Current Treatment and New Trends of Hypertension

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1.ABSTRACT:

One of the most common chronic illnesses in the world today is hypertension, which also poses a significant risk for kidney, heart, and brain problems. Pharmaceutical interventions and lifestyle changes are the mainstays of the current therapeutic approaches for hypertension. Blood pressure control is thought to be based on lifestyle choices such quitting smoking, reducing alcohol intake, exercising frequently, and implementing a balanced diet (such as the DASH or Mediterranean diet). Pharmaceutical treatment is started when non-pharmacological approaches prove inadequate. First-line medications include angiotensin II receptor blockers (ARBs), ACE inhibitors, thiazide diuretics, and calcium channel blockers (CCBs). To increase effectiveness and reduce side effects, combination treatment is frequently utilized in individuals with resistant or uncontrolled hypertension. Comorbidities, age, and ethnicity are patient-specific characteristics that influence drug selection.

Beyond traditional therapies, cutting-edge non-pharmacological strategies like telemonitoring and renal denervation have demonstrated promise in enhancing adherence and delivering better blood pressure control. Precision medicine is driving emerging new trends in the treatment of hypertension, such as targeted medicines based on molecular and genetic causes and genetic testing to determine individual risk profiles. Novel therapeutic treatments that target hypertension pathways, such as aldosterone synthase inhibitors, endothelin receptor antagonists, and vaccines, are also being actively studied.

2.INTRODUCTION:

High blood pressure (hypertension) is usually managed with medications and changes in lifestyle, such as eating healthier and exercising. Recently, there has been a shift toward using technology like artificial intelligence (AI), remote monitoring, and combination drugs that are tailored to each person. Telemonitoring where patients' blood pressure is checked from home is also being used more often to improve care.

Medicines that lower blood pressure help protect organs like the heart, kidneys, and brain, and they reduce the risk of heart disease. However, despite the available treatments, many people still struggle to keep their blood pressure under control.

To address this problem, researchers are exploring new medications and technologies. Some of these are already being tested in clinical trials. New types of drugs in advanced (Phase II/III) stages include:

Inhibitors of vasopeptidase, aldosterone synthase, and soluble epoxide hydrolase
• Medication that stimulates the receptors for VIP (vasoactive intestinal peptide) and natriuretic peptide A
• A novel class of blocker for mineralocorticoid receptors

Other treatments are still in early (Phase I or preclinical) development. These include:

- Vaccines targeting angiotensin II and its receptor
- Inhibitors of the sodium/hydrogen exchanger in the intestines
- Dopamine β-hydroxylase inhibitors
- Aminopeptidase A inhibitors

For people with severe high blood pressure that doesn't respond to medication, two main procedures are being used in some countries:

1. Renal denervation – reduces nerve activity in the kidneys
2. Baroreflex activation therapy – stimulates nerves to help lower blood pressure

Renal denervation is also being studied for treating other health problems like heart failure, irregular heartbeats, and kidney disease. Some newer procedures under investigation include removing part of the carotid body (a small organ near the neck that helps regulate blood pressure) and creating an arteriovenous (AV) fistula.[**1]**

However, it is important to emphasize that none of these emerging treatments have been definitively shown to halt the progression of heart disease or decrease mortality related to high blood pressure

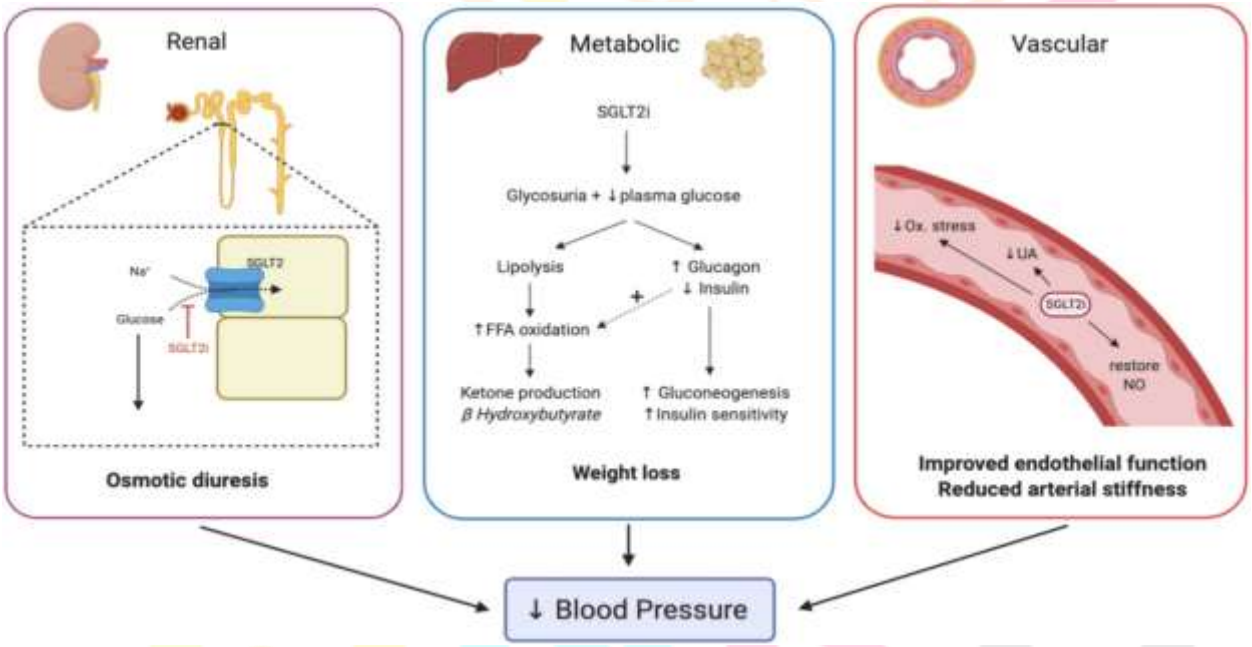

Fig1. Current And Future Perspective

3.CURRENT TREND OF HYPERTENSION

In the United States, more than 70 million individuals suffer from high blood pressure (hypertension), making it one of the primary contributors to heart disease. Data from 2011 to 2014 show that around 30% of adult men and 28.1% of adult women were affected by hypertension. This condition significantly raises the likelihood of developing severe health issues such as heart attacks, heart failure, strokes, and kidney disease even in the absence of additional risk factors. Cardiovascular disease (CVD), which encompasses disorders of the heart and blood vessels, remains the top cause of death nationwide and is responsible for roughly 17% of total healthcare expenditures**.[2]**

