WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

CAPTOPRIL IN HYPERTENSION MANAGEMENT; A COMPARATIVE STUDY WITH ACE INHIBITOR

MS. MARIYAMMATH RAFEEQA K.A[1], MUHAMMED JAVED AKTHAR[2]

MALIK DEENAR COLLEGE OF PHARMACY, SEETHANGOLI

ABSTRACT :

Hypertension is a chronic condition marked by elevated blood pressure, increasing the risk of heart, kidney, and vascular diseases. It may be primary or secondary in origin. Diagnosis involves repeated BP measurements and lab tests.

Captopril, an ACE inhibitor, lowers blood pressure by blocking the conversion of angiotensin I to angiotensin II, causing vasodilation. It has a short half-life, requiring multiple daily doses.

- SAR: Sulfhydryl group binds to ACE; proline enhances activity.
- MOA: Inhibits ACE, reducing vasoconstriction and aldosterone.
- Physicochemical properties: Soluble in water, MW 217.29, pKa ~3.7.
- Assay: HPLC, UV, or titration methods.

INTRODUCTION

A serious and rapidly expanding health issue worldwide is hypertension (HTN), which is defined as systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg. Nearly two-thirds of persons 60 years of age or older are affected, making it the most prevalent risk factor for cardiovascular disease. Uncontrolled hypertension is thought to be the cause of 7.5 million deaths annually worldwide and causes over 47 billion dollars in medical expenses, prescription drug costs, and lost productivity in the United States alone.

TYPES OF HYPERTENSIONS

- **Primary Hypertension** is also known as essential or idiopathic hypertension. Constitutes more than 90-95 percent of all cases of hypertension.
- The etiology of primary hypertension is multifactoral, a number of homeostatic forces are involved
- Characteristics include either a gradual onset or prolonged course (benign hypertension) or an abrupt onset and a short dramatic course that proves rapidly fatal without swift intervention (malignant or accelerated hypertension)
- **Secondary hypertension** results from an identifiable cause
- A variety of specific disease states or problems are responsible. 5-10 percent of hypertensive population has secondary hypertension

OTHERS TYPE OF HYPERTENSION

- **Borderline hypertension:** Borderline or liable hypertension is defined as intermittent elevation of blood pressure interspersed with normal readings.
- Clients with borderline hypertension still carry an increased risk of developing cardiovascular disease
- **Benign hypertension:** benign hypertension is a term used to describe uncomplicated hypertension, usually of long duration and mild to moderate severity
- Benign hypertension may be primary or secondary
- **Malignant hypertension:** Malignant hypertension is a syndrome of elevated BP (diastolic BP over 140mm HG) assocaiated with papilledema.
- Accelerated hypertension presumably develops into malignant hypertension if not well managed.
- **Isolated systolic hypertension:** is defined as systolic blood pressure above 140 mm Hg and diastolic blood pressure under 90 mm Hg. It's the most frequent type of hypertension in older adults an estimated 15 % of people 60 years or older have isolated systolic hypertension. The cause is thought to be the stiffening of arteries with age.

SIGNS AND SYMPTOMS

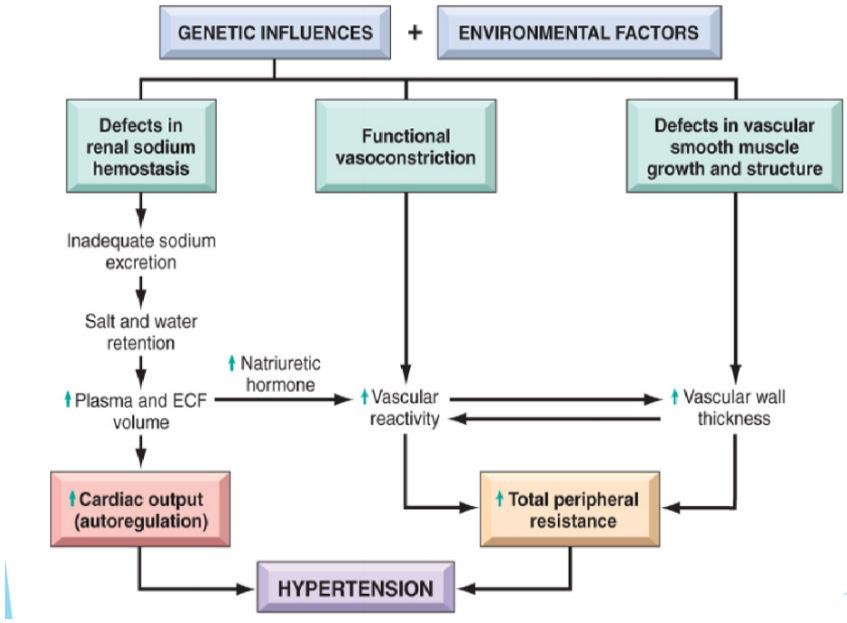
- **Headaches:** Especially severe headaches in the morning upon waking.
- **Nosebleeds:** Sudden and unexplained nosebleeds.
- **Blurred vision:** Changes in vision, like blurry or double vision.
- **Dizziness:** Feeling lightheaded or faint.

Risk Factors:

- Age: The risk of hypertension increases with age.
- Family History: A strong family history of hypertension increases your likelihood of developing it.
- Obesity: Being overweight or obese significantly increases blood pressure.
- Excessive Alcohol Consumption: Drinking too much alcohol can raise blood pressure.
- Medical Conditions: Certain medical conditions, such as chronic kidney disease, metabolic syndrome, sleep apnea, and thyroid problems, can also increase the risk of hypertension.
- Smoking: Smoking both directly increases blood pressure and damages blood vessel walls.

