OPEN ACCESS

Precision Medicine Communications

DOI: doi.org/10.55627/pmc.002.002.0130

Review Article

Genetic Influence on the Antihypertensive and Uricosuric Actions of Losartan

Aemen Haroon, Eman Aamir*, Hareem Arif Siddiqui

Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University Islamabad, Pakistan
*Correspondence: emanaamir18@gmail.com

Abstract

Hypertension (HTN), a globally prevalent non-communicable chronic disease (NCCD), is an international health concern. HTN has multifaceted pathogenesis with a varied prevalence across the globe. Excessive oxidative stress is the underlying cause of the Renin Angiotensin Aldosterone System (RAAS) imbalance leading to elevated blood pressure (BP). Evidence-based medicine (EBM) and suitable lifestyle modifications assist in managing the disease and lowering the risk of disease-associated cardiovascular morbidity and mortality. Losartan, an angiotensin receptor blocker (ARB), is one of the first-line drugs available. One of the complications of HTN is hyperuricemia, a metamorphosis in urate homeostasis. Studies have highlighted the uricosuric action of Losartan along with its antihypertensive effects. However, varied therapeutic outcomes are observed in patients due to genetic polymorphisms based on different ethnical backgrounds. The present review focuses on the single nucleotide polymorphisms (SNPs) of nephrin (NPHS1) and URAT1 genes and the degree to which they affect Losartan's antihypertensive and serum uric acid (SUA) lowering effects, respectively.

Keywords: Losartan, antihypertensive, uricosuric, pharmacogenomics, serum uric acid

1. Introduction

Hypertension (HTN) is the leading cause of cardiovascular morbidity and mortality, with an expiry rate of over 10 million deaths per year. The statistics further state that hypertension is a far more serious problem in low- middle-income countries (LMICs) compared to high-income countries (HICs), with LMICs estimating a figure of more than a billion people with hypertension and HIC estimating half of that. According to the International Society of Hypertension (ISH) guidelines of 2020, HTN is a persistent increase in diastolic and systolic blood pressure (BP). When the systolic blood pressure (SBP) is >140 mmHg and/or the diastolic blood pressure (DBP) is >90 mmHg, a person is diagnosed with HTN. HTN is classified as follows according to the ISH guidelines; normal (<130 mmHg SBP, <85 mmHg DBP), elevated (SBP 130-139 mmHg, DBP 85-89 mmHg), stage 1 (SBP 140-159 mmHg, DBP 90-99 mmHg), stage 2 (SBP ≥160 mmHg, DBP ≥100 mmHg) (Unger et al. 2020).

General guidelines have been established to show how to measure BP, how it is classified based on the SBP and DBP measurements, and how to manage each stage. Patients having SBP >140 mmHg and DBP >90 mmHg are recommended to start medicinal treatment. Additional management of lifestyle changes is required to allow the body to lower its BP naturally. This consists of dietary changes involving a reduction in salt intake along with daily physical activity to allow sufficient blood flow to all organ systems while, at the same time, reducing the resistance to blood flow hence reducing HTN (Gabb et al. 2016).

It is observed that HTN can lead to fatal conditions like cardiovascular disease. Monitoring SBP and DBP during the day and at night will facilitate the early prevention of organ damage and damage at a cellular level. This measurement of BP can be done both at home and at the office since both will demonstrate a direct correlation with the risk of comorbidities (Sega et al. 2005).

HTN has multifaceted pathogenesis. Among the causes, the most major and common ones are salt and water retention, obesity, and specific triggered neurohormonal systems such as the sympathetic nervous system and the Renin Angiotensin Aldosterone System (RAAS). It is treated by certain lifestyle modifications and pharmacological therapies (Unger et al. 2020). The first-line drug agents used include calcium channel blockers (CCBs), thiazide diuretics, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) (Cardiology 2017).

Losartan, a commonly prescribed ARB, inhibits urate transporter 1 (URAT1), an anion exchanger specific to uric acid. Losartan shows its effect within 2-4 hours after administration. Its uricosuric effects are short-term and dose-dependent (Katsiki et al. 2018) (Miao et al. 2011). This effect of Losartan has been seen to be influenced by genetic polymorphisms in the URAT1 gene, of which multiple genetic polymorphs have been identified (Sun et al. 2015) (Wu et al. 2021). Similarly, BP lowering effects of Losartan are also affected by genetic polymorphisms (Frau et al. 2014).