In terms of treatment, thiazide diuretics are commonly prescribed as the first-line therapy, either alone or in combination with other drugs. The European Society of Cardiology (ESC) and the European Society of

Hypertension (ESH) recommend an initial blood pressure target of 140/90 mmHg or lower for all patients. If tolerated, this target can be further reduced to 130/80 mmHg or below. For adults over 65, the optimal systolic pressure is generally between 130 and 139 mmHg, but if well-tolerated, it may also be lowered to around 130/80 mmHg**.[3]**

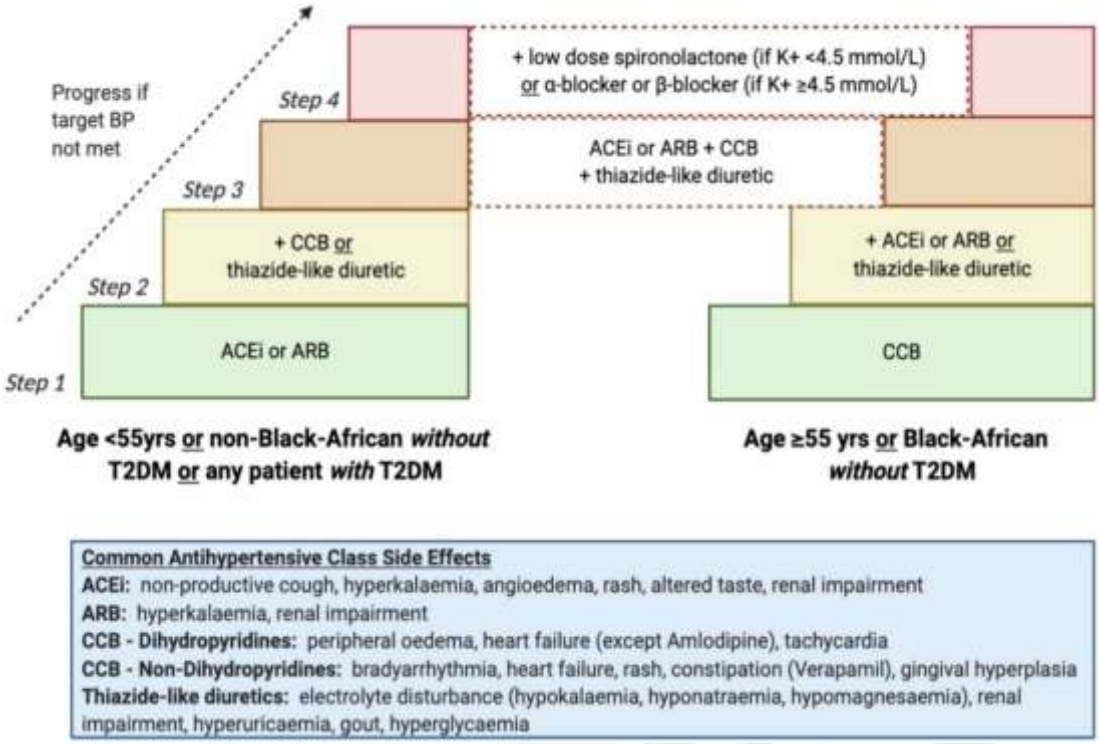

Fig2. Current Trend of Hypertense

4.HYPERTENSION AND COMBINATION THERAPY

For more than half of the people with high blood pressure, using just one medication (monotherapy) is not enough to control it effectively. Because of this, low-dose combination therapy is becoming a preferred option, either as the first treatment or early in the management plan. This approach can help better control blood pressure from the start. For example, adding a small dose of hydrochlorothiazide (12.5 mg) to an angiotensin receptor blocker (ARB) can significantly improve blood pressure control without increasing side effects. Combination therapy means using two or more types of blood pressure medicines together. This method is often more effective than using a single drug**. [4]**

It can also lead to:

- Better blood pressure control
- Improved patient compliance
- Fewer side effects

The primary types of medications commonly used in combination to manage high blood pressure include:

- ACE inhibitors (ACEIs)
- Thiazide diuretics
- Calcium channel blockers (CCBs)
- Angiotensin receptor blockers (ARBs**)**

These drug classes are often combined to achieve better blood pressure control and enhance cardiovascular health. In most cases, treatment involves pairing a calcium channel blocker (CCB) or a diuretic with an ACE inhibitor or an angiotensin receptor blocker (ARB) to maximize effectiveness and minimize side effects.

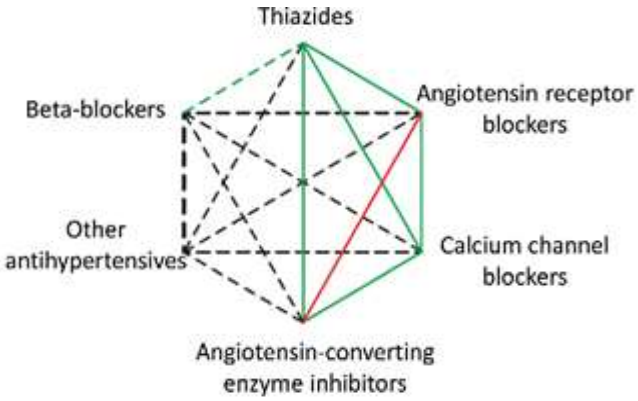

Fig 3. Combination Drug Treatment of Hypertension

4.1. The purpose of combination therapy:
Greater Effectiveness: Combining drugs from different classes usually has additive benefits on decreasing blood pressure, as opposed to raising the dosage of a single drug.

Improved Adherence: Using fewer pills, especially in a single-pill combination (SPC), can significantly improve a patient's ability to adhere to their prescription schedule.

Better Tolerability: Compared to taking one medication at a higher dose, there may be fewer side effects when two medications are taken at lower amounts.

