THE PACKAGE INSERT SERIES

ACE Inhibitors — What Five FDA Labels Say About America's Most Prescribed Blood Pressure Drug Class

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The most prescribed blood pressure medication in the United States carries a boxed warning — the FDA's most serious category — stating that it "can cause injury and death to the developing fetus." That drug is lisinopril. The warning appears on every ACE inhibitor label. It is not new. It is not hidden. It has been there for decades. Most patients taking these drugs have never read it.

> *The labels contain more. ACE inhibitors can trigger angioedema — sudden swelling of the face, tongue or airway — at a higher rate in Black patients. All five labels acknowledge the drugs work less effectively in Black patients when used alone. One drug in the class — quinapril — has never been evaluated for its effect on long-term mortality in heart failure. Every label states that whether the mechanism of action involves bradykinin "remains to be elucidated" — after 35 to 40 years on the market, they still do not fully know how it works. These are statements from the FDA-approved label, written by the manufacturers, reviewed by the regulators, and filed with the agency.*

This installment of The Package Insert covers five ACE inhibitors: lisinopril (Zestril), enalapril (Vasotec), ramipril (Altace), benazepril (Lotensin), and quinapril (Accupril). Together they represent the top five most prescribed drugs in this class by US volume. Their initial FDA approvals span from 1985 (enalapril) to 1991 (ramipril and benazepril), giving the oldest of them four decades on the market. Everything below comes from the prescribing information filed with the FDA.

The Package Insert takes the FDA-approved labels for a major drug class in each installment, reads them front to back, and reports what they actually say — in the manufacturers' own language, reviewed by the regulators, available to anyone who asks for them. If you're currently taking an ACE inhibitor, considering one, or have a family member on one, this is the installment to start with.

What the Labels Say the Drugs Can Do

Not all ACE inhibitors were approved to do the same thing.

Lisinopril carries three indications: hypertension, heart failure and reduction of mortality in acute myocardial infarction. The GISSI-3 trial, a study of over 19,000 patients, showed an 11% lower risk of death at six weeks in patients receiving lisinopril after a heart attack compared to those who did not. That is real mortality data — not a surrogate endpoint, not a blood pressure number, but a difference in who lived and who died.

Enalapril was approved for heart failure and asymptomatic left ventricular dysfunction. Its label contains the sharpest survival data in the class. In the CONSENSUS trial — limited to patients with the most severe heart failure, NYHA Class IV — six-month survival was 74% in the enalapril group versus 56% on placebo. At one year: 64% versus 48%. The SOLVD-Treatment trial, enrolling 2,569 patients with symptomatic heart failure, showed an 11% reduction in all-cause mortality and a 30% reduction in hospitalisation for heart failure. These are the numbers that made enalapril a standard of care in heart failure.

Ramipril has the broadest approved scope of cardiovascular protection. In addition to hypertension and heart failure post-myocardial infarction, it carries a specific indication for reducing the risk of heart attack, stroke and cardiovascular death in high-risk patients over 55. The HOPE study — 9,297 patients followed for a mean of five years — showed a 22% reduction in the combined endpoint (relative risk 0.78, p=0.0001). Cardiovascular death was reduced by 26%. Stroke was reduced by 32%. The label notes that “there were insufficient data to determine whether or not ramipril was equally effective in ethnic subgroups”.

Benazepril and quinapril, by contrast, are approved only for hypertension and heart failure, respectively. Their labels do not contain major mortality outcome trials. Benazepril's clinical studies section describes blood pressure reductions of “about 6 to 12 mm Hg systolic and 4 to 7 mm Hg diastolic” — surrogate endpoints, not survival data. And the quinapril label contains a sentence that should give any patient pause: “The effects of quinapril on long-term mortality in heart failure have not been evaluated.”

That admission sits inside a label for a drug approved to manage heart failure. The drug is prescribed. It lowers blood pressure. Whether it keeps patients alive over the long term has, by the manufacturer's own statement, never been tested.

The lisinopril label adds a note about its own clinical trial data. In the GISSI-3 study, the label acknowledges that limitations — “the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography, and substantial excess use of Zestril between 6 weeks and 6 months in the group randomized to 6 weeks of lisinopril” — “preclude any conclusion” about the combined endpoint at six months. The mortality finding at six weeks stands. The longer-term composite does not.

