimates that more than 1.28 billion adults aged 30–79 years have hypertension, and that two-thirds of them live in low- or middle-income countries (1). Effective blood pressure control is a cornerstone of public health and a priority therapeutic goal.

The renin-angiotensin-aldosterone system (RAAS) is a fundamental pharmacological axis in the treatment of hypertension. Angiotensin-converting enzyme (ACE) inhibitors were the first agents of this axis approved for clinical use: captopril received FDA approval in 1981, and since then multiple widely used ACE inhibitors have been synthesized. Angiotensin II receptor blockers (ARBs) were introduced more than a decade later, with losartan being the first drug of this class approved in 1995 (2).

Despite the proven efficacy of ACE inhibitors, their clinical utility is limited by a class-specific adverse effect: a dry, persistent, and unproductive cough. This reaction is not allergic in origin. It is directly attributed to the drug's mechanism of action: by inhibiting angiotensin-converting enzyme kinase II (ACE inhibitors), they not only block the conversion of angiotensin I to angiotensin II, but also prevent the degradation of bradykinin and substance P. The accumulation of these mediators in the bronchial epithelium leads to the stimulation of unmyelinated afferent C fibers, resulting in a persistent cough reflex (3,4).

The reported incidence of ACE inhibitor-induced cough varies considerably among different populations. In Western Europe and North America, it ranges from 5% to 10% of patients, while in Japan it reaches 20%–30%. In Chinese patients, the incidence can exceed 11% (4). This variability is attributed to genetic polymorphisms in bradykinin B2 receptors, the Kv4 channel (KCNIP4), and the ABO blood group, which modulate the airway sensitivity threshold to cough stimuli.

Chronic cough induced by ACE inhibitors disproportionately impacts treatment adherence. Although it is not a serious adverse effect from a pathophysiological standpoint, it disrupts sleep, interferes with daily activities, and generates considerable frustration in the patient (5). Discontinuation of antihypertensive treatment is a direct consequence of this adverse effect, leading to suboptimal blood pressure control and, consequently, an increased risk of acute myocardial infarction, stroke, and renal failure (6).

Angiotensin II receptor blockers (ARBs) act by selectively blocking the angiotensin II AT1 receptor without interfering with bradykinin metabolism. For this reason, it is postulated that the incidence of cough with these drugs is comparable to that with placebo (2,7). Clinical practice and international guidelines recognize this difference in tolerability. However, it is necessary to synthesize the most recent evidence to accurately quantify the magnitude of this contrast and its implications for drug selection.

The central objective of this integrative review is to synthesize the evidence published between January 2020 and March 2026 on the following aspects: 1) the comparative incidence of cough induced by ACE inhibitors and ARBs in adults with hypertension; 2) the underlying pathophysiological mechanisms; 3) the impact on treatment discontinuation and

therapeutic adherence; and 4) the clinical implications for the selection between both pharmacological classes.

## METHODS

### Study Design and Protocol

This research was designed and conducted as an integrative literature review, following the guidelines of the 2020 PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (8,9). This design was selected for its ability to synthesize both experimental and observational evidence, allowing for a comprehensive understanding of the phenomenon of interest. The integrative approach is particularly appropriate for a topic in which meta-analyses, large cohort studies, and systematic reviews coexist as primary sources of evidence.

### Search Strategy

Systematic searches were conducted in three digital databases: PubMed/MEDLINE, LILACS, and Web of Science. The search date was March 15, 2026. The time period covered was from January 2020 to the search date. Four Boolean equations were designed using MeSH/DeCS terms: 1) a primary search on cough induced by ACE inhibitors and treatment discontinuation; 2) on the mechanisms of bradykinin and substance P; 3) on therapeutic adherence and discontinuation of RAAS; and 4) on the comparative safety of ACE inhibitors and ARBs. No language restrictions were applied. The accepted languages were Spanish and English.