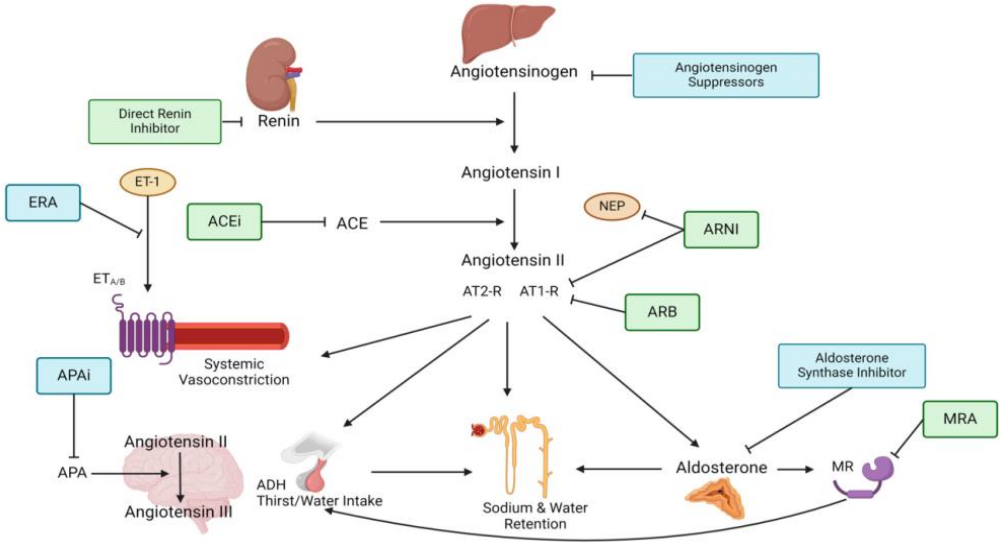
PATHOPHYSIOLOGY

Many different conditions or situations can normally raise blood pressure like physical activity or stressful condition. This temporary increase in blood pressure is not considered as hypertension. A diagnosis of hypertension is made only when a person has multiple high blood pressure readings over a period of time.Hypertension with known cause is called primary hypertension and when hypertension is caused by medical condition, it is called secondary hypertension. Secondary hypertension is also cause of different illness like kidney disorders. Cushing's syndrome and tumors of the pituitary and adrenal glands often increase the levels of the adrenal gland hormones like cortisol, adrenalin, and aldosterone, which are also cause of hypertension. Other conditions like blood vessel disease, thyroid gland disorders, some prescribed drugs, alcoholism, and pregnancy are also the cause of hypertension.There are many risk factors which lead to the development of hypertension which includes: above 60 years of age, sex, race, heredity, salt sensitivity consumption and use of oral contraceptives.



RENIN- ANGIOTENSIN ALDOSTERONE SYSTEM [RAAS] ACTIVATION

The RAAS is a hormonal system that helps regulate blood pressure, fluid balance, and electrolyte homeostasis. In hypertension, the RAAS becomes overactive, leading to increased production of angiotensin II, which causes blood vessel constriction and sodium reabsorption by the kidneys, both of which contribute to elevated blood pressure.



Renin release: Renin is an enzyme produced by the kidneys that cleaves angiotensinogen into angiotensin I. Factors that can stimulate renin release include decreased blood flow to the kidneys, decreased blood pressure, and increased sympathetic nervous system activity.

Angiotensin I conversion to angiotensin II: Angiotensin I is a relatively inactive molecule. However, it is converted to the much more potent angiotensin II by angiotensin-converting enzyme (ACE).

Angiotensin II effects: Angiotensin II has several effects that contribute to hypertension, including:

1.Vasoconstriction: Angiotensin II causes blood vessels to constrict, which increases blood pressure.

2. Aldosterone release: Angiotensin II stimulates the release of aldosterone from the adrenal glands. Aldosterone promotes sodium and water reabsorption by the kidneys, which increases blood volume and blood pressure.

3. Cell growth and inflammation: Angiotensin II can also promote cell growth and inflammation in the blood vessels, which can further contribute to hypertension.

NATRIURETIC HORMONE

- Natriuretic hormone inhibit sodium potassium-ATPase thus interferes sodium transport across cell membranes
- Inherited defects in the kidney's ability to eliminate sodium can cause increased blood volume
- A compensatory increase in the concentration of circulating natriuretic hormone theoretically could increase urinary excretion of sodium and water
- However, this hormone might block the active transport of sodium out of arteriolar smooth muscle cells. The increased intracellular sodium concentration ultimately would increase vascular tone and BP

THE BARORECEPTOR REFLEX SYSTEM

- Baroreceptors are nerve endings lying in the end of large arteries, especially in the carotid arteries and aortic arch
- Changes in the arterial BP rapidly activate baroreceptors that then transmit impulse to the brain system through ninth cranial nerve and vagus nerve.
- In this reflex system, a decrease in the arterial BP stimulates baroreceptors, causing reflex vasoconstriction and increased heart rate and force of cardiac contraction. This baroreceptor reflex mechanism may less responsive in elderly and those with diabetes.

VASCULAR ENDOTHELIAL MECHANISMS

Vascular endothelium and smooth muscle: The play an important role in regulating blood vessel tone and BP.

- These regulating functions are mediated by vasoactive substances that are synthesized by endothelial cells.
- It has been postulated that the deficiency in local synthesis of vasodialingsubstances [eg: prostacyclin, bradykinin] or excess vasoconstricting substances [eg: angiotensin II, endothelin I] contributes to essential hypertension.
- Nitric oxide is produced in the endothelium, relaxes the vascular epithelium, and is a very potent vasodialator. Patients with hypertension may have intrinsic nitric oxide deficiency, resulting in inadequate vasodialtion.

DIAGNOSIS

BLOOD PRESSURE MEASUREMENT

The cornerstone of diagnosing hypertension is accurate and reliable blood pressure measurement**.** Blood pressure measurement is the cornerstone of diagnosing and managing hypertension (high blood pressure). It's a simple yet essential procedure that involves taking an accurate reading of the force exerted by your blood against the walls of your arteries. Here's a breakdown of the key points involved.

Techniques:

- **Manual auscultation:** This traditional method uses a stethoscope to listen for the Korotkoff sounds, which are tapping sounds that occur as blood flow resumes through an inflated cuff placed on your upper arm. These sounds disappear when the cuff pressure exceeds your systolic pressure (peak pressure) and reappear faintly when it falls below your diastolic pressure (minimum pressure). A trained healthcare professional performs this method.
- **Automated devices:** devices this electronic offers a quick and convenient way to measure blood pressure. However, it's crucial to ensure their accuracy is validated against manual methods.
- **Ensuring Accuracy:** Several factors influence the accuracy of blood pressure readings:
  - **Cuff size**: The cuff should be snug but not constricting, fitting comfortably around your upper arm. A cuff that's too small will give falsely high readings, while one that's too large will give falsely low readings.
  - **Arm positioning**: Your arm should be raised and supported at heart level during measurement. This ensures proper blood flow through the brachial artery where the pressure is being measured.
  - **Multiple readings**: It's recommended to take multiple readings at different times during a clinic visit or at home. This helps account for natural fluctuations in blood pressure throughout the day.