Early Blood Pressure Control: You can achieve your objectives more quickly with combination therapy.

The four main types of medicines often used together to treat high blood pressure are:

Thiazide diuretics (help the body get rid of extra salt and water),

- Calcium channel blockers (CCBs) (relax blood vessels),
- ACE inhibitors (ACEIs) (help blood vessels relax by blocking certain chemicals), and
- Angiotensin receptor blockers (ARBs) (work like ACE inhibitors to relax blood vessels).

These medicines are often combined to better control blood pressure.

4.2. Drug Combinations:

There are many possible ways to combine blood pressure medicines since each major drug group has several options. This guide focuses on using two-drug combinations that include classes like diuretics, calcium channel blockers (CCBs), ACE inhibitors, ARB**s,** and beta-blockers, as these have been shown to lower heart and blood vessel risks.
Combinations or more with three drugs are not discussed. Some combinations are preferred because they work well and are safe, while others are less effective or may cause more side effects.

4.3. Diuretic with RAAS Inhibitor:

Using a low-dose thiazide diuretic together with an ACE inhibitor, ARB, or direct renin inhibitor helps lower blood pressure more effectively than using either drug alone. Diuretics reduce blood volume, which can trigger the body's RAAS system, leading to tightening of blood vessels and fluid retention. When combined with a RAAS inhibitor, this reaction is controlled, improving the overall effect. RAAS inhibitors also make diuretics safer by reducing the risk of low potassium levels, though they can sometimes cause high potassium in certain people. Because of their good results and safety, combining an ACE inhibitor or ARB with a low-dose diuretic is commonly recommended. Most fixed-dose combination (FDC) medicines use hydrochlorothiazide (HCTZ**)** as the diuretic. However, some experts prefer chlorthalidone because it keeps blood pressure lower for a longer period and has shown better results in major studies. Although chlorthalidone is not yet combined with ACE inhibitors or ARBs in single-pill options, it can be prescribed separately.

1.CCBs + Diuretics:

Combining a calcium channel blocker (CCB) with a diuretic helps lower blood pressure more effectively than using just one of these drugs alone, although the effect is only partially additive. This means that while both medicines work in different ways, they overlap slightly in their actions. CCB**s** help relax and widen blood vessels, while diuretics remove extra salt and water from the body, lowering blood volume. Because both promote relaxation of blood vessels over time, this combination helps improve blood pressure control, especially in people who do not reach their target levels with a single medication.

Studies such as the VALUE trial showed that adding hydrochlorothiazide (HCTZ**)** to a CCB like amlodipine can enhance long-term blood pressure control. However, unlike combinations such as ACE inhibitor + CCB or ARB + CCB, this pairing does not improve the side-effect profile of either medicine. Despite this, it is still considered an appropriate and effective option for many patients.

Mechanism of Action:

Calcium channel blockers (CCBs) function by blocking the entry of calcium ions into the smooth muscle cells of the heart and blood vessels. This action relaxes the muscle tissue, resulting in the dilation of blood vessels (vasodilation). As a result, blood pressure decreases, and the heart can pump blood more efficiently with less strain.

Diuretics, on the other hand, act on the kidneys to help the body remove excess sodium and water through urine. This decreases blood volume, which reduces the pressure on the blood vessel walls.

When combined, CCBs and diuretics target two main causes of high blood pressure increased vascular resistance (narrow or stiff blood vessels) and excess fluid volume. Together, they provide a balanced and complementary approach to managing hypertension, helping improve blood flow and reduce strain on the heart.

Specific Contraindications:

This combination should be used with caution or avoided in certain situations, including:

1. Heart failure, where fluid management and heart workload need careful monitoring.
2. Heart wall thickening or bradycardia (slow heart rate), as CCBs can worsen these conditions.
3. Severely low blood pressure, since both drugs can further reduce it.
4. Allergic or adverse reactions to any of the medications.
5. Electrolyte imbalance**s**, especially low potassium or sodium, which can be worsened by diuretics.

Possible Side Effects:

Patients using a CCB and diuretic combination may experience side effects such as:

- Constipation
- Headaches
- Dizziness or lightheadedness, especially when standing up
- Low blood pressure (hypotension)
- Swelling in the ankles or legs (edema)
- Frequent urination
- Electrolyte imbalances, which can lead to fatigue or muscle cramps

In some cases, especially among older adults, this combination can increase the risk of hospitalization or emergency visits due to dehydration or blood pressure drops. Regular monitoring by a healthcare provider helps ensure the treatment remains safe and effective.

2.Beta-Blockers Used with Diuretics:

Combining beta-blockers with diuretics is a well-established and effective strategy for managing high blood pressure. While beta-blockers have proven benefits in reducing cardiovascular risks, some studies especially those involving atenolol indicate that they may not provide as much long-term heart protection as other classes like diuretics, ACE inhibitors, ARBs, or calcium channel blockers (CCBs).

Beta-blockers help lower blood pressure by slowing the heart rate, reducing the force of heart contractions, and decreasing renin release a hormone that raises blood pressure. Like ACE inhibitors and ARBs, beta-blockers influence the renin-angiotensin-aldosterone system (RAAS), which often becomes more active during thiazide diuretic use.

When used together, beta-blockers and diuretics have a complementary (additive) effect, making them especially useful for Black patients or those with low-renin hypertension. However, this combination can occasionally cause side effects such as fatigue, sexual dysfunction, or blood sugar imbalances. Despite these potential drawbacks, it remains a safe and effective treatment option for many individuals managing hypertension.

Mechanism of Action:

Diuretics help the kidneys remove extra salt and water, reducing the total amount of fluid in the body. This lowers the pressure inside blood vessels.
Beta-blockers work by blocking the effects of adrenaline, which slows the heart rate and reduces how strongly the heart pumps. This decreases the heart's workload and helps lower blood pressure. When used together, diuretics and beta-blockers target two key factors that raise blood pressure excess fluid volume and overactive heart function. This combined action helps reduce strain on the heart and blood vessels, improving overall cardiovascular health.