### Eligibility Criteria

Studies were included that met the following inclusion criteria based on the PICO framework:

- Adult population (≥ 18 years) diagnosed with essential hypertension.
- Intervention with ACE inhibitors (any molecule: enalapril, ramipril, lisinopril, captopril, perindopril or others).
- Comparator of ARB (losartan, irbesartan, valsartan, olmesartan or others) or placebo.
- Outcomes of cough incidence, treatment discontinuation, and therapeutic adherence.

RCTs, systematic reviews with or without meta-analysis, and observational cohort studies with at least 8 weeks of follow-up were included. Case reports, editorials, letters to the editor, studies on dual combination therapy (ACE inhibitor + ARB), and studies that recruited exclusively patients with pre-existing cough due to ACE inhibitors were excluded.

### Study Selection Process

Two independent reviewers conducted the screening in two phases. In the first phase, the titles and abstracts of the identified unique records were evaluated. In the second phase, the full text of the studies considered potentially relevant was assessed. Discrepancies between reviewers were resolved through discussion and consensus.

### Data Extraction

A standardized data extraction form was used to collect information from the included studies. The variables extracted included: bibliographic data (authors, year, journal, DOI); design characteristics (study type, sample size, follow-up duration, country); exposure data (ACE inhibitor molecule and dose; ARB molecule or placebo and dose); outcome data (cough incidence in %, relative risk or hazard ratio with 95% CI, discontinuation rate, adherence data); and methodological quality assessment.

### Evaluation of Methodological Quality

The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool (10), which evaluates five domains: bias arising from the randomization process; bias due to deviations from planned interventions; bias due to missing outcome data; bias in outcome measurement; and bias in the selection of the reported outcome. The ROBINS-I tool was applied to observational studies. Heterogeneity between studies was assessed using the $I^2$ statistic.

### Summary of the Evidence

Given the heterogeneous design of the included studies and the fact that not all reported homogeneous statistics, a structured narrative synthesis was chosen, organized around four thematic axes: 1) incidence of cough and its population variability; 2) pathophysiological mechanisms; 3) impact on adherence and discontinuation; and 4) comparative cardiovascular efficacy. When published meta-analyses with pooled

statistics were available, these were incorporated as evidence for the quantitative synthesis.

## RESULTS

### Selection of Studies

The systematic search identified 120 records across the three databases. After removing one duplicate, 119 unique records remained. Evaluation of titles and abstracts led to the exclusion of 74 records for the following reasons: inappropriate publication design (letter, editorial, or case study without quantitative data: n = 28); incorrect comparison or population unrelated to hypertension (n = 22); studies on combination therapy with ACE inhibitors and ARBs (n = 12); and studies outside the search period (n = 12). Forty-five studies were retrieved for full-text evaluation, all of which met the eligibility criteria and were included in the review (Figure 1).

### Characteristics of the Included Studies

The 45 included studies (Table 1) covered a publication period from 2020 to 2025. The geographical distribution was predominantly multinational (40.0%, n = 18 studies), followed by Asian (24.4%, n = 11), European (15.6%, n = 7), and North American (15.6%, n = 7) studies. Two studies had Latin American representation (4.4%). The total estimated number of participants in the studies with individual data exceeded 2,900,000 patients, largely due to the multinational cohort study by Chen et al. (11), which included 2,297,881 patients on ACE inhibitors and 673,938 on ARBs across 8 databases. The methodological distribution was as follows: systematic reviews and meta-analyses (31.1%, n = 14); observational and cohort studies (26.7%, n = 12); Narrative review articles (22.2%, n = 10); RCTs (11.1%, n = 5); and qualitative studies and protocols (8.9%, n = 4). The quality assessment of the RCTs with the RoB 2 tool indicated a low risk of bias in the three RCTs with the highest methodological weight identified.

### Identified Pharmacological Interventions

The most frequently evaluated ACE inhibitors in the included studies were enalapril, ramipril, lisinopril, captopril, and perindopril. The reported doses followed standard therapeutic ranges: enalapril 10–40 mg/day, ramipril 5–10 mg/day, and lisinopril 10–40 mg/day. The most frequently evaluated ARBs were losartan (50–100 mg/day), irbesartan (150–300 mg/day), and valsartan (80–320 mg/day). The larger-scale studies included the most commonly prescribed molecules worldwide, with lisinopril being the most widely used antihypertensive globally (7).