HOME VS. CLINIC MEASUREMENT:

- **Clinic monitoring:** Provides a standardized environment for blood pressure measurement. However, some people experience "white coat hypertension," where their blood pressure rises due to anxiety in a clinical setting.
- **Home monitoring:** Allows for more frequent measurements throughout the day, capturing a more complete picture of your blood pressure pattern. However, proper technique is crucial for accurate home readings. [7]

TREATMENT

- Non-Pharmacological
- Pharmacological

NON-PHARMACOLOGICAL

Lifestyle Modifications

Lifestyle modifications are the first line of treatment for most people with hypertension

- **Healthy diet:** A diet low in sodium, saturated fat, and added sugars, and rich in fruits, vegetables, and whole grains can significantly lower blood pressure
- **Weight management:** Losing weight can help reduce blood pressure, especially in overweight or obese individuals.
- **Regular exercise:** Regular physical activity, such as aerobic exercise and strength training, can significantly lower blood pressure
- **Smoking cessation:** Smoking damages blood vessels and increases blood pressure. Quitting smoking is essential for managing hypertension
- **Alcohol moderation:** Excessive alcohol consumption can raise blood pressure. Limiting alcohol intake can help lower blood pressure.
- **Stress management:** Chronic stress can contribute to high blood pressure. Relaxation techniques such as meditation or yoga can help manage stress and lower blood pressure.[8]

PHARMACOLOGICAL

MEDICATIONS

Medications are often needed in addition to lifestyle modifications to control blood pressure. Several classes of medications are used to treat hypertension, each working through different mechanisms.Thiazide diuretics have been proven to be efficient in achieving blood pressure control and preventing the cardiovascular complications of hypertension with few side effects. They also enhance the antihypertensive efficacy of multiple drug regimens. Because

of this, they are used as initial therapy for most patients with hypertension, either alone or in combination with one of the other classes which have been demonstrated to be beneficial in randomized controlled outcome trials. Other more potent loop diuretics such as furosemide, bumetanide have few advantages over thiazide except in patients with renal impairment. If a drug is not tolerated or is contraindicated, then one of the other classes proven to reduce cardiovascular events should be used instead. The other classes of antihypertensive drugs include angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers (BB), calcium channel blockers (CCB), aldosterone antagonists (ALDO ANT) should especially be used for the treatment of hypertension

CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS

SL.NO	**CLASS**	**DRUGS**
1	THIAZIDE DIURETICS	• CHLORTHIAZIDE • CHLORTHALIDONE • HYDROCHLORTHIAZIDE
2	LOOP DIURETICS	• FUROSEMIDE • TORSEMIDE • BUMETANIDE
3	POTASSIUM SPAIRING DIURETICS	• AMILORIDE • TRIAMTERINE
4	ALDOSTERONE RECEPTOR BLOCKERS	• EPLERENONE • SPIRONOLACTONE
5	BETA-BLOCKERS	• ATENOLOL • METOPROLOL • PROPRANOLOL • TIMOLOL • BISOPROLOL
6	COMBINED ALPHA AND BETA BLOCKERS	• CARVEDILOL • LABETALOL
7	ACE INHIBITORS	• CAPTOPRIL • ENALAPRIL • LISINOPRIL
8	ANGIOTENSIN II ANTAGONISTS	• TELMISARTAN • CANDESARTAN • LOSARTAN • OLMESARTAN • VALSARTAN
9	CALCIUM CHANNEL BLOCKERS	• DILTIAZEM • VERAPAMIL • NIFEDIPINE • AMLODIPINE • NISOLDIPINE
10	$ALPHA_1$ BLOCKERS	• PRAZOSIN • TERAZOSIN • DOXAZOSIN
11	CENTRALLY ACTING DRUGS	• CLONIDINE • METHYLDOPA

MECHANISM OF ACTION

DIURETICS

The initial diuresis lasts 4-6 weeks and then replaced by a decrease in PVR. E.g. thiazide diuretics lower BP initially by increasing sodium and water excretion. This causes a decrease in blood volume, resulting in a decrease in cardiac output and renal blood flow. With long-term treatment, plasma volume approaches a normal value, but a hypotensive effect persists that is related to a decrease in peripheral resistance by Na+ in vessel wall then Na+ - Ca++ exchange which Ca++ in smooth muscle wall.

ACE INHIBITORS

- The ACE inhibitors, are recommended as first-line treatment of hypertension in patients with a variety of compelling indications, including high coronary disease risk or history of diabetes, stroke, heart failure, myocardial infarction, or chronic kidney disease.
- ACE is also responsible for the breakdown of bradykinin, a peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators.
- ACE inhibitors decrease angiotensin II and increase bradykinin levels. Vasodilation is result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin).
- By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

ANGIOTENSIN ANTAGONIST (ARBS)

- Angiotensin antagonists: losartan, candesartan, valsartan, telmisartan, olmesartan.
- Their pharmacologic effects of ARBs are similar to those of ACE inhibitors.
- ARBs produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention.
- ARBs may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease. [10]

B-ADRENERGIC BLOCKERS

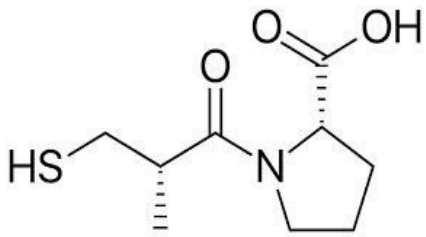
- β-adrenergic blockers are mild antihypertensives and do not significantly lower BP in normotensives. In stage 1 cases of hypertensive patients (30 - 40%), βadrenergic blockers are used alone.
- Propranolol is a first β blocker showed effective in hypertension and ischemic heart disease. • Propranolol has now been largely replaced by cardioselective β blockers such as metoprolol and atenolol.
- All β-adrenoceptor-blocking agents are useful for lowering blood pressure in mild to moderate hypertension.