Specific Contraindications and Precautions:

This combination should be avoided or used carefully in people who have:

1. Cardiogenic shock (when the heart cannot pump enough blood).
2. Heart block (a problem with the heart's electrical signals).
3. Severe asthma or chronic obstructive pulmonary disease (COPD), since beta-blockers can worsen breathing problems.
4. Serious electrolyte imbalances, especially low potassium or sodium levels.
5. Anuria (no urine output) or severe dehydration, as diuretics can worsen these conditions.

Possible Side Effects:

Using beta-blockers and diuretics together may lead to:

- Low heart rate (bradycardia)
- Low blood pressure (hypotension)
- Fatigue or tiredness
- Dizziness or lightheadedness
- Cold hands or feet
- Sexual dysfunction
- In rare cases, sudden cardiac events if the heart rate drops too much

Regular check-ups and monitoring by a healthcare provider can help manage these side effects and ensure the combination remains safe and effective.

3.Diuretics with Potassium-Sparing and Thiazide:

A common side effect of thiazide diuretics, such as hydrochlorothiazide (HCTZ) or chlorthalidone, is a drop in potassium levels (hypokalemia). This condition can be serious, potentially leading to irregular heart rhythms or even sudden cardiac death. To minimize this risk, healthcare providers often prescribe a thiazide diuretic together with a potassium-sparing diuretic like triamterene, amiloride, or spironolactone. These medications help the body retain potassium while still promoting the elimination of excess salt and water, creating a safer and more balanced treatment approach.

Typically, HCTZ at a dose of 50 mg or chlorthalidone at 25 mg is used alongside a potassium-sparing diuretic or occasionally a RAAS inhibitor to maintain normal potassium levels. Research indicates that blocking aldosterone, a hormone responsible for salt and water retention, is particularly effective in managing high blood pressure among obese patients. The combination of spironolactone and HCTZ has been shown to help these individuals achieve better blood pressure control. Similarly, pairing HCTZ with amiloride can effectively prevent hypokalemia while still lowering blood pressure efficiently.

However, these combinations are recommended mainly for patients with normal kidney function (estimated glomerular filtration rate above 50 mL/min/1.73 m^2). In individuals with impaired kidney function, there is an increased risk of developing high potassium levels (hyperkalemia), and thiazide diuretics may become less effective.

Mechanism of Action:

Thiazide diuretics function by targeting the distal convoluted tubule in the kidneys, where they block the sodium-chloride (Na^+/Cl^-) transporter. This inhibition leads to increased excretion of sodium, chloride, and water, thereby lowering blood volume and reducing blood pressure. Additionally, thiazides help retain calcium, which can support bone density and reduce the risk of osteoporosis.

In contrast, potassium-sparing diuretics act primarily in the collecting ducts of the kidney. They either block epithelial sodium channels (ENaC) or inhibit aldosterone receptors, resulting in the elimination of sodium and water while conserving potassium. This mechanism helps prevent hypokalemia, a common side effect of thiazide use, and maintains better electrolyte balance.

This combination should be used carefully or avoided in people who have:

1. Hyperkalemia (high potassium levels).
2. Severe kidney failure, since the drugs can build up in the body.
3. Sulfonamide allergy, because some thiazides are sulfa-based.
4. Anuria (no urine output), as diuretics will not work in this condition.

Possible Side Effects:

- High potassium levels (hyperkalemia), especially in patients with kidney problems.
- Dizziness or low blood pressure from fluid loss.
- Muscle cramps or fatigue due to electrolyte changes.
- In rare cases, hormone-related effects from spironolactone, such as breast tenderness or irregular menstrual cycles.

Combination Therapy – For Patients with Uncontrolled Blood Pressure:

If a patient's blood pressure remains high despite taking medication, combination therapy may be needed. The right combination should be chosen from options proven to be effective and safe. Less effective or risky combinations should be avoided.

The most suitable treatment approach depends on several factors, including:

- The patient's age and general health status
- The presence of other medical conditions**,** such as diabetes or kidney disease
- Previous response to medications,
- Cost and accessibility of drugs, and
- The doctor's clinical judgment.

The main goal is to keep blood pressure under control safely, effectively, and affordably using medicines that work well together and cause the fewest side effects**.[5]**

5.FIRST MEDICATION USED FOR HYPERTENSION:

For most people with uncomplicated hypertension, the first medication of choice is often a thiazide diuretic, such as hydrochlorothiazide (HCTZ). This drug works by increasing the excretion of salt and water through urine, which lowers blood volume and helps reduce pressure within the arteries.

Thiazide diuretics are preferred as initial therapy because they are highly effective, affordable, and well-tolerated by most patients. Over time, maintaining controlled blood pressure with thiazides has been proven to lower the risk of heart attacks, strokes, and heart failure.

However, in individuals with additional health concerns such as diabetes, kidney disease, or heart conditions doctors may choose other first-line agents like ACE inhibitors, angiotensin receptor blockers (ARBs), or calcium channel blockers (CCBs). Despite these alternatives, for the majority of otherwise healthy adults with mild to moderate hypertension, hydrochlorothiazide and other thiazide diuretics remain the standard, safe, and effective starting point for long-term blood pressure control.

6.Normal Cardiac and Vascular Physiology in Hypertension

The cardiovascular system is responsible for supplying blood efficiently to all body tissues. Blood flow occurs because of a pressure difference created by the pumping action of the heart. The relationship between blood pressure and blood flow is analogous to Ohm's Law in electricity and is sometimes referred to as Darcy's Law in physiology.

For the circulatory system as a whole, this relationship can be expressed as:

Mean Arterial Pressure (MAP) = Cardiac Output (CO) × Total Peripheral Resistance (TPR)

This equation emphasizes that an increase in mean arterial pressure and thus hypertension can result only from an increase in cardiac output, total peripheral resistance, or both.

Cardiac Output (CO) is determined by the performance of the left ventricle, which depends on several key factors:

- Preload: The volume of blood filling the heart during diastole, also known as venous return or left ventricular end-diastolic volume (LVEDV).
- Contractility: The ability of the heart muscle to contract and generate force.
- Afterload: The resistance the ventricle must overcome to eject blood into the aorta. While often equated with peripheral vascular resistance (PVR), afterload is more accurately described as aortic input impedance, representing the complex interaction between pulsatile pressure and flow during the cardiac cycle.