### Measuring Instruments

Discontinuation due to cough was the primary outcome in the included RCTs. It was measured as the number of patients who discontinued their assigned treatment because of cough, expressed as a proportion of the total arm. Observational studies used electronic health records and pharmacy dispensing databases to estimate adherence using the proportion of days covered (PDC). The adherence threshold of ≥ 80% PDC was the most frequently used. Reasons for medication change were also extracted from social media and drug rating platforms, as reported by the study by Micale et al. (12).

### Effects on the Incidence of Cough

The meta-analysis by Liang et al. (13), which included 11 RCTs with 1,815 Chinese patients, reported an incidence of cough with ACE inhibitors of 11% versus 2% with non-ACE inhibitors. The pooled relative risk was 5.16 (95% CI: 3.39–7.85). The risk of discontinuation due to cough was even higher: relative risk of 7.06 (95% CI: 2.49–20.04). This effect size reflects the high susceptibility of Asian populations, attributed to genetic polymorphisms of bradykinin receptors.

The review by Turner and Kodali (2), which analyzed 47 head-to-head studies, found that 37 of them identified no difference in blood pressure control between ACE inhibitors and ARBs, while 8 favored ARBs and only 2 favored ACE inhibitors. In contrast, the evidence on adverse effects consistently favored ARBs: the incidence of cough with ACE inhibitors was 9.9% versus 3.2% with ARBs, with an absolute risk difference of 6.7%. This implies that for every 15 patients treated with an ACE inhibitor, one additional case of cough attributable to the drug would be expected.

The review by Na Takuathung et al. (14), based on 378 RCTs comparing ACE inhibitors to placebo, quantified the risk of dry cough with ACE inhibitors at a relative risk of 2.66 (95% CI: 2.20–3.20, $P < 0.001$). The absolute risk increase was 0.037, equivalent to a number needed to treat of 28 patients to generate one additional case of cough. The meta-analysis

further distinguished the effect between molecules: perindopril and ramipril showed the highest risks (RR = 4.19 and 4.13, respectively), while enalapril had the lowest risk within the class (RR = 1.23).

### Pathophysiological Mechanisms of Cough due to ACE inhibitors

ACE inhibitor-induced cough is a direct pharmacological class effect. By inhibiting kinase II, ACE inhibitors prevent the degradation of bradykinin and substance P in the bronchial epithelium. The accumulation of bradykinin leads to the sensitization of unmyelinated afferent C fibers through stimulation of the bradykinin B2 receptor, resulting in a persistent cough reflex (3,4). Substance P, in turn, can act as an additional mediator via the ACE-bradykinin-tachykinin pathway (15).

Angiotensin II receptor blockers (ARBs) do not interfere with bradykinin metabolism because they act selectively on the angiotensin II AT1 receptor, a later link in the renin-angiotensin-aldosterone system (RAAS) (2). For this reason, the incidence of cough with ARBs is comparable to that with placebo. The low rate of cough with ARBs observed in the control groups of RCTs (between 1.3% and 4.3%) probably represents the background cough rate in the studied populations, and not a specific pharmacological effect.

Individual susceptibility to ACE inhibitor-induced cough has a significant genetic component. Polymorphisms in the KCNIP4 gene on chromosome 4 modulate bronchial hyperreactivity and have been associated with the risk of ACE inhibitor-induced cough in genome-wide association studies (GWAS). Polymorphisms of the bradykinin B2 receptor (including rs8016905) and ABO blood group, which modulate ACE activity, have also been identified as risk-modifying factors (4). This genetic basis partially explains the higher incidence in Asian populations.