A-ADRENERGIC BLOCKERS

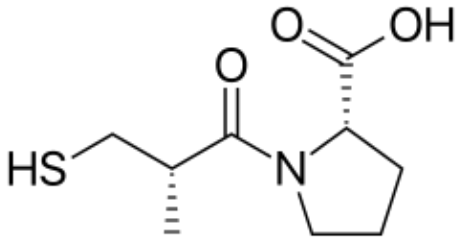
- Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels.
- Prazosin is a prototype α1 -adrenergic blocking agent.
- Terazosin and doxazosin are long-acting congeners of prazosin.

CENTRALLY ACTING ADRENERGIC DRUGS

• Clonidine acts centrally as an α2 agonist to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure. At present, it is occasionally used in combination with a diuretic.
• Methyldopa is an α2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. It is mainly used for management of hypertension in pregnancy, where it has a record of safety.
Captopril is an ACE inhibitor used for the management of essential or renovascular hypertension, congestive heart failure, left ventricular dysfunction following myocardial infarction, and nephropathy.
Captopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII).



SAR OF CAPTOPRIL



Sulfhydryl (-SH) Group: This group binds directly to the zinc ion in the ACE active site, enhancing inhibitory potency.
However, it is also associated with side effects like skin rash and loss of taste due to its reactivity.

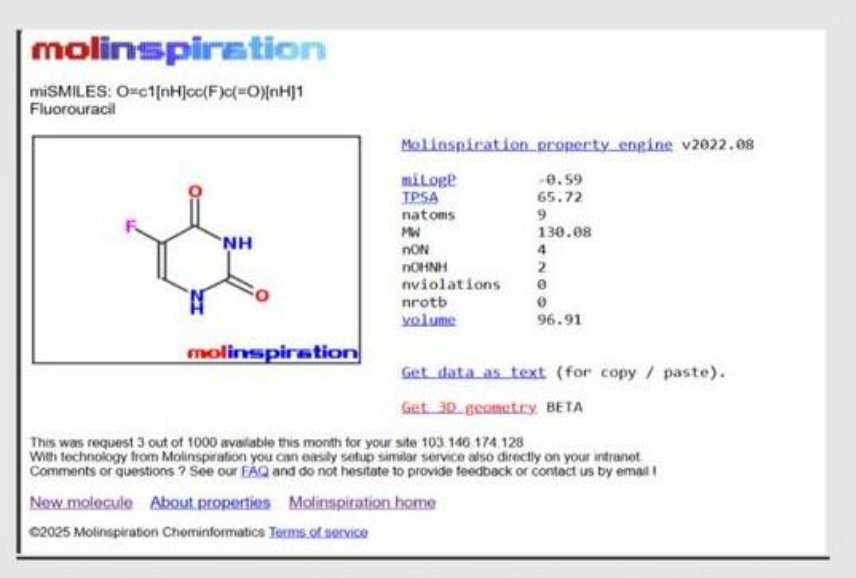
1. Proline Moiety: The L-proline component mimics the C-terminal amino acid of natural ACE substrates, aiding in binding specificity.
2. Amide Carbonyl Group: This group forms hydrogen bonds with ACE, stabilizing the inhibitor-enzyme complex.
3. Alkyl Side Chain: The 2-methyl group in the side chain enhances hydrophobic interactions within the ACE active site, increasing potency.

These structural elements collectively contribute to captopril's efficacy as an ACE inhibitor.

PHYSICOCHEMICAL PROPERTIES

MOLINSPIRATION-

Molinspiration offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructures and similarity searches. Molinspiration supports internet chemistry community by offering free online services for calculation of important molecular properties (logP, polar surface area, number of hydrogen bond donors and acceptors and others), as well as prediction of bioactivity score for the most important drug targets.



The physicochemical properties of 5-fulorouracil studied using molinspiration was found to be as-

PHYSICOCHEMICAL PROPERTY	VALUE
Mi LogP	-0.59
Number of Atoms	9
Molecular weight	130.8
Number of Hydrogen Atom Donors	4
Number of Hydrogen Atom Acceptors	2

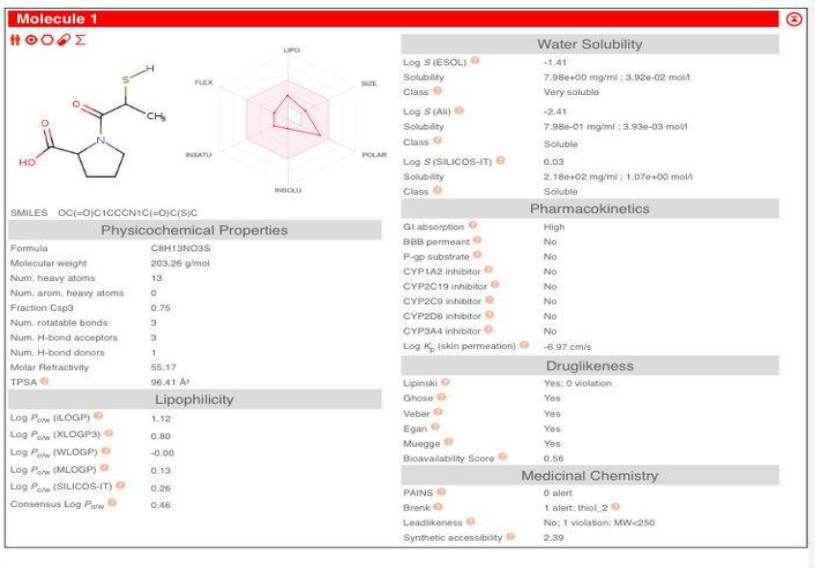
LIPINSKI'S RULE OF FIVE

Lipinski's rule of five, also known as Pfizer's rule of five or simply the rule of five (RO5), is a rule of thumb to evaluate druglikeness or determine if a chemical compound with a certain pharmacological or biological activity has chemical properties and physical properties that would likely make it an orally active drug in humans. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME"). However, the rule does not predict if a compound is pharmacologically active. Lipinski's rule states that, in general, an orally active drug has no more than one violation of the following criteria; • No more than 5 hydrogen bond donors (the total number of nitrogen hydrogen and oxygen–hydrogen bonds) • No more than 10 hydrogen bond acceptors (all nitrogen or oxygen atoms) • A molecular mass less than 500 daltons • A calculated octanol-water partition coefficient (log P) that does not exceed 5

Since all the above conditions are satisfied by captopril, it is considered to comply with Lipinski's Rule of Five.

