From the Mouths of Snakes: ACE Inhibitors

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Arthur E. Schwarting Symposium

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Learning Objectives

01 Review pharmacological hypertension management history and ACE inhibitor discovery

02 Analyze ACE inhibitor mechanism of action and hypertension pathophysiology

03 Investigate approved and off-label uses of ACE inhibitors

04 Characterize ongoing ACE inhibitor research and potential benefits and uses

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Disclosure

Aleksandra Bieniek and Jeannette Wick have no relationships with ineligible companies.

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Off-Label Disclosure

Off-label discussion statement:
"This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of (insert organization) or University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings."

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ACE Inhibitors

- Among most frequently prescribed medication classes
- Study continues in various diseases despite being developed in the mid-20th Century

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Table 1. Total ACE Inhibitor Prescriptions

Drug	Total Prescriptions
Lisinopril	97,608,879
Benazepril	5,920,053
Enalapril	5,182,854
Ramipril	3,989,667
Quinapril	1,012,588

Kane SP. ACE Inhibitors, ClinCalc DrugStats Database. https://clincalc.com/DrugStats/Drugs/TC/AngiotensinConvertingEnzymeACEInhibitors. Updated Sep. 15, 2021.

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Approved and Off-Label Uses

Approved Indications

- Hypertension
- Heart failure
- Myocardial infarction
- Renal Disease

Off-Label Uses

- Autoimmune disorders
- Migraine prophylaxis
- Sarcopenia
- Oligospermia

Dalpoas SE, Samal L. ACE inhibitors. *Johns Hopkins Diabetes Guide*. 2017. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_Diabetes_Guide/

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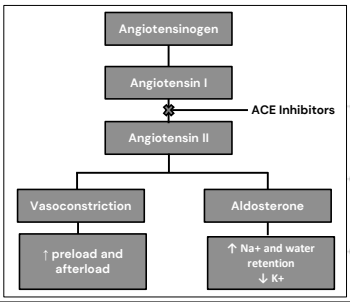
Mechanism of Action



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Hypertension History

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Hard Pulse Disease

- Ancient civilizations associated arterial pulses with the heart's function
  - "Hard pulse disease"
  - Treatments: blood letting or leeches
- Endorsed by The Yellow Emperor of China, Cornelius Celsus, Galen, and Hippocrates

Albinali HH. 4,500-Year voyage: From pulse tension to hypertension. *Heart Views*. 2005;6(3):124-133.

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Hypertension History

- Today, hypertension is easily diagnosed and treated
- In the early 20th Century, treating elevated blood pressures was controversial

Kotchen TA. 2011;58(4):522-538.

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"Hypertension may be an important compensatory mechanism which should not be tampered with, even were it certain that we could control."

- Cardiologist Dr. Paul Dudley White, 1931

Kotchen TA. 2011;58(4):522-538.

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Growing Concern

- In the 1950s, American insurance companies compiled actuarial data about hypertension
  - Associated ↑ blood pressure with ↑ cardiovascular and renal disease mortality
- Framingham Heart Study and other longitudinal epidemiologic studies yielded similar conclusions
  - Advocated for therapeutic interventions

Harold JG. Harold on History: Historical Perspectives on Hypertension. American College of Cardiology. http://www.acc.org/latest-in-cardiology/articles/2017/11/14/14/42/harold-on-history-historical-perspectives-on-hypertension. Published November 20, 2017

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Growing Concern

- President Franklin D. Roosevelt's death in 1945 showed the dangers of untreated hypertension
- "Appeared to be have had signs of 'hardening of the arteries disease' and had a few months to live."
- Blood pressure measured 300/190 mmHg on the morning of his death

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20th Century Treatments

- Limited hypertension treatment available until the 1960s
  - Often for only severe malignant hypertension
- Sodium-restriction
- Pyrogen injections and surgical interventions

Kotchen TA.. *Hypertension*. 2011;58(4):522-538.