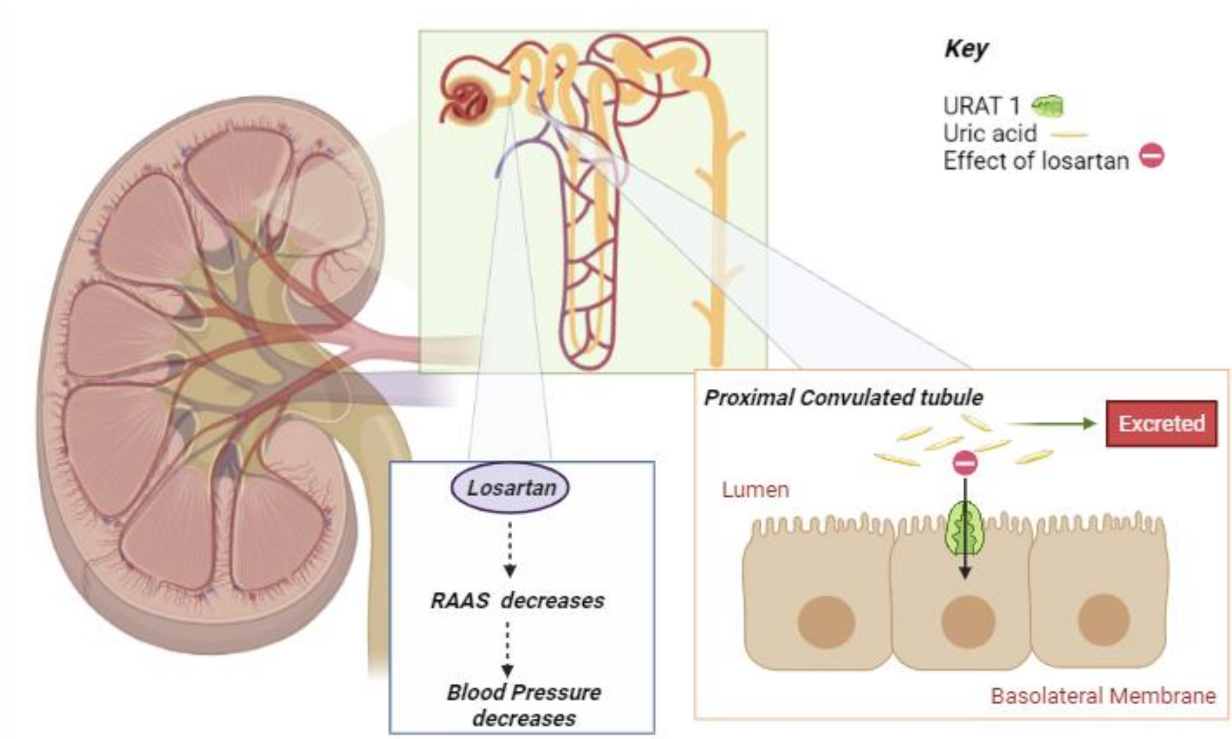


Figure 1. Losartan inhibits the action of the URAT1 transporter. In doing so, uric acid is not reabsorbed into the bloodstream.

1. Epidemiology of HTN

HTN burden is one of the leading causes of morbidity and mortality globally, deeming for 7% of global disability-adjusted life years (Rahimi, Emdin, and MacMahon 2015). Statistics show that 31.1% of adults (1.39 billion) worldwide had HTN in 2010. Concentrated among the older population, the prevalence of

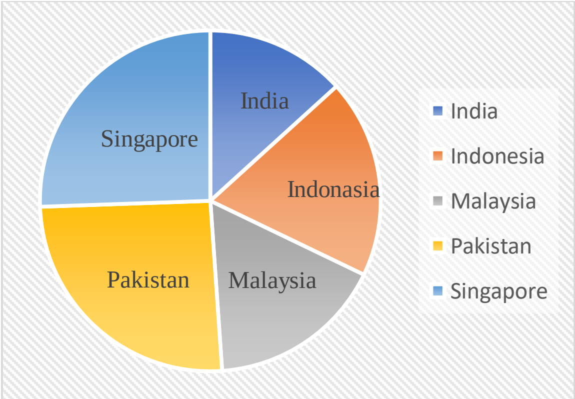
HTN has increased in LMICs. In adults of LMICs, the prevalence of HTN was higher: 31.5%, 1.04 billion people, than in HICs: 28.5%, 349 million people. Geographical heterogeneity in the prevalence of the disease may be due to the varied extent of the population's risk factors and genetic susceptibility (Mills, Stefanescu, and He 2020). Despite the high prevalence, the awareness rate among individuals (47 % worldwide), of which 41% received treatment while only 13% of the patients managed their BP successfully. A further decline has been seen in LMICs (Prospective Urban Rural Epidemiology study, PURE) (Rahimi, Emdin, and MacMahon 2015).

HTN turnout doubled from 1990 to 2019, with 626 million women and 652 million men (2019). In 2019, a previous diagnosis of HTN was reported in 59 % of women and 49% of men with HTN worldwide. The control rates for women were 23% and 18% for men. The highest control rates were reported for South Korea, Canada, Iceland, the USA, Costa Rica, Germany, Portugal, and Taiwan (Zhou et al. 2021).

South Asian population has become prone to HTN due to having a lifestyle consisting of increased intake of high-calorie foods, decreased physical activity, and stress. It is approximated that hypertension is present in 1/3 of adults in South Asian countries such as Pakistan and India (Shivashankar et al. 2017). In a study performed by the Prospective Rural Urban Epidemiology (PURE), it was demonstrated that 40.4% had knowledge that they had HTN, and 31.9% were currently receiving treatment. Furthermore, only 31.7% of participants from low-income countries were taking medicine to treat their HTN, which was lowest when looking at LMICs (36.9%), upper-middle-income countries (48.3%), and HICs (46.7%). In another evaluation, it was seen that in low-income countries, medications such as aspirin, statin, beta-blockers, and ACEI/ARBs were not afforded by 60% of households. Lack of resources and awareness increases the incidence of HTN, as indicated by the results given above (Rehman et al. 2018).

In the countries of Bangladesh, Pakistan, and Sri Lanka, screening was done for the participants of ages 40 or greater. Among the hypertensive participants, 74.9%, 40.4%, and 80.4% received treatment, respectively. However, the amount of uncontrolled HTN in these individuals was 52.8%, 70.6%, and 56.5%, respectively, demonstrating the impact of lifestyle and adherence to disease control (Jafar et al. 2018). The Center for Cardio-metabolic Risk Reduction in South Asia (CARRS) used 16,287 participants from Chennai, Delhi, and Karachi to collect data on HTN. The results showed that 30.1% of men and 26.8% of women had HTN (Prabhakaran et al. 2017).