ADMET Prediction:

Swiss ADME allows to compute physicochemical descriptors as well as predict pharmacokinetics properties and druglike nature of one or multiple small molecules. The absorption, distribution,metabolism and excretion of chloroquine was assessd using the Swiss ADME software.



Bioavailability Radar

Bioavailability Radar is displayed for a rapid appraisal of drug-likeness. Six physicochemical properties are taken into account: lipophilicity, size, polarity, solubility, flexibility and saturation. A physicochemical range on each axis was defined by descriptors and depicted as a pink area.

Physicochemical property

The physicochemical property of Captopril was analysed using SwissADME and was found to be;

PHYSICOCHEMICAL PROPERTY	**VALUE**
Molecular weight	203.26g/mol
Number of heavy atoms	13
Number of aromatic heavy atoms	0
Number of hydrogen bond donors	1
Number of hydrogen bond acceptors	3

Lipophilicity

The partition coefficient between n-octanol and water (log Po/w) is the classical descriptor for Lipophilicity. It has a dedicated section in Swiss ADME due to the critical importance of this physicochemical property for pharmacokinetics drug discovery. Swiss ADME give access to five freely available predictable models; which are XLOGP3, WLOGP, MLOGP, SILICOS-IT, iLOGP. The lipophilicity of Captopril was studied using Swiss ADME which determines the
solubility, the ability to penetrate through cell barriers, and transport across the membrane.

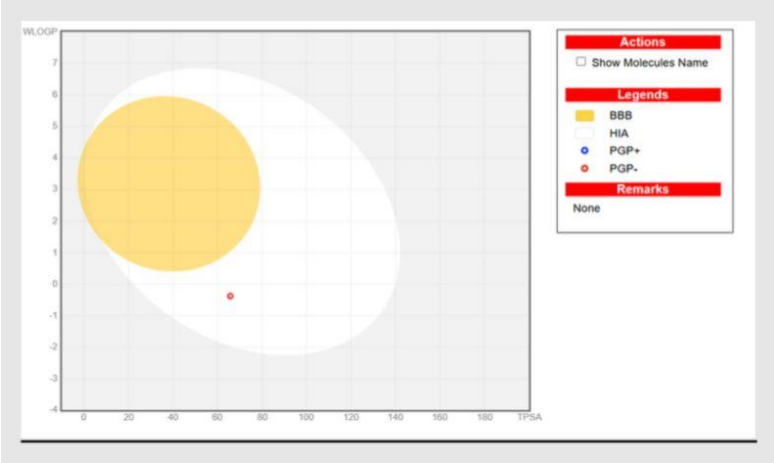
LIPOPHILICITY	VALUE
LogPo/w(ILOGP)	1.12
LogPo/w(XLOGP3)	0.80
LogPo/w(WLOGP)	-0.00
LogPo/w(MLOGP)	0.13
LogPo/w(SILICOS-IT)	0.26
ConsenusLogPo/w	0.46

Water solubility

soluble molecule greatly facilitates many drug development activities, primarily the ease of handling and formulation. Moreover, for discovery projects targeting oral administration, solubility is one major property influencing absorption. As well, a drug meant for parenteral usage has to be highly soluble in water to deliver a sufficient quantity of active ingredient in the small volume of such pharmaceutical dosage. Two topological methods to predict Water Solubility are included in Swiss ADME. The first one is an implementation of the ESOL model36 and the second one is adapted from Ali et al. The water solubility of Captopril was studied using Swiss ADME.

Pharmacokinetics

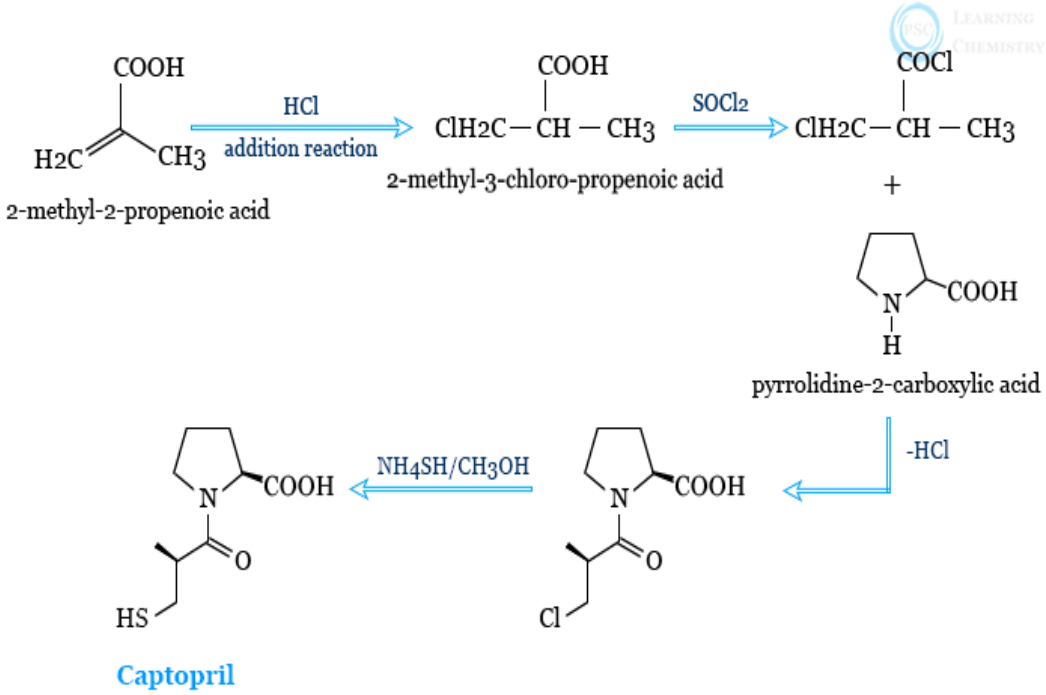
Pharmacokinetics is essential for the knowledge about interaction of molecules with cytochromes P450 (CYP). This superfamily of isoenzymes is a key player in drug elimination through metabolic biotransformation. The pharmacokinetics of Captopril was studied using Swiss ADME. study shows that Captopril is not an inhibitor of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4. Hence the drug do not possess any pharmacokinetics-related drug-drug interactions leading to toxic or other unwanted adverse effects due to the lower clearance and accumulation of the drug or its metabolites.