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Table 2. Antihypertensive Medications in the Early 20th Century

Drug Class	Time Period
Veratrum Alkaloids	1930s
Ganglion Blocking Agents	1940s
Catecholamine Depletors	1940s
Vasodilators	1950s
Central Sympathetic Inhibitors	1950s

Moser M. *J Clin Hypertens (Greenwich)*. 2006;8(8 Suppl 2):15-39.

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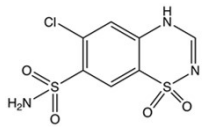
A Major Breakthrough



- Oral diuretics revolutionized hypertension management in the 1950s
  - Safe, effective, well-tolerated
- Chlorothiazide - the first diuretic
- Hypertension management continued to become a growing public health initiative

Harold JG. Harold on History: Historical Perspectives on Hypertension. American College of Cardiology. http://www.acc.org/latest-in-cardiology/articles/2017/11/14/14/42/harold-on-history-historical-perspectives-on-hypertension. Published November 20, 2017

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Question

ACE inhibitors work by blocking the conversion of:

a. Angiotensin I to angiotensin II
b. Angiotensin II to angiotensin I
c. Renin to angiotensin I

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Vipers, Venom, and Vasodilation

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The Drug Discovery Process

- Significant advances over time
- Natural products remain essential in lead compound identification
  - About 50% of approved drugs were linked to natural products in 2012
- Captopril, the first ACE inhibitor, is an example

Veeresham C. *J Adv Pharm Technol Res*. 2012;3(4):200-201.

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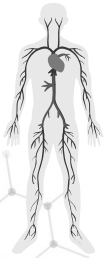
Hypertension Pathophysiology



- Contributing research leading to the discovery of the first ACE inhibitor began as early as 1898
- Understanding the renin-angiotensin-aldosterone (RAAS) system, a collaborative effort between many researchers

Opie LH, Kowolik H. 1995;30(1):18-25.

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Table 3. Timeline of Essential Events in ACE Inhibitor Discovery	
1898	Roger Tigerstedt and Per Bergman discover the enzyme renin, observing its ability to increase blood pressure
1934	Harry Goldblatt proposes that decreased blood flow in the kidneys causes renal hypertension
1940	Separate American and Argentinian research groups simultaneously identify the pressor substance that increases blood pressure in response to renin. They agree to name the potent vasoconstrictor "angiotensin," combining the separate names each group originally created: "angiotonin" and "hypertensin"
1954	Leonard T. Skeggs Jr. and colleagues discover that angiotensin is present in two forms. A plasma enzyme converted angiotensin I to the angiotensin II, which was the vascular and smooth muscle constrictor. The plasma enzyme was simply named the "angiotensin converting enzyme," now commonly termed "ACE"

Opie LH, Kowolik H. 1995;30(1):18-25.

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Viper's Venom

- Brazilian physician and pharmacologist Sérgio Henrique Ferreira was fascinated by the Brazilian pit viper's venom
- Exposure caused victims to become incapacitated and blood pressure to plumet
- Ferreira extracted the bradykinin potentiating factor (BPF) from the venom and brought it to pharmacologist John Vane

Smith CG, Vane JR. *FASEB Journal*. 2003;17(8):788-789.

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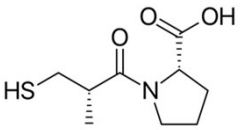
An Unlikely Source

- In 1975, an analog of a viper's venom peptide, captopril, became the first ACE inhibitor
  - Created by E.R. Squibb & Sons Pharmaceuticals (now Bristol-Meyers Squibb)
- By 1980, the FDA approved captopril for medical use



Opie LH, Kowolik H. 1995;30(1):18–25.

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Captopril Shortcomings

Adverse Drug Reactions	Limitations
Cough	Short half-life
Angioedema	Frequent dosing
Hyperkalemia	Sulfa allergies

Li JJ. *Drug Discovery*. 2013:1–42.

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Continuous Improvement

- Merck & Co. synthesized enalaprilat, seeking to overcome captopril's shortcomings
  - Poor oral bioavailability limited use to IV only
- Merck later developed enalapril and granted rights to Zeneca (now Astrazenca) to co-market lisinopril

Li JJ. *Drug Discovery*. 2013:1–42.