Table 1 Prevalence of hypertension in South Asian countries.



The prevalence of HTN in Pakistan has increased over the years. In an alarming rise, incidence went up from 19.55% in the 1990s to 23.95% in the 2000s to 29.95% in the 2010s, with more cases being reported in males compared to females (24.99% and 24.76%, respectively) (Shah, Shah, and Shah 2018). Research has shown that patients with HTN are also known to suffer from chronic diseases like diabetes mellitus, chronic kidney disease (CKD), and cardiovascular diseases. Their sociodemographic and certain behavioral characteristics were similar, like family history, smoking, obesity, and minimal to no exercise (Riaz et al. 2021). Lack of awareness is a major reason for the high prevalence. A study conducted in rural Punjab during 2008-2015 showed a 35.1% prevalence, of which only 62.3% were aware of having HTN (Shafi and Shafi 2017). The overall prevalence of HTN in Pakistan was 46.2%. Rural areas have more prevalence than urban areas, 46.8% and 44.3%, respectively, except in Khyber Pakhtunkhwa (KP), where more prevalence is observed in urban areas. The highest rates have been observed in Punjab (49.2%), followed by Sindh (46.3%), Baluchistan (40.9%), and KPK (33.3%) (Basit et al. 2020). Many reasons contribute to the increase in HTN prevalence and incidence, ranging from not having access to medication, economic status, lack of awareness, and risk factors including age, gender, lifestyle, and diet (Gupta et al. 2017).

2. Pathophysiology of HTN

HTN is an elevation in blood pressure that occurs in the human body due to many reasons, including lack of physical activity, high fat and carbohydrate diet, diabetes, genetic factors, age, and gender. Various risk factors of HTN are male gender, weight, hyperlipidemia, ethnicity, smoking, underlying diseases, education, and socioeconomic level (Mohammed Nawi et al. 2021). The common underlying mechanism is oxidative stress.

All the factors listed above cause stress on the organs and organ systems of the body. This stress causes further production of chemicals that can cause an increased sympathetic stimulation, and disturb body pathways, ultimately resulting in HTN. Oxidative stress, vascular inflammation, and endothelial dysfunction lead to imbalances in the blood pressure homeostasis of the body (Siti, Kamisah, and Kamsiah 2015).

Excess reactive oxygen species (ROS) are formed at the vascular level, which is not balanced by antioxidants leading to oxidative stress, which ultimately imbalances homeostasis. They can react with cells and are unstable in nature. One of the stimuli for ROS production is angiotensin II, which is part of RAAS and is involved in the elevation of blood pressure (Masi, Uliana, and Virdis 2019). This system, located in the kidneys, increases blood pressure by causing sodium retention and water reabsorption, increasing blood volume and thus increasing blood pressure. ROS can control pathways that cause a decrease in the amount of nitric oxide (NO), disturb salt and water homeostasis, and RAAS cause inflammation.

NO decreases blood pressure and total peripheral resistance through the vasodilation of vascular smooth muscle. It is naturally made by the body to enhance blood circulation. However, an increase in ROS levels disintegrates the endothelial-dependent vasodilator, NO. Due to this dysfunction, endothelial-dependent vasodilation does not take place. Collectively and/or independently, all these mechanisms initiate the development of HTN. Once they have reached a certain threshold depending on individualized factors that vary from person to person, HTN will continue to affect and target individual organs and organ systems, leading to cardiovascular disease, renal impairment, etc., unless it is monitored and effectively controlled (Larsen and Matchkov 2016).

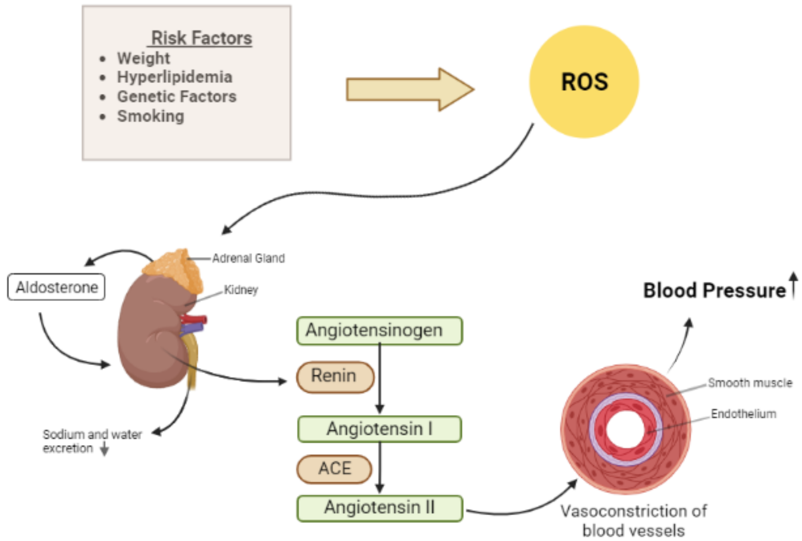


Figure 1. This illustration shows a simplified version of the pathogenesis of HTN.

3. Management of HTN

HTN, a globally prevalent NCCD, finds its management in EBM, but the control rates are still low. Antihypertensive agents and suitable lifestyle modifications lessen the risk of malady-associated cardiovascular morbidity and mortality.

3.1. Pharmacological Treatment

3.1.1. Angiotensin Converting Enzyme Inhibitors (ACEIs)

Angiotensin-Converting Enzyme Inhibitors (ACEIs) are the first-line antihypertensive medications, according to AHA/ACC and the European Society of Cardiology (ESC). However, this class of antihypertensives has not been of much clinical benefit to African Americans.