The boiled-egg allows for intuitive evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) in function of the position of the molecules in the WLOGP- versus-TPSA referential. In addition the points are coloured in blue if predicted as actively effluxed by P-gp (PGP+) and in red if predicted as non-substrate of P-gp (PGP−). In case Captopril is located in white region of boiled egg which shows that Captopril has high probability of passive absorption by the gastrointestinal tract. Captopril is not subject to active efflux by P-gp. (PGP+(red dot)).[71][72]

SYNTHESIS

The chemical synthesis of captopril drug from 2-methyl-propanoic acid and pyrrolidine-2-carboxylic acid is given below ;



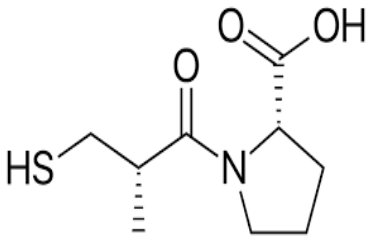
ASSAY

- **Weigh the Sample:**Accurately weigh about 0.15 g of captopril (equivalent to ~1 mmol).
- **Dissolve:**Dissolve the captopril in 50 mL of distilled water in an iodine flask or conical flask.
- **Add Starch Indicator:**Add 1 mL of freshly prepared starch solution.
- **Titrate:**Titrate with 0.05 N iodine solution from a burette.Swirl continuously during the titration.
- **Endpoint:** The first permanent blue color indicates the endpoint (excess iodine forms a blue complex with starch).

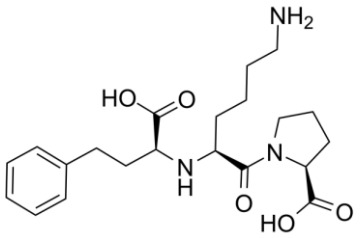
COMPARITIVE STUDY OF ACE INHIBITORS

STRUCTURAL COMPARISON
Mechanism of action &efficacy

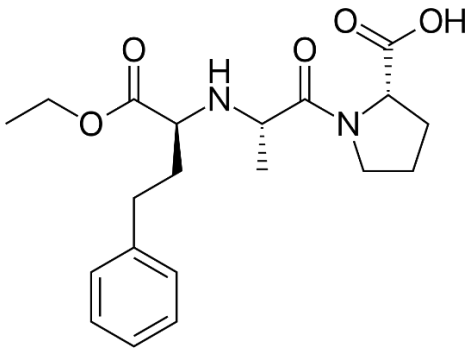
- **Captopril**: Not a prodrug; it is active in its administered form. It inhibits ACE and increases bradykinin levels, leading to vasodilation and blood pressure reduction.
- **Lisinopril**: Also not a prodrug; it is active in its administered form. Lisinopril works by inhibiting ACE, leading to decreased angiotensin II levels and increased bradykinin levels, resulting in vasodilation.
- **Enalapril**: A prodrug that is converted to its active form, **e**nalaprilat, in the body. Enalaprilat inhibits ACE, leading to decreased angiotensin II levels and increased bradykinin levels, contributing to blood pressure reduction.



Captopril



Lisinopril



Enalapril

COMPARITIVE SAR OF ACE INHIBITORS

1.Captopril

- *Structural Significance*:
  - *Thiol group (-SH)***:** Essential for binding to the zinc ion at the active site of ACE, enhancing inhibitory potency.
  - *Methyl group (-CH_3)***:** Modifies the acyl chain length, optimizing enzyme interaction.
  - *Proline ring*: Confers conformational rigidity, aiding in enzyme binding.
- *SAR Insights*:
  - The thiol group has a high affinity for the zinc ion in ACE, making captopril a potent inhibitor.
  - Methylation of the acyl chain improves binding affinity.
  - The proline ring maintains the correct orientation for enzyme interaction.
- *Clinical Implications*:
  - High potency but associated with side effects like a metallic taste due to the thiol group.

2. **Lisinopril**

- *Structural Significance*:
  - *Lysine residue*: Enhances solubility and oral bioavailability.
  - *Amide linkage*: Facilitates enzyme binding.
  - *Hydrophobic side chain*: Contributes to binding affinity.
- *SAR Insights*:
  - The lysine residue improves water solubility, aiding in oral administration.
  - The amide group and hydrophobic side chain enhance binding to ACE.

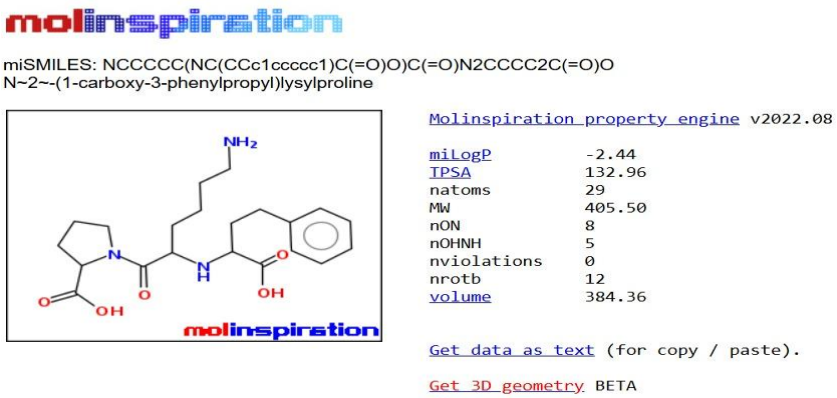
- *Clinical Implications*:
    - Suitable for patients with liver dysfunction as it is not metabolized hepatically.

Enalapril

- *Structural Significance*:
    - *Proline derivative*: Provides conformational rigidity.
    - *Diethyl ester group*: Enhances oral bioavailability.
    - *Amide group*: Facilitates ACE binding.
- *SAR Insights*:
    - The proline derivative maintains the correct orientation for enzyme interaction.
    - The ester group improves oral absorption.
- *Clinical Implications*:
    - Available in both oral and intravenous forms, providing flexibility in treatment administration.