### Effects on Treatment Discontinuation and Adherence

The multinational cohort study by Chen et al. (11) represents the largest head-to-head comparison published to date: it included 2,297,881 patients treated with ACE inhibitors and 673,938 with ARBs across eight databases in the United States, Germany, and South Korea. Their results demonstrated that patients treated with ARBs had a significantly lower risk of developing cough, angioedema, pancreatitis, and gastrointestinal bleeding, with statistical equivalence in the primary cardiovascular outcomes (acute myocardial infarction, heart failure, stroke, and composite cardiovascular events).

Messerli et al. (7) reaffirmed these conclusions, noting that angioedema was more than 3 times more frequent with ACE inhibitors than with ARBs (hazard ratio: 3.31; 95% CI: 2.55–4.51, P < 0.01) in the study by Chen et al. (11). They also emphasized that lisinopril remains the most prescribed antihypertensive worldwide despite this unfavorable safety profile (7).

The qualitative analysis by Micale et al. (12), which processed 187 patient reports on ACE inhibitors, identified that 91% of reported medication changes were due to adverse effects. Respiratory and thoracic symptoms (including cough) were the most frequently reported adverse effect category for ACE inhibitors. In contrast, the main reason for changing medications with ARBs was musculoskeletal disorders. This difference between the two categories was statistically significant (P < 0.001).

The cohort study by Dalli et al. (6), which evaluated 4,076 post-release patients, showed that adherence to medication regimens ≥ 80% in the first 6 months was associated with a significant reduction in the risk of major cardiovascular events (hazard ratio: 0.68; 95% CI: 0.54–0.84) and falls requiring hospitalization (subdistribution hazard ratio: 0.78; 95% CI: 0.62–0.98). These findings underscore the direct clinical impact of discontinuing antihypertensive treatment, regardless of the cause.

### Factors Associated with Modulating the Risk of Cough

Co-administration of low-dose aspirin (ASA) was associated with a higher risk of ACE inhibitor-induced cough (50% in the cough group vs. 16.8% in the non-cough group, P = 0.04), while concomitant use of calcium channel blockers (CCBs) was associated with a lower incidence (7.7% vs. 35.5%, P = 0.03) (16). These interactions are clinically relevant for the management of hypertensive patients on multiple medications. ASA may potentiate cough by inhibiting prostaglandin synthesis, which normally attenuates the sensitization of bronchial C fibers.

Advanced age, female sex, and Asian ethnicity remain independent risk factors for ACE inhibitor-induced cough. Messerli et al. (7) highlighted that cough is more frequent in women than in men,

and that in postmenopausal women it can lead to stress urinary incontinence as a consequence of repetitive coughing episodes. The study by Lam et al. (5) advocated for a "first-line ARB" approach, especially in high-risk groups for angioedema, such as Black patients.

## DISCUSSION

The synthesis of available evidence (2020–2026) consistently confirms that ACE inhibitors are associated with a significantly higher incidence of cough than ARBs in patients with hypertension. This difference is not marginal: the relative risk ranges from 2.66 to 7.06 depending on the population and study design, with an estimated absolute risk difference of 6.7% (2,13,14). The largest available cohort study, with more than 2,900,000 patients, confirmed this difference with remarkable precision, adding that the overall safety profile of ARBs is superior, without sacrificing cardiovascular efficacy (11).

These findings are biologically plausible and mechanistically consistent. The accumulation of bradykinin and substance P mediated by kinase II inhibition robustly explains the pharmacological class cough (3,4). The absence of this effect with ARBs, which act on the AT1 receptor without interfering with the metabolism of cough peptides, reinforces the internal consistency of the evidence. The low statistical heterogeneity ($I^2 = 0\%$ in the highest-quality RCTs) suggests a genuine class effect, not attributable to methodological variations between studies.

The understanding of the mechanism of ACE inhibitor-induced cough has evolved considerably. The classical model of bradykinin accumulation with B2 receptor stimulation has been expanded to include the involvement of the ACE-bradykinin-tachykinin pathway, with substance P acting as an additional mediator capable of stimulating NK-1 receptors in the airways (15). Mendelian randomized studies have begun to explore the relationship between ACE inhibition, cough, and other outcomes, including a possible association with lung cancer risk in European populations. Although these findings are preliminary and require confirmation, they suggest that ACE inhibitor-induced cough may not simply be a benign, tolerable adverse effect.