In essence, normal cardiovascular physiology maintains equilibrium between pressure, flow, and resistance. When this equilibrium is disturbed due to an increase in cardiac output, vascular resistance, or both mean arterial pressure rises, leading to the development of hypertension**.[6]**

7.Clinical Trials on Combination Therapy for Hypertension

Clinical research on combination therapy for hypertension focuses on determining how two medications work together compared to their effects when given separately. In most studies, patients first receive a single antihypertensive drug, either at a fixed dose or adjusted to reach a specific target. If this initial treatment fails to achieve the desired blood pressure reduction, a second medication is added. This sequential approach helps researchers measure the additional effect of the second drug in individuals who respond poorly to monotherapy. It is also a practical strategy when trials face constraints such as limited participant numbers or short study duration.

A more detailed and statistically robust approach is the randomized factorial design, in which several doses of one medication or placebo are combined with different doses of another often a diuretic. This structure forms a grid of treatment combinations, enabling a comprehensive evaluation of dose–response interactions. It allows researchers to determine the most effective and balanced combination of two antihypertensive agents objectively. For optimal results, the study should include a wide range of doses, extending even beyond typical therapeutic limits, to thoroughly analyze how each drug functions both alone and together**.**

The study described here utilized this approach in a multicenter, factorial-design clinical trial that tested a slow-release formulation of diltiazem hydrochloride (Cardizem SR; Marion Laboratories Inc., Kansas City, MO**)** either as monotherapy or combined with hydrochlorothiazide (HCTZ) for patients with mild to moderate essential hypertension**.** This design allowed an in-depth examination of various dose combinations and their effects on blood pressure, contributing valuable data for optimizing combination antihypertensive therapy.[7]

8.Hydrochlorothiazide (HCTZ)

Recent reviews have highlighted that hydrochlorothiazide (HCTZ) is less effective than thiazide-like diuretics and several other classes of antihypertensive agents. The chemical structure and renal site of action of HCTZ differ from those of thiazide-like diuretics (Figure 2). HCTZ has a relatively short duration of action less than 24 hours and demonstrates lower potency compared to indapamide (INDAP), chlorthalidone (CTDN), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and calcium channel blockers, with a systolic blood pressure difference of approximately 4.2–6.2 mm Hg.

Clinical trials have shown that HCTZ provides less cardiovascular protection than other medications: it was less effective than enalapril in the ANBP2 study, amlodipine in the ACCOMPLISH trial, and both CTDN and HCTZ-amiloride combinations in network meta-analyses (Table 4). Additionally, HCTZ and CTDN show comparable risks of gout and hypokalemia. In patients with hypertension and diabetes, HCTZ has been found to be inferior

to indapamide in improving endothelial function and cardiac longitudinal strain, and less effective than spironolactone (SPIR) in enhancing coronary flow reserve. **[8]**

8.1. HYDROCHLOROTHIAZIDE AS IT RELATES TO HYPERTENSION:

(Thalitone, Chlorthalidone, Microzide, and Aquazide) Hydrochlorothiazide is a thiazide diuretic (water tablet). It helps reduce the body's water content by speeding up the flow of urine. hydrochlorothiazide-containing tablets or capsules. One medication used to treat hypertension is hydrochlorothiazide. It also helps reduce edema caused by heart, liver, or kidney disease. It is a diuretic that helps the kidneys eliminate moisture and salt from the blood through urine.

Fig 4. Information Of Hydrochlorothiazide

Common brand names: Hydrodiuril, Oretic, Microzide, Esidrix, and BPzide.
Generic names that are frequently used: HCTz stands for hydrochlorothiazide.
The correct way to pronounce it: - HyE-droe, or KLOR-oh-THYE-a-zide instead.
Class of Drugs: Antihypertensive, thiazide-diuretic.
Availability: Prescription only; only generic.
In what way is it utilized? This tablet or capsule is swallowed.

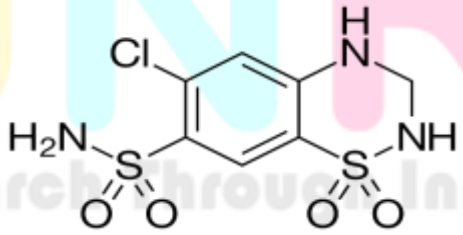

Fig 5. Structure Of Hydrochlorothiazide

Chemical Names

Hydrochlorothiazide is the internationally recognized nonproprietary name (INN) for the compound known by several chemical descriptions, including:

- 6-Chloro-3,4-dihydro-7-sulfamoyl-2H-1,2,4-benzothiadiazine-1,1-dioxide
- 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide

- 6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide
- 2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-, 1,1-dioxide

CAS Registry Number**:** 58-93-5**[9]**

8.2. Impact of Large and Small Doses of Hydrochlorothiazide**:**

The exact relationship between the diuretic (fluid-removing) and blood pressure-lowering effects of benzothiadiazines. The drug family that includes hydrochlorothiazide (HCTZ**)** is still not completely clear. In the short term, these medicines lower blood pressure mainly by reducing the amount of fluid in the bloodstream through increased urination. This reduction in plasma volume helps decrease pressure on the blood vessel walls. However, with long-term use, blood pressure remains controlled even after plasma volume returns to normal. This suggests that the drug's antihypertensive effect is not solely due to its ability to remove water and salt from the body. Some studies, including those on diazoxide (a related drug that does not cause diuresis), have shown that these medicines may also relax blood vessels directly, improving blood flow and lowering resistance within the arteries. Experts generally agree that the blood pressure-lowering benefits of hydrochlorothiazide over time are not directly linked to its diuretic (fluid loss) effects. Instead, the long-term control of hypertension likely involves other mechanisms, such as changes in how the blood vessels react to salt and hormones or how the body regulates sodium balance.[**10]**

Dosage Effects:

Research has shown that the maximum daily dose of hydrochlorothiazide as a diuretic is about 200 mg, and increasing the dose up to 400 mg does not significantly increase the amount of sodium, potassium, or chloride excreted in urine. This means that after a certain point, higher doses do not make the drug more effective in promoting fluid loss.