The Angiotensin Converting Enzyme (ACE) catalyzes the conversion of Angiotensin I (Ang I) to Angiotensin II (Ang II), an effective vasoconstrictor formed by the RAAS, which elevates the BP. This conversion is actively triggered by sympathetic stimulation, low levels of circulating sodium, and reduced renal perfusion. Ang II, thus produced, expands the blood volume through sodium, water retention, and renal vasoconstriction, causes cardiac hypertrophy and remodeling, and activates the Kallilrein-kinin system (KKS), releasing Bradykinin.

ACEIs lessen the effects of RAAS and potentiate the KKS, leading to reduced peripheral vascular resistance, diuresis, and natriuresis, prevention of cardiac remodeling, and restriction of bradykinin breakdown (Herman et al. 2017) (Regoli and Gobeil Jr 2015).

The reno-protective effects of this class make it the chief agent for treating HTN in CKD. However, they still are contraindicated in individuals with idiopathic or hereditary angioedema and pregnancy (Category D). In addition, hypotension, non-productive paroxysmal cough (10% patients), angioedema (higher incidence rate in African-Americans), a reversible plummet in renal function, hyperkalemia, anaphylactoid reactions, and cholestatic jaundice are some side effects that might make it necessary to switch to another class of antihypertensives (Herman et al. 2017).

3.1.2. Angiotensin Receptor Blockers (ARBs)

ARBs can be given as monotherapy or in combination with other first-line antihypertensive drugs i.e. thiazide diuretics and dihydropyridine CCBs. ARBs and ACEIs are not given in combination as evidence shows that incorporating renin-angiotensin system-blocking agents causes renal function impairment (Abraham, White, and White 2015). ARBs have been shown to be more effective in blocking RAAS than ACEI (Mulla and Siddiqui 2022). The function of ARBs is focused on the RAAS, specifically Ang II. Ang II is a highly potent vasopressor. Its effects are mediated by the Ang II type 1 receptor (AT_1R) and the Ang II type2 receptor (AT_2R). AT_2R balances out the stimulatory effects of AT_1R (Arumugam et al. 2016). ARBs selectively and competitively block AT_1R and, as a result, stops its effects of vasopressin release and reduce thirst along with suppressing vasoconstriction and aldosterone action induced by Ang II hence allowing BP to lower (Mulla and Siddiqui 2022).

Among the available antihypertensive ARBs, Losartan was the first and most commonly prescribed. In addition to its antihypertensive effects, it has shown remarkable results in preventing stroke and reducing hyperuricemia and albuminuria. It has also shown a decrease in the frequency of onset of other HTN-related comorbidities (Katsiki et al. 2018). Unfortunately, however, its use has been known to cause hyperkalemia, renal insufficiency, and angioedema (Mulla and Siddiqui 2022).

4.1.3 Diuretics

Diuretics include loop diuretics, and thiazide diuretics. Their general mechanism of action is to increase urinary sodium and water loss to lower blood pressure. Loop diuretics inhibit sodium reabsorption through Na-K-2Cl cotransporters located in the thick ascending limb of the loop of Henle, allowing sodium to be excreted out of the body (Malha and Mann 2016). Thiazide diuretics also target the kidneys to reduce blood pressure by decreasing cardiac output by lowering extracellular volume. This occurs by inhibiting the Na-Cl cotransporter located in the distal convoluted tubule of the nephron, causing natriuresis (Sinha and Agarwal 2019).

Both classes of diuretics can cause hypokalemia, hyperuricemia, glucose intolerance, increase in blood urea nitrogen (BUN) and creatine. Hyponatremia is commonly caused by thiazide diuretics. Loop diuretics are preferred over thiazide diuretics as a first-line treatment in managing primary hypertension. Hypertensive patients with chronic kidney disease (CKD) stop thiazide diuretic therapy when the glomerular filtration rate (GFR) becomes below 30 ml/min per 1.73 m^2. At this time, the patient is given loop diuretics (Sinha and Agarwal 2019).

3.1.3. Calcium channel blockers (CCBs)

CCBs are divided into 2 categories, dihydropyridine calcium channel blockers (DHP-CCBs) and non-dihydropyridine calcium channel blockers (non-DHP-CCBs). DHP-CCBs are preferred due to their good tolerance among patients and lack of interaction with drugs such as statins. Also, non-DHP-CCBs given in combination with beta-blockers (BBs) may induce heart block. DHP-CCBs are metabolized and excreted through the liver; therefore, their dosing is not dependent on kidney function. An enhanced blood pressure reduction is observed when administered with ACEIs and ARBs. Calcium channel blockers work by decreasing the concentration of cytosolic calcium by binding to the α_1-subunit of the L-type calcium channel located in the cell membranes of muscle cells, lowering the uptake of calcium into the cells and thus lowering muscle contraction. Edema is observed at the end of the treatment regimen. However, that can be overcome with the use of diuretics. It is seen that a combination of diuretics and DHP-CCBs is recognized as first-line treatment in black hypertensive patients, whereas ACEIs and ARBS are used in patients of other races (Sinha and Agarwal 2019).

3.2. Lifestyle Modifications

Lifestyle modifications are a multifaceted approach aiming at more than one intervention over a span of at least 6-12 months. Lifestyle modifications include exercise, dietary changes, stress avoidance, and reduced alcohol consumption. Hypertensive patients have certain nutritional requirements like low sodium intake. These requirements can be fulfilled by adopting diets like dietary approaches to stop HTN (DASH) or the traditional Mediterranean diet (Mahmood et al. 2019). DASH diet has been shown to decrease cardiovascular risk factors, and is very effective in lowering BP and total cholesterol levels (Siervo et al. 2015).