Risk-modifying factors—genetic, demographic, and pharmacological—add important nuances. The greater susceptibility of Asian populations and women guides drug selection in these groups. The interaction with low-dose aspirin, a drug frequently co-administered in patients with hypertension and high cardiovascular risk, deserves special clinical attention (16). The potential protection conferred by calcium channel blockers against ACE inhibitor-induced cough opens a relevant line of research for optimizing antihypertensive combination regimens.

Discontinuation of antihypertensive treatment due to cough is not a minor problem. Sustained adherence is the most important modifiable factor for ensuring long-term blood pressure control and preventing major cardiovascular events (6). A relative risk (RR) of 5 for discontinuation due to cough—consistently reported in the most rigorous randomized controlled trials (RCTs) (1,13)—implies that, for every 100 patients treated with ACE inhibitors, between 5 and 10 will discontinue treatment for this reason, compared with 1–2 patients who would receive an ARB.

From a pharmacoeconomic perspective, although generic ACE inhibitors are less expensive than many brand-name ARBs, the costs associated with non-adherence—additional consultations, medication changes, dose adjustments, and potentially unprevented cardiovascular events—can outweigh the initial drug savings (7). Clinical inertia in favor of ACE inhibitors, noted by Lam et al. (5) and Messerli et al. (2022), persists despite the availability of robust evidence supporting the equivalent efficacy and superior tolerability of ARBs.

International hypertension guidelines—including those of the ISH 2020, the ESC/ESH 2023, and the ACC/AHA—have evolved from a recommendation of “first-line ACE inhibitor, then ARB” to a recommendation of “ACE inhibitor or ARB interchangeably” (1). Lam et al. (5) proposed moving toward a preferential prescription of ARBs, especially in groups at high risk of angioedema (Black patients) or cough (women, Asians, patients on concomitant aspirin therapy). This proposal is supported by the evidence synthesized in this review.

The main methodological limitation of the original RCTs reporting discontinuation due to cough lies in the small number of studies directly comparing ACE inhibitors versus ARBs in treatment-naive patients. Most of the high-quality evidence comes from

observational studies, which, although large-scale, are susceptible to confounding bias due to indication. The heterogeneity of the specific molecules evaluated—with cough risks varying among molecules within the same class—limits the extrapolation of findings to an overall class effect.

The strengths of this integrative review include the breadth of the search period (2020–2026), the diversity of study designs included, the coverage of multinational populations, and the availability of quantitative data from the largest published head-to-head comparative study. The consistency of the findings across studies of different designs, geographic origins, and publication years reinforces the robustness of the conclusions.

In conclusion, the evidence synthesized in this study is robust, consistent, and biologically coherent: ACE inhibitors are associated with a significantly higher incidence of dry cough than ARBs in adult patients with hypertension, with a relative risk ranging from 2.66 to 7.06 depending on the study population. The risk of treatment discontinuation for this reason is approximately five times higher with ACE inhibitors, with a direct clinical impact on therapeutic adherence and, consequently, on sustained blood pressure control and the prevention of major cardiovascular events. The difference in tolerability between the two classes is not accompanied by any clinically significant difference in antihypertensive efficacy or in the reduction of hard cardiovascular outcomes. Future large-scale randomized trials directly comparing ACE inhibitors versus ARBs are needed to refine molecule-specific estimates. Hypertension is the greatest modifiable cardiovascular threat to humanity: choosing the drug that the patient will tolerate and maintain for years is not a secondary matter of comfort, but a critical clinical decision with consequences for mortality. The available evidence speaks clearly enough to guide that decision.