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Meet the Family

Benazepril	Captopril	Enalapril Enalaprilat
Lisinopril	Moexipril	Perindopril
Quinapril	Ramipril	Trandolpril

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Cornerstone Antihypertensives

- ACE inhibitors are a first-line treatment therapy for most patients for with hypertension
  - No clinically meaningful difference between the different drugs
- Choice depends on extraneous factors
  - Cost
  - Availability
  - Co-morbid condition
  - Dosing frequency
  - Metabolism

Elsevier Inc. Angiotensin-Converting Enzyme (ACE) Inhibitors. Clinical Pharmacology. https://www.elsevier.com/__data/assets/pdf_file/0010/1140220/Drug-Class-Overviews_-Angiotensin-Converting-Enzyme-ACE-Inhibitors-Clinical-Pharmacology.pdf. Published 2021

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Beyond Hypertension

- Additional FDA-approved indications for, among others
  - Acute coronary syndrome
  - Cardiovascular mortality reduction
  - Diabetic neuropathy
  - Heart Failure
  - Hypertensive emergencies
  - MI and/or stroke prophylaxis
  - Chronic kidney disease

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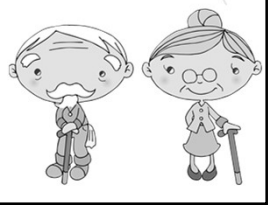
Target Population

- Hypertension prevalence increases with age
- Many elderly patients have other comorbid conditions
  - Diabetes, heart failure, renal failure, and vascular disease



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ACE Inhibitor Patients

- ACE inhibitors are valuable treatment options
  - Renoprotective and cardioprotective effects
  - Low adverse drug reaction profile
  - Uncommon CNS effects and/or orthostatic hypotension incidence

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Absolute Contraindications

Pregnancy	Angioedema/ Hypersensitivity
Drugs that affect the RAAS are fetotoxic (especially in the 2nd and 3rd trimesters)	ACE inhibitor hypersensitivity or ACE inhibitor-induced, hereditary, or idiopathic angioedema

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Table 4. ACE Inhibitor Special Considerations

Renal Function	Potential increase potassium, serum creatinine, and blood urea nitrogen and decrease in renal function
Hepatic Impairment	Potentially decreased drug clearance and efficacy
Hypotension	Especially in patients with heart failure, prolonged diuretic therapy, and hypovolemia
Hyperkalemia	Potassium level abnormalities should be treated before starting therapy and monitored closely
Bone Marrow Suppression	Potential anemia, neutropenia, and/or agranulocytosis

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Table 5. ACE Inhibitor Side Effects

Adverse Reaction	Incidence
Dry cough	10% – 20%
Dizziness	12% – 19%
Hypotension	7% – 11%
Nephrotoxicity and increases in serum creatinine	2% - 11%
Syncope	5% – 7%
Hyperkalemia	2% – 6%

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Post-Market Adverse Drug Reactions

- Cardiac arrest
- Hepatic necrosis
- Hyponatremia
- Pulmonary embolism
- Systemic lupus erythematous
- Steven-Johnson Syndrome
- Transient Ischemic Attack

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Table 6. Signifiant ACE Inhibitor Drug Interactions

Drug(s)	Effect(s)	Recommendation
Aliskiren	Increased non-fatal stroke, renal complications, hyperkalemia, and hypotension risk	Avoid in patients with comorbid diabetes or renal impairment
Angiotensin Receptor Blockers (ARBs)	Increased toxicity and adverse effects	Avoid drug combination
Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)	Increased angioedema, hypotension, AKI, and hyperkalemia risk	Avoid drug combination; wait 36 hours before after discontinuing ACE inhibitors
Antipsychotics	Increased hypotension risk	Monitor blood pressure
Azathioprine	Increased myelosuppressive effects	Monitor for myelosuppression
Lithium	Increased serum lithium concentrations and lithium toxicity (ataxia, confusion, tremor)	Decrease lithium dose and monitor serum concentrations for 4-6 weeks following ACE inhibitor treatment changes
Nonsteroidal Anti-Inflammatory Agents (NSAIDs)	Increased NSAID adverse effects, decreased renal function and ACE inhibitor efficacy	Avoid drug combination if feasible; monitor renal function, adverse effects, and blood pressure
Potassium-sparing diuretics and potassium supplements	Increased hyperkalemia risk	Closely monitor serum potassium, especially in renal impairment