> ASK YOUR DOCTOR
> *Does the specific ACE inhibitor you're prescribing have mortality outcome data, or is it approved based on blood pressure reduction alone?*

The Swelling That Can Kill You

All five ACE inhibitor labels warn about angioedema — swelling of the face, extremities, lips, tongue, glottis and larynx. All state that angioedema associated with laryngeal involvement can be fatal. And all instruct physicians that if the tongue, glottis or larynx are involved, emergency treatment with subcutaneous adrenaline should be administered promptly.

The labels also describe intestinal angioedema, a form that presents as abdominal pain, sometimes with nausea or vomiting, diagnosed by CT scan, ultrasound or surgery. In some cases, patients had no prior history of facial angioedema and their C-1 esterase levels were normal. The labels instruct physicians to include intestinal angioedema in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain — language that implies this form is underdiagnosed.

The racial data is on every label. All five state, with variations in phrasing, that ACE inhibitors have been associated with a higher rate of angioedema in Black patients than in non-Black patients. The quinapril label provides the most specific post-marketing data: in two large US trials enrolling over 3,000 Black patients and over 19,000 non-Blacks, angioedema was reported in 0.30% and 0.55% of Black patients (across the two studies) compared to 0.39% and 0.17% of non-Black patients. The ramipril label cites a large US post-marketing study: angioedema reported in 3 of 1,523 Black patients (0.2%) versus 8 of 8,680 non-Black patients (0.09%). The label notes these rates "were not different statistically" — but the numbers are included on the label nonetheless. The benazepril label puts it plainly: "ACE inhibitors have been associated with a higher rate of angioedema in Black than in non-Black patients."

Patients receiving mTOR inhibitors (temsirolimus, sirolimus, everolimus) or neprilysin inhibitors are flagged across the class as being at increased risk. This is consistent language on all five labels.

> ASK YOUR DOCTOR
> *Has anyone discussed with you the signs of angioedema — including abdominal pain as a possible symptom — and what to do if it occurs?*

A Class of Drugs That Still Can't Explain Itself

Every ACE inhibitor label contains the same sentence, with minor variations: "Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of [drug name] remains to be elucidated."

ACE (angiotensin-converting enzyme) is identical to kininase II, an enzyme that degrades bradykinin. When you inhibit ACE, you simultaneously increase bradykinin levels. The labels acknowledge this. They describe the primary mechanism — inhibition of the conversion of angiotensin I to angiotensin II, resulting in decreased vasopressor activity and decreased aldosterone secretion. But whether the bradykinin pathway contributes to the therapeutic effect is, after four decades of clinical use, still described as unresolved.

The unresolved question has a practical edge. Bradykinin is also the suspected mechanism behind the most common side effect of ACE inhibitors: cough. And behind the most dangerous one: angioedema. The same pathway the labels cannot confirm as contributing to the drug's benefit is the pathway implicated in its most serious harms.

The benazepril label adds its own admission: “While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension.” The drug works in patients where the proposed primary mechanism should not account for the effect. The label offers no explanation.

The Cough They Didn't Recognise

The ramipril label contains a disclosure that says something about how clinical trials work. In its placebo-controlled trials, there was “an excess of upper respiratory infection and flu syndrome in the ramipril group, not attributed at that time to ramipril”. The label explains: “As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough.”

In a later one-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% requiring discontinuation of treatment. The earlier trials had categorised this side effect as something else entirely — upper respiratory infections, flu symptoms. The trial design didn't catch it because no one was looking for it.

The quinapril label reports cough in 4.3% of heart failure patients (versus 1.4% on placebo). The lisinopril label identifies cough as 2.5% more common on the drug than on placebo in hypertension trials. Every label in the class acknowledges that “persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy”. The mechanism is “presumably” the same bradykinin pathway that remains to be elucidated.

The cough story matters because it reveals a structural problem. If early clinical trials can misclassify a side effect affecting up to 12% of patients as a different condition, what other effects might be miscategorised in the trial data that forms the basis for these labels?

> ASK YOUR DOCTOR
> *If I develop a persistent cough on an ACE inhibitor, how long should I wait before reconsidering the medication?*

What the Labels Say About Your Brain

Scattered across the post-marketing and adverse reaction sections of these five labels is a constellation of neurological and psychiatric findings that rarely gets discussed at the prescribing visit.

Lisinopril's post-marketing section lists "mood alterations (including depressive symptoms), mental confusion, hallucinations". These are not trial findings with percentages — they are spontaneous reports collected after the drug was already on the market, reported "from a population of uncertain size" where "it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure".