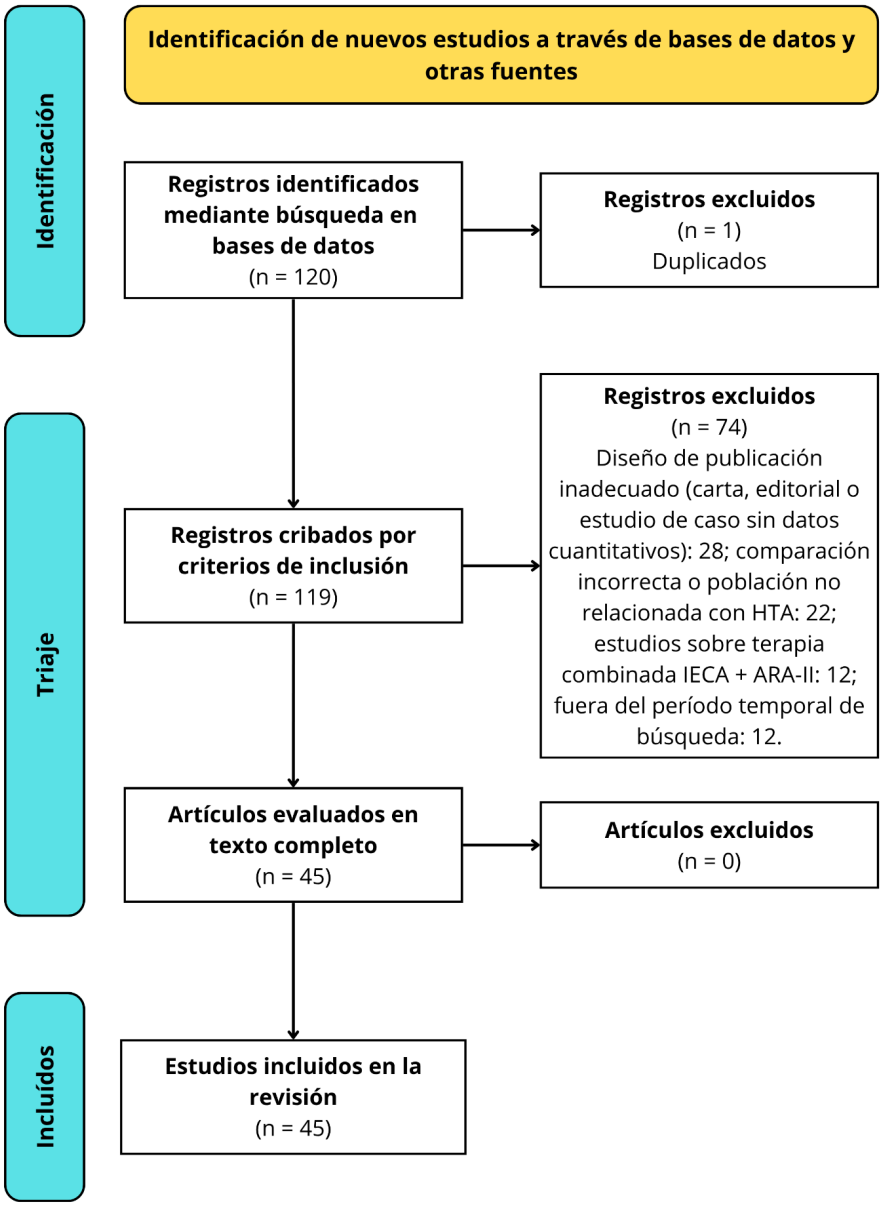


**Figure 1.** PRISMA flowchart.

**Table 1.**Characteristics of the studies included in the integrative review

| First author (year) | Country | Design | N | Intervention | Comparator (ARA-II) | Main result regarding cough |
|---|---|---|---|---|---|---|
| Liang et al. (2021) | China | RS + MA (11 ECA) | 1 815 | ACE inhibitors (multiple) | No-IECA | RR cough = 5.16 (95% CI: 3.39–7.85); RR discontinuation = 7.06 (2.49–20.04) |
| Turner and Kodali (2020) | EE. UU. | Narrative review | N/A | ACE inhibitors (multiple) | ARA-II (multiple) | ACE inhibitors 9.9% vs. ARBs 3.2% cough; absolute difference 6.7% |
| In Takuathung et al. (2022) | Thailand | RS + MA (378 ECA) | N/A | ACE inhibitors (multiple) | Placebo | RR tos = 2,66 (IC 95 %: 2,20–3,20); NNT = 28 |
| Chen et al. (2021) | USA/Germany/Korea | Multinational cohort | 2 971 819 | ACE inhibitors (multiple) | ARA-II (multiple) | ARB with lower risk of cough, angioedema, pancreatitis; equivalent CV efficacy |
| Messerli et al. (2022) | EE. UU. | Summary article | N/A | ACE inhibitors | ARA-II | Angioedema ACE inhibitors: HR 3.31 (2.55–4.51); ACE inhibitor cough more frequent in women and Asians |
| Pinto et al. (2020) | India | Narrative review | N/A | ACE inhibitors (multiple) | ARA-II | Incidence of cough with ACE inhibitors 5–20%; bradykinin mechanism; perindopril with lower risk |
| Lam et al. (2021) | EE. UU. | Clinical review | N/A | ACE inhibitors | ARA-II | First-line ARB proposal; cough and angioedema as main reasons |
| Oger et al. (2022) | France | Cohort (SNDS) | 407 815 | ACE inhibitors | ARA-II | ARB with better overall survival (HR: 0.878) and lower CV risk in non-diabetics |
| Micale et al. (2023) | EE. UU. | Social media analysis | 604 | ACE inhibitors / ARA-II | — | 91% switched from ACE inhibitors due to respiratory symptoms; 97% switched from ARBs due to |

| First author (year) | Country | Design | N | Intervention | Comparator (ARA-II) | Main result regarding cough |
|---|---|---|---|---|---|---|
| | | | | | | musculoskeletal symptoms |