In terms of blood pressure control, studies have also found that raising the long-term dose of hydrochlorothiazide above the level that produces maximum diuresis does not significantly improve blood pressure reduction. In other words, once the optimal dose is reached (usually much lower than 200 mg for hypertension treatment typically between 12.5 mg and 50 mg per day), increasing the amount provides little to no additional benefit.

Higher doses may also increase the risk of side effects, such as low potassium (hypokalemia), dizziness, dehydration, muscle weakness, and electrolyte imbalances. Therefore, doctors usually prescribe the lowest effective dose that can control blood pressure while minimizing these risks.

Summary:

- Small doses of hydrochlorothiazide are generally effective and safer for long-term blood pressure control.
- Large doses do not significantly enhance the antihypertensive or diuretic effects but increase side effects.
- The drug's ability to lower blood pressure is likely linked to changes in blood vessel function and sodium regulation, rather than just water loss.
- For most patients, keeping the dosage within the recommended therapeutic range achieves good blood pressure control and maintains overall safety.

8.3. How Hydrochlorothiazide Works:

Hydrochlorothiazide (HCTZ) is a commonly used thiazide diuretic that helps lower blood pressure by acting on the kidneys. It mainly works in a specific part of the kidney called the distal convoluted tubule, which is responsible for regulating the balance of salts and water in the body.

The main action of HCTZ is to block the sodium-chloride (Na^+/Cl^-) cotransporter, a protein that normally helps the body reabsorb sodium and chloride from the filtered fluid before it becomes urine. When this transporter is blocked, the kidneys are unable to take back as much sodium and chloride. Because water naturally follows sodium, more water stays in the urine and is excreted from the body. This leads to a reduction in fluid volume in the bloodstream, which helps to lower blood pressure.

Step-by-Step Mechanism:

- Blockade of the Na^+/Cl^- cotransporter (NCC): Hydrochlorothiazide (HCTZ) binds at the apical surface of cells in the distal convoluted tubule and inhibits the sodium–chloride cotransporter, so less sodium and chloride are taken back into the bloodstream.

- Increased renal excretion of salt and water**:** With more sodium left in the tubular fluid, water follows osmotically, producing a larger urine output (diuresis).

- Decrease in circulating blood volume: The loss of salt and water lowers total blood volume, which reduces the pressure exerted on vessel walls.

- Sustained drop in vascular resistance: Beyond the initial volume loss, thiazides produce longer-term reductions in peripheral vascular resistance (vessel tone relaxes and vessels dilate), helping to keep blood pressure lower even after fluid balance has partially returned to baseline.

Overall Effect:

Hydrochlorothiazide works by eliminating excess salt and water from the body while relaxing the blood vessels. This action eases the strain on the heart and lowers pressure within the arteries, making it effective for managing high blood pressure (hypertension) and fluid retention (edema)

Examples of Hydrochlorothiazide**:** Hydrochlorothiazide (HCTZ) is available on its own or in combination with other blood pressure medicines. Some common examples include:

1. Hydrochlorothiazide (HCTZ**)** – the generic form, often prescribed alone.
2. Microzide – a brand name for hydrochlorothiazide capsules.
3. HydroDIURIL – another brand name version of HCTZ tablets.
4. Losartan/HCTZ (Hyzaar**)** – a combination of an ARB (losartan) and hydrochlorothiazide.
5. Lisinopril/HCTZ (Zestoretic or Prinzide**)** – a mix of an ACE inhibitor (lisinopril) with hydrochlorothiazide.
6. Valsartan/HCTZ (Diovan HCT**)** – combines an ARB (valsartan) with hydrochlorothiazide.
7. Metoprolol/HCTZ (Lopressor HCT**)** – combines a beta-blocker (metoprolol) with hydrochlorothiazide.

These medicines help lower blood pressure and reduce swelling caused by fluid buildup. Hydrochlorothiazide is often used as **a** first-line treatment for high blood pressure because it is effective, affordable, and well-tolerated by most patients.

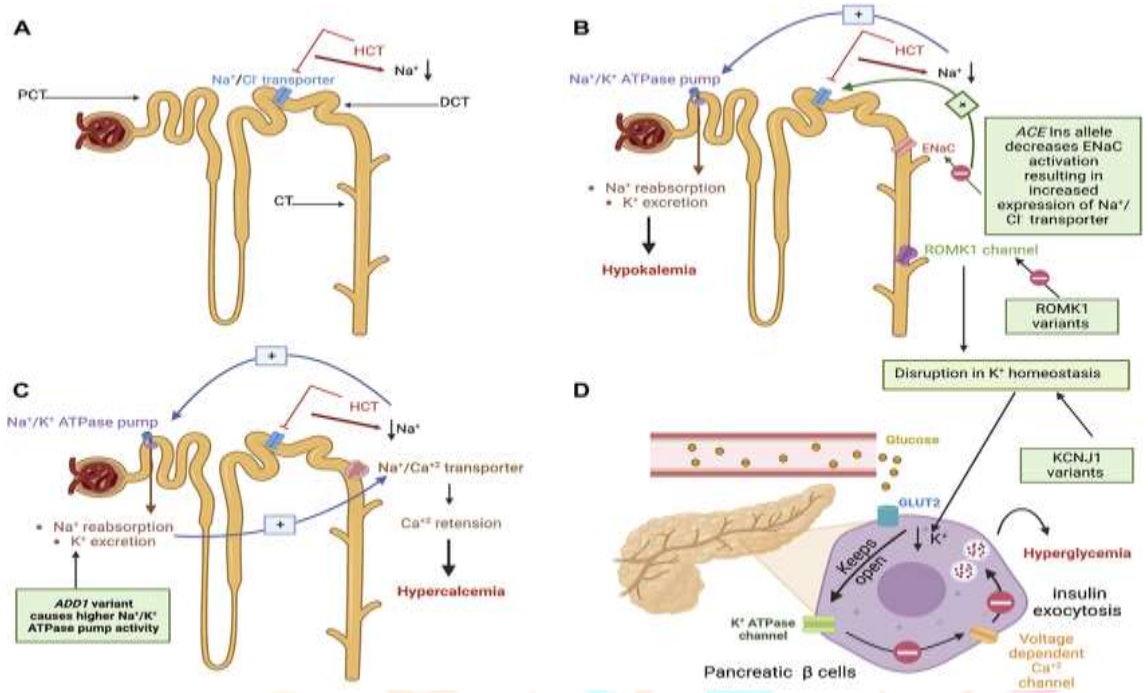

Fig 6. Mechanism of action hydrochlorothiazide

8.4. Techniques Used to Investigate the Antihypertensive Mechanism of Hydrochlorothiazide (HCT)

To understand how hydrochlorothiazide (HCT) exerts its blood pressure lowering effects, a variety of experimental and physiological methods were applied. These approaches were aimed at distinguishing the central, reflex, cardiac, and peripheral vascular influences of the drug.