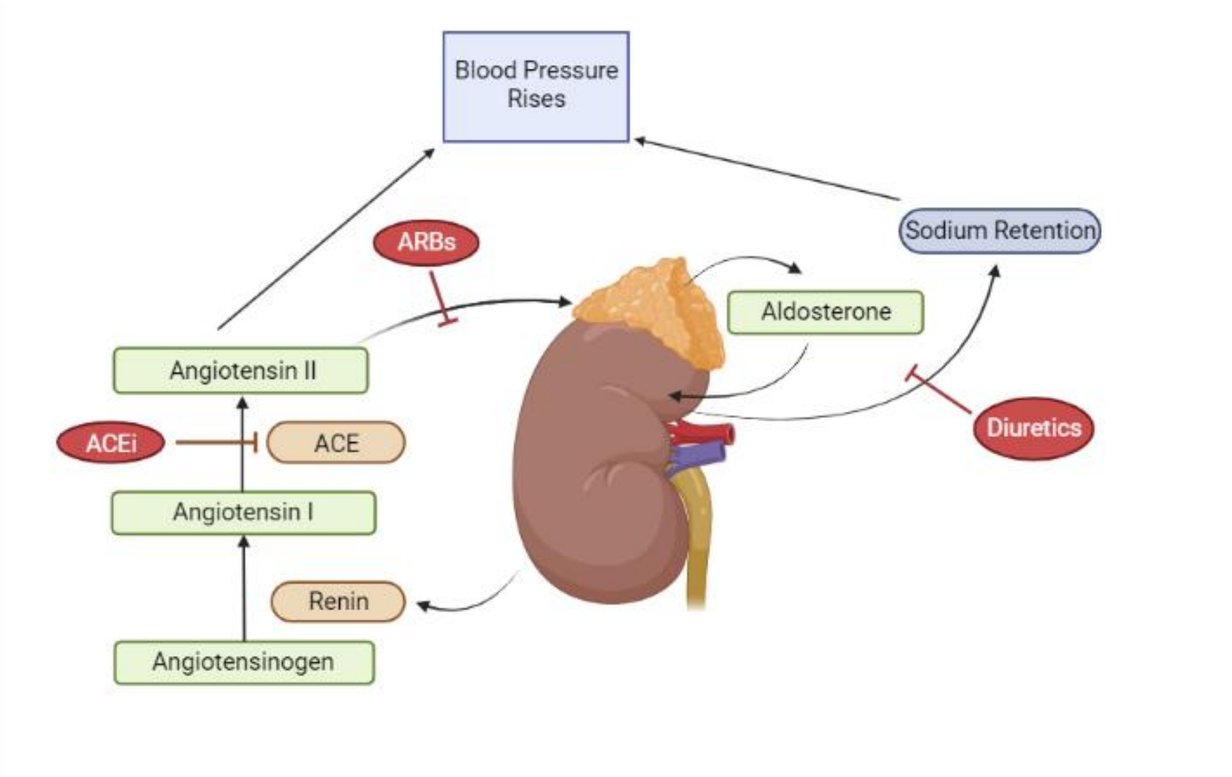


Figure 2. This illustration shows various approaches to the treatment of HTN.

4. Uricosuric Action of Losartan

Losartan has reno-protective potential alongside its antihypertensive effects. It helps in the excretion of uric acid in the form of urate. Studies demonstrate that it does so by inhibiting uric acid reabsorption (Krajčoviechová et al. 2020). Transporters involved in the reabsorption of uric acid in the proximal convoluted tubule are URAT1, GLUT9, and OAT3 (Chung and Kim 2021). URAT1 has been identified to be majorly affected by Losartan (Wu et al. 2021b) which is involved in the excretion and reabsorption of uric acid (Li et al. 2019). Losartan helps reduce serum uric acid by inhibiting the URAT1. Its effect can be observed 2 to 4 hours after administration, suggesting that the uricosuric effect is mediated by Losartan, not its active metabolite. (Miao et al. 2011)

5. Genetic Polymorphisms Affecting Antihypertensive Actions of Losartan

Treatment of HTN includes a long list of different medications that facilitate blood pressure reduction. However, some variations are seen at an individual genomic level, leading to the development of patient-specific pharmacotherapy plans. Losartan's pharmacological output is affected by genetic variations.

A genome-wide association study was performed to select which genes affect males' hypertensive response. The components consisted of antihypertensive drugs from 4 classes being tested on 228 male patients. The average age of this sample size is 50. 6 years, with a body mass index of 26.7 kg/m^2. Initially, the average BP was 135 mmHg (SBP) and 93 mmHg (DBP). Amongst these drugs was Losartan, given at a dose of 50mg/daily for 4 weeks, while patients had a prior 4-week placebo period. The gene coding for nephrin (*NPHS1*) was the focus with Losartan. Nephrin is a transmembrane protein located on podocytes. It forms a glomerular filtration barrier in the kidneys with endothelial cells. This facilitates BP maintenance. The patients had no previous liver, kidney, pulmonary, heart, or cerebrovascular disease or drug-treated diabetes. Twenty gene loci along with their effect on blood pressure (increase or decrease), were identified (Hiltunen et al. 2015).