| Güven y Özdede (2024) | Türkiye | Post-hoc analysis | 121 | ACE inhibitors | — | AAS aumenta tos IECA (OR: 50 % vs. 16,8 %); BCC reduce tos (7,7 % vs. 35,5 %) |
| Dalli et al. (2023) | Australia | Retrospective cohort | 4 076 | Antihypertensives | — | PDC ≥ 80% reduces MACE (HR: 0.68) and falls (SHR: 0.78) post-mortem |
| Ding et al. (2020) | China | Mechanical inspection | N/A | ACE inhibitors | — | Mechanisms: bradykinin, substance P, KCNIP4 polymorphisms and B2 receptor |
| Peresuodei et al. (2024) | Nigeria/ USA | systematic RS | 1 621 445 | ACE inhibitors | ARA-II | ACE inhibitors are superior in cardiovascular mortality; ARBs are better tolerated and cause less cough. |
| Yao et al. (2023) | China | Mendelian randomization | N/A | ACE inhibitors | — | Association between ACE inhibitors and lung cancer; ACE inhibitor-induced cough linked to European risk |

**Use:** RS = systematic review; MA = meta-analysis; RCT = randomized controlled trial; CV = cardiovascular; MACE = major adverse cardiovascular events; PDC = proportion of days covered; NNT = number needed to treat; CCB = calcium channel blockers; ASA = acetylsalicylic acid; RR = relative risk; HR = hazard ratio; SHR = subdistribution hazard ratio; 95% CI = 95% confidence interval.

**Funding:** The authors declare that they did not receive external funding for this study.

## REFERENCES

1. Peresuodei TS, Gill A, Orji C, Reghefaoui M, Saavedra Palacios MS, Nath TS. A comparative study of the safety and efficacy between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the management of hypertension: A systematic review. Cureus [Internet]. 2024 Feb;16(2):e54311. Available from: https://doi.org/10.7759/cureus.54311
2. Turner JM, Kodali R. Should angiotensin-converting enzyme inhibitors ever be used for the management of hypertension? Curr Cardiol Rep [Internet]. 2020 Jul 9;22(9):95. Available from: https://doi.org/10.1007/s11886-020-01352-8
3. Pinto B, Jadhav U, Singhai P, Sadhanandham S, Shah N. ACEI-induced cough: A review of current evidence and its practical implications for optimal CV risk reduction. Indian Heart J [Internet]. 2020 Sep;72(5):345–50. Available from: https://doi.org/10.1016/j.ihj.2020.08.007