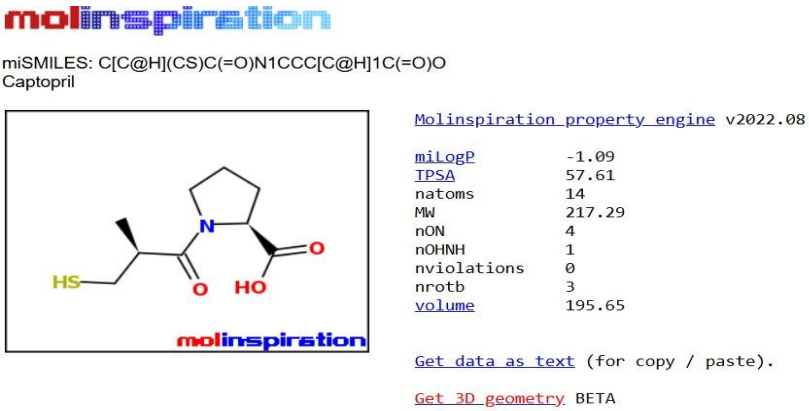
PHYSICOCHEMICAL PROPERTIES

Lisinopril



Enalapril

Captopril



ACE INHIBITORS DOSAGE FORM AVAILABILITY Vs. MARKET AVAILABILITY

Captopril

- *Dosage Forms*:
    - *Tablets*: 12.5 mg, 25 mg, 50 mg, and 100 mg

- *Capsules*: Less commonly available

- *Market Availability*:
  - Widely available as a *generic medication* globally, including in India.
  - Brand names include *Capoten* (original) and various generics.
  - Manufactured by companies such as *Hikma Pharmaceuticals***,** *Solco Healthcare*, and *Advacare Pharma***.**

Lisinopril

- *Dosage Forms*:
  - *Tablets*: 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg
  - *Oral Solution*: 1 mg/mL (e.g., *Qbrelis*)
  - *Combination Tablets*: Available in combinations with *amlodipine* (e.g., *Zestoretic***)** and *hydrochlorothiazide* (e.g., *Prinzide***)**
- *Market Availability*:
  - Approved by the *U.S. FDA* in 1987 and is available as a *generic medication* worldwide.
  - Brand names include *Zestril* and *Prinivil***.**
  - Manufactured by companies such as *AstraZeneca***,** *Lupin Pharmaceuticals***,** *Teva Pharmaceuticals*, and *Mylan*.
  - In India, lisinopril is available under various brand names and strengths.

Enalapril

- *Dosage Forms*:
  - *Tablets*: 2.5 mg, 5 mg, 10 mg, and 20 mg
  - *Injection*: Available as enalaprilat for intravenous use
  - *Combination Tablets*: Available in combinations with *hydrochlorothiazide* (e.g., *Vaseretic***)**
- *Market Availability*:
  - Approved by the *U.S. FDA* in 1984 and is available as a *generic medication* worldwide.
  - Brand names include *Vasotec* and *Renitec*.
  - Manufactured by companies such as *Merck & Co.***,** *Teva Pharmaceuticals***,** and *Sandoz***.**
  - In India, enalapril is available under various brand names and strengths.

SUMMARY OF CLINICAL USE BY POTENCY

Captopril

- *Potency*: Moderate
- *Onset & Duration*: Rapid onset (~1 hour), short duration (~6–8 hours)
- *Clinical Use*:
  - Effective for *hypertension* and *congestive heart failure*
  - Historically the first ACE inhibitor used in clinical practice
- *Efficacy*:
  - Comparable to other ACE inhibitors in lowering blood pressure
  - Associated with a higher incidence of adverse effects, including *cough* and *taste disturbances*
- *Limitations*:
  - Shorter duration of action necessitates multiple daily dosing
  - Higher incidence of side effects may limit tolerability

Lisinopril

- *Potency*: Moderate
- *Onset & Duration*: Onset within 1 hour, duration up to 24 hours
- *Clinical Use*:
    - Indicated for *hypertension***,** *heart failure*, and *post-myocardial infarction*
    - Available in combination with diuretics for enhanced efficacy
- *Efficacy*:
    - Demonstrated effectiveness in improving exercise tolerance in heart failure patients
    - Comparable to captopril in blood pressure reduction
- *Limitations*:
    - Potential for *renal dysfunction* and *hyperkalemia*
    - Not metabolized by the liver, excreted unchanged in the urine

Enalapril

- *Potency*: High
- *Onset & Duration*: Onset within 1 hour, duration up to 24 hours
- *Clinical Use*:
    - Indicated for *hypertension***,** *heart failure*, and *diabetic nephropathy*
    - Available in both oral and intravenous formulations
- *Efficacy*:
    - Significantly reduces systolic blood pressure compared to placebo
    - Associated with improved cardiac function in heart failure patients
- *Limitations*:
    - Higher incidence of *cough* and *renal dysfunction* compared to other ACE inhibitor.

SCREENING METHODS OF ANTIHYPERTENSIVE AGENTS:

IN VIVO MODELS:

- Goldblatt hypertension
- ACE Inhibition in rats
- Salt sensitive Dahl Rats
- Hypertension Induced by Chronic NO-synthase Inhibition

IN VITRO MODELS

- ACE Inhibition in GUENIA PIG ileum
- Pulmonary Hypertension Induced by Monocrotaline

IN VIVO MODELS

GOLDBLATT METHOD

Three variants of hypertension are produced by this method.

1. Two kidney one clip method(2K1C)
2. One kidney one clip method(1K1C)
3. Two kidney two clip method(2K2C)

ACUTE RENAL HYPERTENSION IN RATS/2K 1C

PRINCIPLE:

Ischemia of the kidneys causes elevation of blood pressure by activation of renin-angiotensin system.