Ramipril's adverse reaction section is more granular: "Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances." All occurred in less than 1% of patients in controlled clinical trials.

Benazepril reports headache in 6% of patients (versus 4% on placebo), dizziness in 4% (versus 2%), somnolence in 2% (versus 0%), and postural dizziness in 2% (versus 0%). Its adverse reaction section adds anxiety, decreased libido, insomnia, nervousness and paraesthesia. Quinapril adds somnolence and malaise.

None of these labels contain long-term cognitive outcome data. The effects listed are those observed during relatively short clinical trials or reported after marketing. Whether years of ACE inhibition produce any cumulative neurological effects is not addressed — it has not been studied.

> ASK YOUR DOCTOR
> *Should I be monitoring for mood changes or cognitive symptoms while on an ACE inhibitor, and how would we distinguish drug effects from other causes?*

Fetal Toxicity and the Kidney Damage Window

Every ACE inhibitor carries a boxed warning — the FDA's strongest — about fetal toxicity. The language is uniform across the class: drugs that act on the renin-angiotensin system during the second and third trimesters "reduce fetal renal function and increase fetal and neonatal morbidity and death". Potential neonatal effects include skull hypoplasia, anuria, hypotension, renal failure and death. Resulting oligohydramnios — reduced amniotic fluid — "can be associated with fetal lung hypoplasia and skeletal deformations".

The labels instruct that when pregnancy is detected, the drug should be discontinued "as soon as possible". They note that oligohydramnios "may not appear until after the fetus has sustained irreversible injury". The damage, then, may be done before it becomes detectable.

The enalapril label contains an additional piece of data that does not appear on the others. In its animal toxicology section, it reports that "rat pups exposed to daily enalapril from birth to post-natal Day 13 (the period of nephrogenesis in this species) developed irreversible renal toxicity". Treatment after post-natal Day 14 was not toxic to the more mature kidney. The label maps this to humans: "Rat kidney development at birth and at 14 days is similar to the human at mid-trimester and in infancy, respectively." It adds that "the toxic dosages in these studies were about 10X, on a mg/m² basis, the highest recommended oral pediatric dosages". Lower dosages were not studied.

The ramipril label notes that "irreversible kidney damage has been observed in very young rats given a single dose of ramipril". A single dose.

On lactation, the data is thin. The lisinopril label states: "It is not known whether this drug is excreted in human milk." Milk of lactating rats contained radioactivity after labelled lisinopril was administered. The quinapril label is more direct: "ACCUPRIL is secreted in human milk." The enalapril label advises against breastfeeding. The other labels recommend caution or a decision between discontinuing nursing or discontinuing the drug.

> ASK YOUR DOCTOR
> *If I'm a woman of childbearing age, what's the plan for transitioning off this medication before or immediately upon discovering a pregnancy?*

The Tumour Findings in One Drug

Four of the five ACE inhibitors in this review showed no evidence of tumourigenic effects in animal carcinogenicity studies. Lisinopril: no tumourigenic effect in rats (105 weeks) or mice (92 weeks). Enalapril: no tumourigenic effect in rats (106 weeks) or mice (94 weeks). Ramipril: no tumourigenic effect in rats (24 months) or mice (18 months). Benazepril: no mutagenic activity detected; no adverse effect on reproductive performance.

The quinapril label is the outlier. While quinapril was not carcinogenic overall in mice or rats at doses up to 75 or 100 mg/kg/day, the label reports that "female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas".

Haemangiomas are vascular tumours. Lipomas are fatty tissue growths. The quinapril label does not offer an explanation for why these findings appeared in female rats on this drug and not in the carcinogenicity studies of the other four. The finding has not led to a contraindication or boxed warning, and the label classifies the drug as not carcinogenic. But the data is on the label. The other four drugs' labels do not report analogous findings.

> ASK YOUR DOCTOR
> *Are there reasons to prefer one ACE inhibitor over another based on the safety data in their labels?*

NSAIDs and the Interaction Most Patients Don't Know About

Every ACE inhibitor label warns about the interaction with NSAIDs — non-steroidal anti-inflammatory drugs, including over-the-counter medications like ibuprofen and naproxen, as well as prescription COX-2 inhibitors. The language is consistent across the class: in patients who are elderly, volume-depleted or have compromised renal function, combining NSAIDs with ACE inhibitors "may result in deterioration of renal function, including possible acute renal failure".