Table 2: Single-Nucleotide Polymorphisms Involved in Losartan Blood Pressure Effect

SNP	Chromo-some	SBP (mmHg)	DBP (mmHg)
rs1370555	15	-2.6	-2.1
rs7086428	10	3.3	1.7
rs4953045	2	-3.5	-2.2
rs711513	7	-2.4	-2.3
rs12814605	12	-4.0	-3.0
rs12602832	17	-2.8	-2.7
rs4759885	12	-2.7	-2.0
rs10754459	1	-2.3	-2.1
rs1357265	17	2.6	2.2
rs11841583	13	-4.5	-3.1
rs2279989	9	-4.0	-3.3
rs7597606	2	2.9	1.4
rs1559557	2	3.3	1.9
rs1432232	2	3.8	2.2
rs1993802	3	-3.9	-2.6
rs2038912	10	2.0	1.8
rs771574	3	-3.2	-2.3
rs1392874	4	-1.8	-1.9
rs3814995	19	-2.8	-1.6
rs17271855	19	-2.9	-2.4

Four hundred sixty individuals from Finland were used for the Losartan Intervention for Endpoint Reduction in Hypertension Study. The focus was to determine the effect of the *NPHS1* gene (similar to the previous study) **rs3814995** on chromosome 19 in blood pressure reduction with the use of Losartan. Nephrin has a physical effect on maintaining the glomerular membrane for blood filtration. Therefore, monotherapy of 50mg losartan was administered for 2 months. The results indicated a 0.9 mmHg decrease in DBP, indicating that this gene can be used in further studies as a target to help compile a better pharmacotherapy plan more suited to the individualized patient (Rimpelä et al. 2016).

A study was performed with 372 white Caucasian hypertensive patients from Italy and Sardinia who were given 50mg/day of Losartan for 4 weeks. During the previous 8 weeks before administering Losartan, all the patients were given a similar diet so that they would be at a similar starting point. This consisted of a daily intake of 100-140mEq sodium and 50-70mEq potassium. The correlation of HTN with the *CAMK1D* gene, involved in coding a protein that is part of the regulatory pathway of aldosterone synthesis, was to be determined. 24.7% of the patients were women, and the average age of the group was 45.7 years. Initially, SBP and DBP averaged out to be 148.9 ± 7.1 mmHg and 96.5 ± 3.7 mmHg, respectively. It was seen that the GG genotype of the SNPs **rs10752271** and **rs10737062** had the greatest response to Losartan with close to 25 mmHg reduction in SBP (Frau et al. 2014).

Endogenous ouabain is a steroid hormone secreted by the adrenal gland increasing Na reabsorption in the renal tubules by activating the Na-K pump, leading to water retention and hence an increase in blood pressure. Chinese and Caucasian patients were given 50mg/daily Losartan over a period of 9 weeks. To ensure uniformity and minimize underlying factors, all the patients did not have underlying forms of hypertension, either renal or adrenal, had fasting glucose levels lower than 125mg/d, creatinine clearance greater or equal to 50ml/min, and not currently using statins. In the case of female patients, they must not be pregnant, nursing, and not taking contraceptives. *LSS gene* contributes to endogenous ouabain synthesis. *LSS* **rs2254524** AA and CC genotypes showed a reduction in blood pressure. AA genotype demonstrated about 17 mmHg and 6 mmHg reduction in SBP and DBP, respectively. CC genotype demonstrated about 20 mmHg and 13 mmHg reduction in SBP and DBP, respectively (Citterio et al. 2021).

Table 3. Average Blood Pressure Reduction in LSS rs2254524 gene

	AA Genotype	**CC Genotype**
SBP (mmHg)	-17.0	-20.0
DBP (mmHg)	-6.0	-13.0

6. Genetic Polymorphisms Affecting Uricosuric Actions of Losartan

Uric acid absorption and secretion occur in the proximal renal tubules and are governed by urate transporters. The urate transporters linked to SUA levels are OAT3, URAT1, GLUT9, OAT1, OAT2, OAT4, NPT1, NPT4, ABCG2, and PDZK1. Imbalances in urate homeostasis is called hyperuricemia (Chung and Kim 2021). The diuretic-induced hyperuricemia is a complication in HTN patients for which Losartan has been shown to reduce the SUA effectively. Studies reveal that losartan targets URAT1 as the URAT1 gene SNP is linked to hyperuricemia. Therefore, SNPs of the *SLC22A12* gene, which encodes for URAT1, affect the SUA levels differently in distinct populations worldwide (Wang et al. 2020).

A Japanese analysis revealed **rs121907896** and **rs121907892** SNPs to make an impression on the SUA levels, and **rs3825016**, **rs1529909**, and **rs505802** SNPs affecting the Chinese community (Wu et al. 2021). The **rs11231825** SNP in Vietnamese and **rs3825017** polymorphism in the Czechoslovakian population was correlated to hyperuricemia. A Korean cohort study showed that **rs75786299**, **rs7929627**, and **rs3825017** SNPs were linked to gout (Chung and Kim 2021).

Table 4 Genetic Polymorphism in Different Ethnicities

Ethnicity	URAT1 SNP
Japanese	rs121907896
	rs121907892
Chinese	rs3825016
	rs1529909
	rs505802
Vietnamese	rs11231825
Czechoslovakian	rs3825017
Korean	rs75786299
	rs7929627
	rs3825017

An investigation was conducted to evaluate the influence of polymorphisms of the *SLC22A12* gene on the uricosuric action of Losartan which showed that only URAT1 **rs3825016** SNP was remarkably associated with hyperuricemia. CC, TT, and CT are three genotypes of **rs3825016** polymorphism. In HTN complicated with hyperuricemia, patients carrying the heterozygous CT genotype presented a definite drop in the SUA levels on treatment with Losartan. The prevalence of CT genotype varies among different ethnicities, with 27.5% in Japanese and 41.9% in Germans. This signifies that the effectiveness of losartan treatment for hyperuricemia has a genotypic correlation (Wu et al. 2021). The polymorphisms affecting the uricosuric action of Losartan could be useful in individualizing the treatment of hyperuricemia in hypertensive patients. The potential genetic markers for the optimization of Losartan's uricosuric performance are the rs3825016 CT genotype and rs1529909 TC genotype (Sun et al. 2015).