a) Carotid Artery Injection:
Doses ranging from 1–3 mg/kg of HCT were injected into the common carotid arteries of dogs, following the method developed by Heymans, Bouckaert, and Dautrebande. This procedure was used to identify whether the resulting alterations in blood pressure and respiration were of central origin or due to reflex responses involving baroreceptors and chemoreceptors.

b) Carotid Region Infiltration:
Each carotid sinus area received an infiltration of 1 mg of HCT per side, as described by Heymans and Van den Heuvel-Heymans. The same method was repeated before and after bilateral infiltration with 100 µg of adrenaline (A) or noradrenaline (NA) on each side. This allowed the evaluation of how HCT influenced adrenergic receptor activity within the carotid regions.

c) Acute Neurogenic Hypertension Model:
An experimental model of acute neurogenic hypertension, established according to Heymans and Bouckaert, was used to assess HCT's action under conditions of heightened sympathetic activity.

d) Vascular and Neural Stimulation Tests:
Further tests involved bilateral occlusion of the carotid arteries and electrical stimulation of both peripheral and central vagus nerves. Blood pressure changes were recorded after the intravenous administration of several vasoactive compounds adrenaline (5 µg/kg), noradrenaline (5 µg/kg), HP II (5 µg/kg), acetylcholine (5–10 µg/kg), and histamine (2.5 µg/kg) administered both before and after HCT treatment (0.8–66 mg/kg). These experiments helped identify how HCT modified vascular reactivity and autonomic responses.

e) Nolf Manometer Method:
The three-manometer technique developed by Nolf was utilized to differentiate central, cardiac, and peripheral vascular components of the drug's hypotensive effect. This setup was complemented by electrical stimulation of the lumbar sympathetic chain, which supplied the limb that received HCT injections (1–2 mg/kg), enabling researchers to observe local sympathetic and vascular reactions**.[11]**

8.5. Limitations of Hydrochlorothiazide (HCTZ):

Although hydrochlorothiazide (HCTZ) is commonly prescribed to manage high blood pressure, it has several drawbacks that can influence its overall effectiveness and safety compared to other antihypertensive medications.

1. Lower Effectiveness (Reduced Efficacy):

At standard low doses, hydrochlorothiazide (HCTZ) is generally less effective in maintaining blood pressure control over a full 24-hour period compared to other drug classes such as ACE inhibitors, ARBs, beta-blockers, and calcium channel blockers (CCBs).

This reduced efficacy is largely due to HCTZ's short half-life, which means it is eliminated from the body relatively quickly. As a result, its blood pressure lowering effects tend to wear off before the next dose, particularly during nighttime and early morning hours times when blood pressure naturally increases. This can lead to misleadingly normal readings during daytime doctor visits, even though blood pressure may not remain controlled throughout the day and night.

In contrast, other thiazide-type diuretics like chlorthalidone and indapamide provide longer-lasting effects, offering more consistent blood pressure reduction over a 24-hour period.

2. Limited Cardiovascular Protection:

Although hydrochlorothiazide is effective in lowering blood pressure, research indicates that there is limited evidence showing it substantially reduces the risk of major cardiovascular events such as heart attacks or strokes particularly when used at lower doses.

Research comparing HCTZ with other antihypertensive medications suggests that it may be less effective at preventing heart failure, stroke, and coronary artery disease. Other thiazide-like diuretics, such as chlorthalidone, have been proven to provide stronger cardiovascular protection and better long-term outcomes. This makes chlorthalidone or indapamide the preferred choice for many patients who require diuretic therapy to prevent complications from high blood pressure.

3. Negative Metabolic Effects:

Long-term use of hydrochlorothiazide has been associated with several adverse metabolic changes, particularly at higher doses. These side effects are important to monitor, as they can increase the risk of other health problems.

a. Electrolyte Imbalance:
HCTZ can disturb the balance of key minerals in the body, leading to:

- Hypokalemia (low potassium), which can cause muscle weakness, fatigue, or heart rhythm problems.
- Hyponatremia (low sodium), leading to confusion, headaches, or dizziness.
- Hypomagnesemia (low magnesium), which can cause cramps or irregular heartbeat.
- Hypercalcemia (high calcium), which may cause kidney stones or other calcium-related issues.

b. Impaired Glucose Metabolism:

Hydrochlorothiazide (HCTZ) can reduce the body's sensitivity to insulin, which may cause elevated blood sugar levels. This effect can increase the likelihood of developing type 2 diabetes, especially in individuals who already have risk factors for the condition.

b. High Uric Acid Levels:
HCTZ can raise uric acid levels in the blood, which may trigger or worsen gout a painful joint condition caused by uric acid crystal buildup.

c. Photosensitivity and Skin Cancer Risk:
Because HCTZ can make the skin more sensitive to sunlight (photosensitizing effect), long-term use especially at high doses has been linked to a slightly increased risk of non-melanoma skin cancers, such as basal cell carcinoma and squamous cell carcinoma.

4. Comparison with Other Thiazide-Type Diuretics:

Other drugs in the same class, such as chlorthalidone and indapamide, are often preferred because they:

- Have a longer half-life, allowing for better 24-hour blood pressure control.
- Are more potent, meaning they achieve greater blood pressure reduction at lower doses.
- Have stronger evidence showing that they reduce the risk of heart attacks, strokes, and heart failure.

Because of these advantages, many experts recommend chlorthalidone instead of hydrochlorothiazide for long-term blood pressure management, especially in patients at higher risk of cardiovascular disease.