The labels describe a two-part problem. First, NSAIDs can damage the kidneys in the presence of ACE inhibition. Second, NSAIDs may reduce the blood-pressure-lowering effect of the ACE inhibitor — meaning the drug becomes less effective at its primary job while the combination becomes more dangerous to the kidneys.

The enalapril label includes clinical pharmacology data: a study in which indomethacin or sulindac was administered to hypertensive patients receiving enalapril found "no evidence of a blunting of the antihypertensive action". But the label immediately adds that "reports

suggest that NSAIDs may diminish the antihypertensive effect of ACE inhibitors".

The scale of this interaction is worth registering. ACE inhibitors are chronic daily medications. NSAIDs are available without a prescription — ibuprofen, naproxen — and taken routinely for headaches, arthritis, muscle pain, menstrual cramps. The labels say to monitor renal function periodically in patients taking both. Most patients taking an ACE inhibitor have never been told that their over-the-counter pain reliever may be undermining their blood pressure medication and damaging their kidneys simultaneously.

Other drug interactions flagged across the class include lithium (increased serum lithium levels and toxicity symptoms), potassium-sparing diuretics and potassium supplements (risk of hyperkalaemia), and injectable gold (nitritoid reactions — facial flushing, nausea, vomiting and hypotension). The lisinopril label adds an interaction with antidiabetic medications: concomitant use "may cause an increased blood-glucose-lowering effect with risk of hypoglycemia".

> ASK YOUR DOCTOR
> *Should I avoid over-the-counter NSAIDs like ibuprofen while on this medication, and if so, what should I use instead for pain relief?*

The Drugs Work Differently in Black Patients

All five labels state that ACE inhibitors, as monotherapy, have a smaller blood-pressure-lowering effect in Black patients than in non-Black patients. The phrasing varies slightly across labels — lisinopril's label says the drug "was less effective in reducing blood pressure in Blacks than in Caucasians" — but the clinical observation is universal to the class.

The ramipril label's hypertension section adds a comparison: "In both caucasians and blacks, hydrochlorothiazide (25 or 50 mg) was significantly more effective than ramipril." The quinapril label places its racial note directly in the indications section — not buried in pharmacology, but at the point of prescribing decision.

This is a pharmacological observation about differential drug response. The labels describe it but do not fully explain it. What they do make clear is that for Black patients prescribed an ACE inhibitor as the sole blood pressure medication, the expected therapeutic effect is smaller. The drug may not achieve the target blood pressure reduction, and additional medications may be needed sooner.

Combined with the higher angioedema risk in Black patients — a potentially fatal adverse reaction occurring more frequently in the population where the drug is simultaneously less effective — the risk-benefit calculation is different for Black patients than the labels' general

data would suggest.

> ASK YOUR DOCTOR
> *Given the data on differential effectiveness and angioedema risk, is an ACE inhibitor the best first-line choice for me specifically?*

The Rest of the Damage

The major warnings get their own sections in the label. The rest of the damage is scattered across adverse reaction tables, post-marketing reports and clinical laboratory findings. Read together, they describe what it means to inhibit ACE systemically — in every tissue, every organ — while treating one number on a blood pressure cuff.

Hypotension — the blood pressure dropping too far — is the most common problem in heart failure patients. The ramipril label reports it in 11% of patients in the AIRE mortality study (versus 5% on placebo). Lisinopril-treated patients with acute myocardial infarction had a 9.0% incidence of persistent hypotension — systolic below 90 mmHg for more than an hour — compared to 3.7% without the drug. A blood pressure medication that causes dangerously low blood pressure in nearly one in ten post-MI patients is worth understanding before the first dose.

The kidneys take damage too. Lisinopril patients in the GISSI-3 trial had 2.4% incidence of renal dysfunction compared to 1.1% on placebo. Across the class, blood urea nitrogen and creatinine increases occurred in about 2% of hypertensive patients, rising to 11.6% in heart failure patients on diuretics. The drugs prescribed to protect the cardiovascular system can, by their own labels' accounting, compromise the renal system — particularly in the sickest patients.

Hyperkalaemia — elevated potassium, which can cause fatal cardiac arrhythmias — occurred in 2.2% of hypertensive patients and 4.8% of heart failure patients on lisinopril. Ramipril reports approximately 1% of patients exceeding 5.7 mEq/L.

The liver carries its own risk. Every label describes a syndrome: cholestatic jaundice that progresses to fulminant hepatic necrosis and sometimes death. The language across all five labels is the same: “The mechanism of this syndrome is not understood.” After four decades, the labels cannot say why it happens, who is at risk, or how to prevent it.