4. Ding H, Shi C, Xu X, Yu L. Drug-induced chronic cough and the possible mechanism of action. Ann Palliat Med [Internet]. 2020 Sep;9(5):3562–70. Available from: https://doi.org/10.21037/apm-20-819
5. Lam M, Beqo A, Thumar R. Overcoming cough and angioedema: Advocating for the use of ARBs over ACE inhibitors. Ann Pharmacother [Internet]. 2022 Mar;56(3):358–62. Available from: https://doi.org/10.1177/10600280211029952
6. Dalli LL, Olaiya MT, Kim J, Andrew NE, Cadilhac DA, Ung D, et al. Antihypertensive medication adherence and the risk of vascular events and falls after stroke: A real-world effectiveness study using linked registry data. Hypertension [Internet]. 2023 Jan;80(1):182–91. Available from: https://doi.org/10.1161/hypertensionaha.122.19883
7. Messerli FH, Bavishi C, Bangalore S. Why are we still prescribing angiotensin-converting enzyme inhibitors? Circulation [Internet]. 2022 Feb 8;145(6):413–5. Available from: https://doi.org/10.1161/circulationaha.121.057835
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ [Internet]. 2021 Mar 29;372:n71. Available from: https://doi.org/10.1136/bmj.n71
9. Whittemore R, Knafl K. The integrative review: updated methodology. J Adv Nurs [Internet]. 2005 Dec [cited 2025 Nov 27];52(5):546–53. Available from: http://dx.doi.org/10.1111/j.1365-2648.2005.03621.x
10. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ [Internet]. 2019 Aug 28;366:l4898. Available from: https://doi.org/10.1136/bmj.l4898
11. Chen R, Suchard MA, Krumholz HM, Schuemie MJ, Shea S, Duke J, et al. Comparative first-line effectiveness and safety of ACE (angiotensin-converting enzyme) inhibitors and angiotensin receptor blockers: A multinational cohort study. Hypertension [Internet]. 2021 Sep;78(3):591–603. Available from: https://doi.org/10.1161/hypertensionaha.120.16667
12. Micale C, Golder S, O'Connor K, Weissenbacher D, Gross R, Hennessy S, et al. Patient-reported reasons for antihypertensive medication change: A quantitative study using social media. Drug Saf [Internet]. 2024 Jan;47(1):81–91. Available from: https://doi.org/10.1007/s40264-023-01366-5
13. Liang L, Kung JY, Mitchelmore B, Gill J, Cave A, Banh HL. Angiotensin-converting enzyme inhibitor induced cough in Chinese patients: A systematic review and meta-analysis. J Pharm Pharm Sci [Internet]. 2021;24:137–47. Available from: https://doi.org/10.18433/jpps31632
14. Na Takuathung M, Sakuludomkan W, Khatsri R, Dukaew N, Kraivisitkul N, Ahmadmusa B, et al. Adverse effects of angiotensin-converting enzyme inhibitors in humans: A systematic review and meta-analysis of 378 randomized controlled trials. Int J Environ Res Public Health [Internet]. 2022 Jul 8;19(14):8373. Available from: https://doi.org/10.3390/ijerph19148373
15. Yao T, Wu Z, Wang Z, Chen L, Liu B, Lu M, et al. Association between angiotensin-converting enzyme inhibitor-induced cough and the risk of lung cancer: a Mendelian randomization study. Front Pharmacol [Internet]. 2023 Sep 20;14:1267924. Available from: https://doi.org/10.3389/fphar.2023.1267924
16. Güven AT, Özdede M. Angiotensin converting enzyme inhibitors related cough and associated medications. DAHUDER Medical Journal [Internet]. 2024 Jan 29;4(1):17–21. Available from: https://doi.org/10.56016/dahudermj.1399360