The **rs7929627**, **rs75786299**, and **rs3825017** variants of the URAT1 were studied in another fact-finding. Clinical reports of 100 hypertensive patients with high SUA levels, compared after losartan therapy, showed a pronounced reduction in serum urate levels. Furthermore, the scope of reduction in urate levels was found to be better in the TT genotype than in the CC and TC genotypes (Wang et al. 2020).

To analyze the impact of URAT allele *6092* polymorphism of Losartan, 101 Chinese patients were given Losartan 100 mg/day orally for 2 weeks. Upon comparing the biochemical reports after the drug therapy, the TC and CC genotype manifested remarkably lower SUA levels than the TT genotype. This proposes URAT *6092* polymorphism as a probable genetic marker for optimizing Losartan's uricosuric action (Xu-hui et al. 2015).

7. Conclusions

In this review, we have identified how genetic polymorphisms affect the action of Losartan in decreasing SUA levels and lowering BP. This allows us to customize medication regimens according to the patients, leading to more effective therapeutic outcomes. The antihypertensive effect of Losartan was affected by genetic variations in *NPHS1*, *CAMK1D*, and *LSS* genes, mainly affecting the degree of BP reduction. The most common genetic polymorphisms in the URAT1 gene were SNPs **rs3825017**, **rs7929627**, and **rs75786299**, which are the main contender for the variation of Losartan's urate-lowering effects. This shows that patients with hyperuricemia secondary to

HTN will benefit significantly from having Losartan in their treatment regimens.

Conflict of Interest
The authors declare that they have no competing interests.

Funding
There was no funding available for this investigation.

Study Approval
NA.

Consent Forms
NA.

Authors Contribution
AH conceptualized the study and wrote the final manuscript, EA helped in the analysis and writing the first draft, and HAS did the literature search and analysis and wrote the final manuscript.

Acknowledgments
We thank Dr.Sagheer Ahmed for guiding and supervising us throughout the writing process and Dr.Haleema Usman for imparting conceptual advice and keeping us on track.

References

Abraham, Hazel Mae A, C Michael White, and William B White. 2015. "The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases." *Drug safety* 38 (1): 33-54.

Cardiology, American College of. 2017. Guideline for high blood pressure in adults.

Citterio, Lorena, Giuseppe Bianchi, Giuseppe A Scioli, Nicola Glorioso, Roberto Bigazzi, Daniele Cusi, Jan A Staessen, Silvio Cavuto, Mara Ferrandi, and Chiara Lanzani. 2021. "Antihypertensive treatment guided by genetics: PEARL-HT, the randomized proof-of-concept trial comparing rostafuroxin with losartan." *The pharmacogenomics journal* 21 (3): 346-358.

Frau, Francesca, Roberta Zaninello, Erika Salvi, Maria Francesca Ortu, Daniele Braga, Dinesh Velayutham, Giuseppe Argiolas, Giovanni Fresu, Chiara Troffa, and Emanuela Bulla. 2014. "Genome-wide association study identifies CAMKID variants involved in blood pressure response to losartan: the SOPHIA study." *Pharmacogenomics* 15 (13): 1643-1652.

Gabb, Genevieve M, Arduino A Mangoni, Craig S Anderson, Diane Cowley, John S Dowden, Jonathan Golledge, Graeme J Hankey, Faline S Howes, Les Leckie, and Vlado Perkovic. 2016. "Guideline for the diagnosis and management of hypertension in adults—2016." *Medical Journal of Australia* 205 (2): 85-89.

Gupta, Rajeev, Manmeet Kaur, Shofiqul Islam, Viswanathan Mohan, Prem Mony, Rajesh Kumar, Vellappillil Raman Kutty, Romaina Iqbal, Omar Rahman, and Mohan Deepa. 2017. "Association of household wealth index, educational status, and social capital with hypertension awareness, treatment, and control in South Asia." *American journal of hypertension* 30 (4): 373-381.

Herman, Linda L, Sandeep A Padala, Intisar Ahmed, and Khalid Bashir. 2017. "Angiotensin converting enzyme inhibitors (ACEI)."

Hiltunen, Timo P, Kati M Donner, Antti-Pekka Sarin, Janna Saarela, Samuli Ripatti, Arlene B Chapman, John G Gums, Yan Gong, Rhonda M Cooper-DeHoff, and Francesca Frau. 2015. "Pharmacogenomics of hypertension: a genome-wide, placebo-controlled cross-over study, using four classes of antihypertensive drugs." *Journal of the American Heart Association* 4 (1): e001521.

Jafar, Tazeen H, Mihir Gandhi, Imtiaz Jehan, Aliya Naheed, H Asita de Silva, Hunaina Shahab, Dewan Alam, Nathasha Luke, Ching Wee Lim, and COBRA-BPS Study Group. 2018. "Determinants of uncontrolled hypertension in rural communities in South Asia—Bangladesh, Pakistan, and Sri Lanka." *American journal of hypertension* 31 (11): 1205-1214.