- Clamping of renal artery for 4h
- Accumulated renin released into circulation after releasing the vessel
- Protease renin catalyses the first & rate limiting step in the formation of angiotensin2
- Acute hypertension

PROCEDURE

- Sprague - Dawley Rats (300gm) are anesthetized c Hexobarbital sodium (100mg/kg) Intra peritonially.
- Cannulate the trachea for respiration and the Jugular vein for test compound administration.
- A transducer is connected to the carotid artery for recording the pressure.
- A PVC coated clip is placed in the left hilum of the kidney by fixing with the back muscle for 3.5 - 4hr.
- Pentolinium (10mg/kg i.v) is administered for ganglionic blockade.
- Release the clip and record the rise in B.P.
- Administer the test drug through I.V. and monitor the pressure continuously.
- Increase in B.P after releasing the clip and reduction after the drug administration is determined.
- Compare using percentage values

EVALUATION:

- Increase in blood pressure is determined after reopening of the renal artery.
- Reduction in blood pressure is determined after administration of the test drug.
- Percent inhibition of hypertensive blood pressure values under drug treatment are calculated as compared to pretreatment hypertension values.
- Duration of the effect is determined (min].

ACE INHIBITION IN RATS

PROCEDURE:

- Male Sprague- Dawley rats (200-225gm) are selected.
- They are anaesthetized with 60mg/kg of phenobarbitone sodium i.v
- The intubated trachea is artificially respirated with 30strokes/ min and a stroke volume of 6-8ml.
- The right artery is cannulated for recording the pressure.
- The jugular vein is cannulated for i.v test injection.
- The B.P is diminished by the administration of 5mg/kg of pentolinium i.p.
- Atropine(40pg/kg) is also injected i.m to inhibit the mucous secretion.
- Now 310ng/kg of Angiotensin I is injected i.v in 0.1ml saline.
- The injection is repeated in 5min interval until an identical pressure is attained.
- The test drug is administered at a dose of 10mg/kg intravenously or 25mg/kg intradeudenally.
- Again, Angiotensin l is injected as the similar dose above.
- The diminution of the pressure after the administration of potent ACE inhibitors is compared.

HYPERTENSION INDUCED BY CHRONIC NO-SYNTHASE INHIBITION

Chronic blockade of NO synthesis in the rat produces systemic hypertension and glomerular damage (Baylis et al. 1992). This was recommended by Ribeiro et al. (1992) as a model of hypertension**.**

- The detrimental sequels of chronic NO synthase inhibition in rats can be inhibited by treatment with ACE inhibitors.

PROCEDURE

- Male Wistar rats at an age of 7-8 weeks weighing 210 10 g were placed at random in metabolic cages, divided in four to six groups of six to eight rats each.
- Group 1 (control) had free access to tap water and food.
- Groups 2-4 were treated with 0.02% L-NAME water solution for 6 weeks in a daily dose of 25 mg/kg.
- Groups 3 and 4 received the angiotensin receptor antagonists fonsartan (10 mg/kg) or losartan (30 mg/kg) for 6 weeks daily per stomach tube.
- Groups 5 and 6 received fonsartan and losartan alone.

- At the end of the study, 24-h urine samples were collected and retrobulbar blood samples were taken in short inhalation anesthesia. For clearance evaluation rats were anesthetized with 50 mg/kg thiopentone i.v.
- In order to determine glomerular filtration rate and renal plasma flow, clearances of inulin and para-amino hippurate were performed. [19]

IN VITRO MODELS.

ACE INHIBITION IN ISOLATED GUINEA PIG ILEUM

ACE Inhibition:

- decreased activity of angiotensin 2
- increased activity of bradykinin
- The Guinea Pig Ileum responds powerfully for both Angiotensin Il, and Bradykinin.

PROCEDURE:

- Guinea Pig of either sex (300 - 500gm) is selected.
- Animals are sacrificed by stunning, and abdomen is opened.
- A chord is tied around the starting of intestine.
- The intestine is gradually removed from the bottom and the mesentry is cut away.
- When reached the colon, the intestine is cut halfway bypassing Tyrode solution to clean the surface.
- The distal pieces (more sensitive) are fixed in the tissue clamp and brought into organ bath of 37°C (oxygenated) Angiotensin is added (10ng/ml) after 30mts of equilibrium in bath solution and contraction is recorded.
- 5 min after the addition of ACE Inhibitor (test drug), the diminished contraction is recorded.
- The opposite response can be observed while using Bradykinin. [20]

EFFECTS OF ANTIHYPERTENSIVE AGENTS

- Antihypertensive drugs, according to their mode of action, will affect the blood pressure in certain types of experimental hypertension, and not in all.
- Vasodilators like Minoxidil, Hydralazine and Diazoxide are effective in Renal hypertensive rats.
- Calcium channel blockers, ACE Inhibitors and AT-1 antagonists decrease BP in nephrectomised SHR.
- Diuretics, are active in mineralocorticoid or salt induced hypertension.

CONCLUSION

The most important point from direct comparison of these animal models is that, despite the well-known heterogeneity of hypertension, the outcome of hypertension can be similar in some respects.

- Not all classes of antihypertensives are equally effective in all rat models of hypertension.
- These models of hypertension provide ample opportunity not only to investigate the mechanisms involved in the pathogenesis of hypertension, but also to learn about the critical balance between stress and its overcoming which eventually determines prognosis.

Summary

Captopril is the first orally active angiotensin-converting enzyme (ACE) inhibitor, widely used in the management of hypertension. It acts by inhibiting the conversion of angiotensin I to angiotensin II, thereby reducing vasoconstriction and aldosterone-mediated sodium and water retention. Captopril is characterized by a short half-life, requiring 2–3 doses per day, and contains a sulfhydryl group, which contributes to both efficacy and some side effects like skin rash and taste disturbances.

In this comparative study, captopril is evaluated alongside other ACE inhibitors such as enalapril, lisinopril, ramipril, and perindopril with respect to:

- Pharmacokinetics
- Efficacy in blood pressure control
- Side effect profile
- Dosing frequency
- Organ protection (renal and cardiovascular)

Conclusion

Captopril remains a potent antihypertensive agent, especially useful in *emergency situations* or *short-term management* due to its rapid onset. However, when compared with other ACE inhibitors, drugs like *lisinopril* and *ramipril* offer better patient compliance due to once-daily dosing and sustained blood pressure control. The choice of ACE inhibitor should be individualized based on patient comorbidities, duration of action needed, tolerability, and renal function. While newer ACE inhibitors may be preferred for chronic use, captopril maintains its value in specific clinical settings.