8.6. Hydrochlorothiazide (HCTZ) Trend:

In recent years, the use of hydrochlorothiazide (HCTZ) has decreased in several countries, including Switzerland and Canada. This decline is mainly attributed to safety warnings from health authorities such as the U.S. Food and Drug Administration (FDA), Health Canada, and Swissmedic. These agencies have reported that prolonged use of HCTZ may be linked to a higher risk of developing non-melanoma skin cancers (NMSC), especially basal cell carcinoma and squamous cell carcinoma.

While HCTZ remains a commonly used medication for managing high blood pressure, healthcare professionals are increasingly exploring safer and more effective alternatives. There is also growing emphasis on patient education informing individuals about possible skin cancer risks and promoting protective habits like regular sunscreen use and limiting sun exposure.

Ongoing research and clinical discussions now focus on creating personalized hypertension treatment strategies that maximize therapeutic benefits while minimizing potential health risks, ensuring patients receive the most appropriate and safe medication for their needs.

8.7. Current Treatment with Hydrochlorothiazide (HCTZ):

As of 2025, hydrochlorothiazide (HCTZ) continues to be one of the most frequently prescribed medications for treating high blood pressure (hypertension) and edema (fluid retention). It belongs to the thiazide diuretic class, which works by helping the kidneys remove excess salt and water from the body. This reduction in fluid volume decreases blood vessel pressure and improves blood circulation. HCTZ remains a preferred choice due to its

proven effectiveness, affordability, and good tolerability, making it a standard first-line therapy for uncomplicated hypertension. It is available in various forms such as tablets, capsules, and oral solutions allowing for flexibility based on patient requirements.

HCTZ may be prescribed alone or in combination with other antihypertensive agents, including ACE inhibitors, ARBs, or beta-blockers, to achieve better blood pressure control. Combination therapy enables the use of lower doses of each medication, which helps minimize side effects while enhancing overall efficacy. Typically, doctors initiate treatment with a low dose of HCTZ, as this is often effective for blood pressure regulation and helps reduce the likelihood of electrolyte disturbances.

Patients taking HCTZ are generally advised to undergo regular blood tests to monitor potassium, sodium, and kidney function levels. Although some concerns remain regarding long-term safety particularly in relation to skin sensitivity and metabolic changes HCTZ continues to be a widely trusted medication because of its well-documented effectiveness, accessibility, and cost-efficiency in treating hypertension.

8.8. Common Side Effects of Hydrochlorothiazide (HCTZ):

Hydrochlorothiazide can cause some mild to moderate side effects in certain people. The most common ones include feeling weak or tired, dizziness, and changes in electrolyte levels (such as low potassium or sodium). Some people may also experience headaches, increased blood sugar levels, or sexual difficulties. If you notice any serious symptoms like vomiting, sudden extreme weakness, confusion, or anything unusual seek medical help immediately. Regular checkups and blood tests can help monitor and manage these side effects safely.

8.9. Adverse Effects and Special Considerations of Hydrochlorothiazide (HCTZ):

1. Electrolyte Imbalances:

Hydrochlorothiazide may cause disturbances in electrolyte levels, including decreased potassium (hypokalemia), sodium (hyponatremia), and magnesium (hypomagnesemia), as well as increased calcium (hypercalcemia) and metabolic alkalosis. These effects result from the drug's action on the distal convoluted tubule, where it inhibits the sodium-chloride (Na^+/Cl^-) cotransporter. The risk of developing these imbalances is higher when HCTZ is taken at doses above 25 mg or combined with loop diuretics.

2.Hyperglycemia:

Hydrochlorothiazide use has been associated with increases in fasting blood glucose levels. While the precise mechanism remains unclear, it is thought that reduced potassium levels caused by the drug may interfere with insulin secretion from the pancreas. As a result, individuals with diabetes or prediabetes should use hydrochlorothiazide carefully and be regularly monitored for changes in blood sugar levels.

3. Gout:

Hydrochlorothiazide can raise uric acid levels in the blood (hyperuricemia), which may trigger gout attacks, especially in susceptible individuals. This occurs due to fluid loss and increased uric acid reabsorption in the kidneys. Gout symptoms typically appear within the first few weeks of treatment.

5. **Dyslipidemia:**
   Some studies have shown that hydrochlorothiazide use may be associated with elevated cholesterol levels (hypercholesterolemia), though the mechanism behind this effect remains unclear.

5.Sulfa Allergy:

Hydrochlorothiazide contains a sulfonamide group, making it unsuitable for individuals with a known allergy to sulfa drugs. In such patients, the medication may trigger allergic reactions, including rashes, hives, or, in severe

cases, serious skin conditions like Stevens–Johnson syndrome, toxic epidermal necrolysis, or even anaphylaxis. Although true cross-reactivity with sulfonamide antibiotics is uncommon, healthcare providers should still exercise caution when prescribing HCTZ to patients with a history of sulfa sensitivity.

6. **Ocular Effects:**
   In rare instances, hydrochlorothiazide may cause temporary vision problems, such as acute angle-closure glaucoma or short-term nearsightedness (myopia). These effects typically occur within the first few days of starting treatment and are thought to be related to the drug's sulfonamide structure.
7. **Special Considerations:**
   In patients with liver cirrhosis, hydrochlorothiazide can cause significant drops in sodium levels (hyponatremia) or trigger hepatic encephalopathy. Such patients should be monitored closely during therapy. Additionally, healthcare providers should use caution when prescribing HCTZ before or after surgery to prevent dehydration or other complications related to fluid balance**.[12]**

9.CONCLUSION: -.

Individualized, high-tech care has replaced traditional pharmaceutical therapy for hypertension. Combining lifestyle modifications, effective medication, and state-of-the-art technology such as genetic testing, telemonitoring, and renal denervation offers a holistic approach. The burden of cardiovascular disease could be reduced globally and optimal blood pressure control could be attained with future advancements that focus on precision medicine and novel treatments Hydrochlorothiazide, a thiazide diuretic, is an FDA-approved medication in the United States used to manage high blood pressure and peripheral edema. Hydrochlorothiazide functions by preventing the reabsorption of sodium in the distal convoluted tubules of the kidneys. This action promotes the elimination of excess salt and water from the body, which helps decrease blood volume, lower blood pressure, and reduce fluid retention.

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