Impotence appears in the ramipril adverse reactions (0.4% — among the most common reasons for discontinuation), the benazepril label and the lisinopril label. The lisinopril label also lists diabetes mellitus and inappropriate antidiuretic hormone secretion. The ramipril label adds post-marketing reports of hypoglycaemia in patients on oral antidiabetics or insulin.

Skin reactions run from rash and photosensitivity across the class to Stevens-Johnson syndrome and toxic epidermal necrolysis on the ramipril and benazepril labels. Small decreases in haemoglobin and haematocrit occurred “frequently” on lisinopril, though the label adds these “were rarely of clinical importance in patients without some other cause of anemia”. The significance in patients with anaemia is not addressed.

> ASK YOUR DOCTOR
> *How often should my kidney function, potassium levels and liver enzymes be monitored while I'm on this medication?*

What the Labels Admit Has Never Been Studied

Read across five labels, the gaps form a pattern — not of isolated omissions, but of a class of drugs where the boundaries of knowledge were drawn early and never pushed outward.

Whether bradykinin contributes to the therapeutic effect: not determined. Whether quinapril reduces mortality in heart failure: not evaluated. Whether ramipril works equally across ethnic subgroups: insufficient data, even from a 9,297-patient trial. Whether lisinopril is excreted in human milk: not known. Whether lower dosages of enalapril still produce irreversible renal toxicity in developing kidneys: not studied. Whether quinapril carries the same agranulocytosis risk as captopril: the label states that “available data from clinical trials of ACCUPRIL are insufficient to show that ACCUPRIL does not have a similar risk”. It does not resolve the question. It does not recommend further study. It presents the gap and moves on.

Paediatric safety and effectiveness have not been established for quinapril at any age, and for the other four, not in children under 6 or those with low glomerular filtration rates. Long-term cognitive effects of sustained ACE inhibition have not been studied for any drug in the class. The haemoglobin and haematocrit reductions on lisinopril — described as “frequent” — have not been characterised for clinical significance in patients who already have anaemia.

These are not accusations of negligence. They are the labels' own accounting of what was never tested, never measured, never followed up on. For drugs taken daily by tens of millions of people, for decades.

Questions to Take to Your Doctor

1. Does the specific ACE inhibitor I'm taking have evidence of reducing death, or is it approved only for lowering blood pressure numbers?

2. Am I aware of the signs of angioedema — including sudden abdominal pain — and do I know to seek emergency treatment immediately?
3. Has anyone discussed the higher rate of angioedema and the lower blood pressure response in Black patients, and how that affects my specific risk-benefit profile?
4. Should I avoid over-the-counter NSAIDs (ibuprofen, naproxen) while on this medication?
5. How often should my kidney function and potassium levels be checked?
6. If I develop a persistent dry cough, how quickly should we reconsider this medication?
7. Should I be monitoring for mood changes, confusion or memory issues?
8. If I'm a woman of childbearing age, what is the specific plan for stopping this drug before or at the earliest detection of pregnancy?
9. Am I taking any other medications that raise potassium — including potassium supplements or salt substitutes?
10. Has my liver function been tested, and should it be monitored periodically?
11. Are there reasons to prefer one ACE inhibitor over another based on the safety and outcomes data in their labels?
12. Is the dose I'm on actually controlling my blood pressure through the full 24-hour dosing interval, or has trough effectiveness been assessed?

> ### Disclaimer
> This article is not medical advice. It is a reading of publicly available FDA-approved prescribing information. The purpose is to help readers understand what the labels say and to ask better questions of the physicians who prescribe these medications. No one should start, stop or change any medication based on this article without consulting their doctor.

Sources

- Lisinopril: Zestril prescribing information, AstraZeneca Pharmaceuticals LP (Reference ID: 3678295)
- Enalapril: Enalapril Maleate Oral Solution prescribing information, Bionpharma Inc. (NDA 69452-237), revised July 2024
- Ramipril: Ramipril Capsules prescribing information (NDA 71335-1056/57237-223), revised May 2024; Altace prescribing information (NDA 022021), revised December 2011
- Benazepril: Lotensin prescribing information, Validus Pharmaceuticals LLC (NDA 30698), revised January 2019
- Quinapril: Accupril prescribing information, Pfizer (NDA 019885), revised September 2013

All labels available at FDA.gov/drugsatfda.