Katsiki, Niki, Konstantinos Tsioufis, Dilek Ural, and Massimo Volpe. 2018. "Fifteen years of LIFE (Losartan Intervention for Endpoint Reduction in Hypertension)—Lessons learned for losartan: An "old dog playing good tricks"." *The Journal of Clinical Hypertension* 20 (8): 1153-1159.

Larsen, Monica Korsager, and Vladimir V Matchkov. 2016. "Hypertension and physical exercise: the role of oxidative stress." *Medicina* 52 (1): 19-27.

Malha, Line, and Samuel J Mann. 2016. "Loop diuretics in the treatment of hypertension." *Current hypertension reports* 18 (4): 1-10.

Masi, Stefano, Monica Uliana, and Agostino Virdis. 2019. "Angiotensin II and vascular damage in hypertension: Role of oxidative stress and sympathetic activation." *Vascular pharmacology* 115: 13-17.

Miao, Yan, Stefan A Ottenbros, Goos D Laverman, Barry M Brenner, Mark E Cooper, Hans-Henrik Parving, Diederick E Grobbee, Shahnaz Shahinfar, Dick De Zeeuw, and Hiddo J Lambers Heerspink. 2011. "Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial." *Hypertension* 58 (1): 2-7.

Mohammed Nawi, Azmawati, Zulkefley Mohammad, Kavita Jetly, Mohamad Aznuddin Abd Razak, Nur Suhada Ramli, Wan Abdul Hannan Wan Ibadullah, and Norfazilah Ahmad. 2021. "The prevalence and risk factors of hypertension among the urban population in southeast asian countries: a systematic review and meta-analysis." *International Journal of Hypertension* 2021.

Prabhakaran, Dorairaj, Panniyammakal Jeemon, Shreeparna Ghosh, Roopa Shivashankar, Vamadevan S Ajay, Dimple Kondal, Ruby Gupta, Mohammed K Ali, Deepa Mohan, and Viswanathan Mohan. 2017. "Prevalence and incidence of hypertension: results from a representative cohort of over 16,000 adults in three cities of South Asia." *Indian heart journal* 69 (4): 434-441.

Rahimi, Kazem, Connor A Emdin, and Stephen MacMahon. 2015. "The epidemiology of blood pressure and its worldwide management." *Circulation research* 116 (6): 925-936.

Regoli, Domenico, and Fernand Gobeil Jr. 2015. "Critical insights into the beneficial and protective actions of the kallikrein–kinin system." *Vascular pharmacology* 64: 1-10.

Rehman, Hasan, Zainab Samad, Shiva Raj Mishra, Anwar T Merchant, Jagat P Narula, Sundeep Mishra, and Salim S Virani. 2018. "Epidemiologic studies targeting primary cardiovascular disease prevention in South Asia." *Indian Heart Journal* 70 (5): 721-730.

Rimpelä, J, TP Hiltunen, F Fyhrquist, and KK Kontula. 2016. "[OP. 7C. 10] IDENTIFICATION OF GENE VARIANTS ASSOCIATED WITH ANTIHYPERTENSIVE RESPONSES TO BETA BLOCKERS AND LOSARTAN." *Journal of Hypertension* 34: e92-e93.

Sega, Roberto, Rita Facchetti, Michele Bombelli, Giancarlo Cesana, Giovanni Corrao, Guido Grassi, and Giuseppe Mancia. 2005. "Prognostic Value of Ambulatory and Home Blood Pressures Compared With Office Blood Pressure in the General Population." *Circulation* 111 (14): 1777-1783. https://doi.org/doi:10.1161/01.CIR.0000160923.04524.5B. https://www.ahajournals.org/doi/abs/10.1161/01.CIR.0000160923.04524.5B.

Shivashankar, Roopa, Dimple Kondal, Mohammed K Ali, Ruby Gupta, Rajendra Pradeepa, Viswanathan Mohan, Muhammad Masood Kadir, KM Narayan, Nikhil Tandon, and Dorairaj Prabhakaran. 2017. "Associations of sleep duration and disturbances with hypertension in metropolitan cities of Delhi, Chennai, and Karachi in South Asia: cross-sectional analysis of the CARRS study." *Sleep* 40 (9).

Sinha, Arjun D, and Rajiv Agarwal. 2019. "Clinical pharmacology of antihypertensive therapy for the treatment of hypertension in CKD." *Clinical Journal of the American Society of Nephrology* 14 (5): 757-764.

Siti, Hawa N, Y Kamisah, and JJVP Kamsiah. 2015. "The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review)." *Vascular pharmacology* 71: 40-56.

Sun, Hong, Qiang Qu, Jian Qu, Xiao-Ya Lou, Yan Peng, Ying Zeng, and Guo Wang. 2015. "URAT1 gene polymorphisms influence uricosuric action of losartan in hypertensive patients with hyperuricemia." *Pharmacogenomics* 16 (8): 855-863.

Unger, Thomas, Claudio Borghi, Fadi Charchar, Nadia A Khan, Neil R Poulter, Dorairaj Prabhakaran, Agustin Ramirez, Markus Schlaich, George S Stergiou, and Maciej Tomaszewski. 2020. "2020 International Society of Hypertension global hypertension practice guidelines." *Hypertension* 75 (6): 1334-1357.

Wu, Liting, Yingchao Fan, Yuan Wang, Zhumeng Li, Delong Mao, and Wenfang Zhuang. 2021. "The impact of an URAT1 polymorphism on the losartan treatment of hypertension and hyperuricemia." *Journal of Clinical Laboratory Analysis* 35 (10): e23949.