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Question

Which of the following characteristics was a limitation of captopril?

a. Hypotension
b. Acute kidney injury
c. Frequent dosing

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Off-Label Uses

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Repurposing ACE Inhibitors

- Off-label use has extended ACE inhibitor utility
- While target indications may have other preferred treatments, ACE inhibitors may be valuable second- or third-line options for refractory cases

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Captopril and Raynaud's Phenomenon

- Raynaud's syndrome (or Raynaud's phenomenon) - ↓ blood flow resulting from arterial vasospasms
  - No cure
- Treatment includes lifestyle changes, medication, and potentially surgery
- Captopril may be potentially benefit patients with Raynaud's
  - Evidence is scare and requires more research, a large population, and a longer observation period

Shinn BW. The Description and Treatment of Raynaud's Disease/Phenomenon. U.S. Pharmacist. Published April 18, 2008.

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ACE Inhibitors and Sarcopenia

- Sarcopenia - skeletal muscle loss resulting in ↓ muscle mass and function
- Primarily affects elderly patients and may cause physical disability, increased fall risk, and even death
- Single cause is unknown but chronic inflammation may be a contributing factor

Caulfield L, et al. J Am Med Dir Assoc. 2021;22(6):1215-1221.e2

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ACE Inhibitors and Sarcopenia

- Angiotensin II promotes inflammation and decreases skeletal muscle structure and function
  - Thus, ACE inhibitors may be beneficial
- Research has yielded mixed results with no definite consensus

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ACE Inhibitors and Oligospermia

- Abnormal ACE expression may contribute to both male and female infertility
- Difference ACEs involved in
  - Ovulation
  - Follicle development
  - Steroidogenesis
  - Sperm cell function
- One crossover randomized control trial found lisinopril increased total sperm cell count and sperm motility in 53.6% of participants

Mbah AU, et al. Clin Pharmacol Ther 2012; 91:582–589

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ACE Inhibitors and COVID-19

- Interested spiked when COVID-19 was revealed to enter the cell via the ACE2 receptor
  - Concern if ACE inhibitors worsened or increased infection risk
- Research found ACE inhibitor use during COVID infection was NOT harmful
  - Patients should continue to take ACE inhibitors or ARBs regardless if COVID+

Davidson AM, et al. Hypertension. 2020;76(5):1339-1349.

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Future and Current Research

- Investigated if ARBs or ACE inhibitors use after pancreatic cancer diagnosis impacted survival
  - Angiotensin inhibition potentially associated with lower cancer incidence
- ACEs and ARBs were significantly associated with improved prognosis
  - 20% (ARBs) and 13% (ACEIs) mortality risk reduction

Keith SW, et al. BMC Cancer 2022;22:150.

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Future and Current Research

- ACEIs may ↑ endogenous opioid effects in the brain
- Potential strategy to boost opioid signaling leading to protective and beneficial effects and ↓ dependence risk
- Further research neede to explore ACE inhibitor potential in brain conditions

Trieu BH, et al. 2022;375(6585):1177-1182.

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Question

What is the rationale behind using ACE inhibitors for sarcopenia?

a. Increased vasodilation may alleviate skeletal muscle symptoms
b. Decreased angiotensin II may help reduce inflammation
c. ACE inhibition may prevent skeletal muscle loss

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Summary

- Since the beginning of the 20th Century, understanding of hypertension has developed tremendously
- As a drug class, ACE inhibitors have stood the test of time and remain a first-line treatment for hypertension and other cardiorenal illnesses
- Today, ACE inhibitor research continues to seek new potential benefits and effects in patients with a variety of different conditions

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SESSION CODE

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