INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Recent advance in clinical evaluation of antihypertensive Drug

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ARTICLE INFO

Received: 14 Jan 2024
Accepted: 18 Jan 2024
Published: 23 Jan 2024

Keywords:
Hypertension, Clinical Evaluation Method, Clinical Practice Guidelines, Clinical Study

DOI:
10.5281/zenodo.10557184

ABSTRACT

Hypertension, a prevalent cardiovascular condition, has been recognized as a significant risk factor for various adverse health outcomes, including stroke, myocardial infarction, and renal failure. Over the decades, a plethora of antihypertensive drugs have been developed and introduced into clinical practice. This review synthesizes the current state of research and evaluation of these drugs, providing an overview of their mechanisms of action, efficacy profiles, safety considerations, and comparative effectiveness. The paper commences with a discussion on the pathophysiology of hypertension, laying the foundation for understanding the targets and mechanisms of action of antihypertensive medications. Subsequent sections delve into the classes of antihypertensive drugs, including diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, ARBs, and newer agents like mineralocorticoid receptor antagonists. For each class, the review presents pivotal clinical trials, highlighting key findings related to blood pressure reduction, cardiovascular outcomes, and adverse effects. Safety profiles, drug interactions, and considerations for monitoring are critically evaluated to provide clinicians with evidence-based guidance for optimizing therapeutic outcomes while minimizing potential harms. The review also underscores the evolving landscape of antihypertensive drug development, with a focus on emerging therapies and research directions.

INTRODUCTION

A systolic blood pressure (SBP) of at least 140 mmHg and/or a diastolic blood pressure (DBP) of at least 90 mmHg are indicators of hypertension. [1] HTN is very important clinically even though it is much less common in children and adolescents than in adults. This is because young people's elevated blood pressure increases the risk of developing chronic HTN in adulthood. [2]. The first therapeutic approach to take in these situations, as in adulthood, should be non-pharmacological treatment, i.e., changing unhealthy lifestyle choices that could raise blood pressure. [3,4M]. Many individuals with

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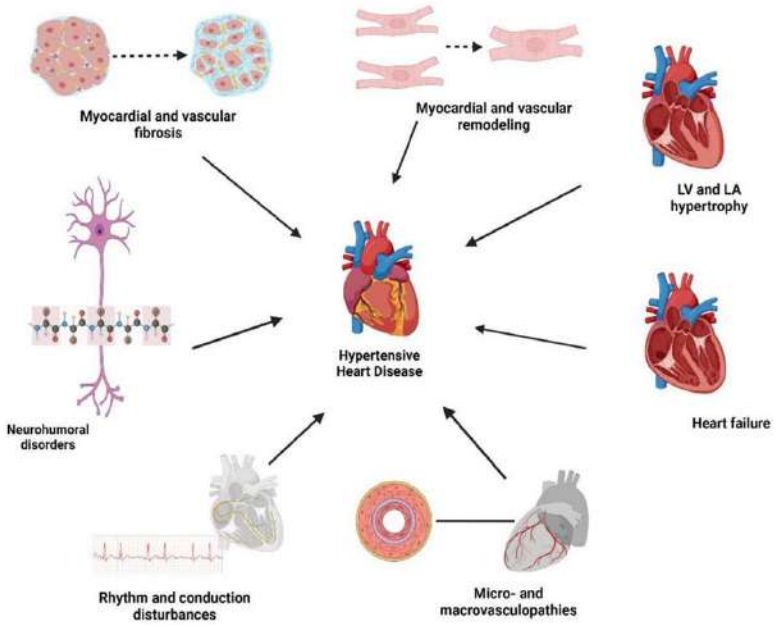
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

hypertension remain unmanaged due to either not following their treatment or experiencing side effects from existing blood pressure medications. [5,6,7,8,9]. Hypertension (HTN) stands as a primary contributor to heart-related illnesses and deaths globally. It denotes a persistent rise in blood pressure (BP) levels and impacts individuals across all age groups, genders, and ethnic backgrounds. [10]. In the last two decades, numerous countries in sub-Saharan Africa and Oceania have not seen any advancements in awareness, treatment, or management of hypertension. [11,12,1314]. Hypertension is a key contributor to cardiovascular ailments such as heart attacks, strokes, aneurysms, heart failure, and myocardial infarctions. Maintaining a healthy blood pressure level is crucial for safeguarding health and minimizing the chances of these severe health issues. [15]. Research indicates that lowering blood pressure by 5mmHg can lead to a 34% decrease in stroke risk, a 21% reduction in ischemic heart disease risk, and also lower the chances of developing dementia, heart failure, and mortality related to cardiovascular conditions. [16]. In recent years, there has been a rise in the number of younger individuals diagnosed with hypertension. This trend is partly attributed to the increased frequency of blood pressure screenings. [17]. Similar to adults, the initial treatment approach in such situations should prioritize non-drug interventions. This involves making lifestyle adjustments that could be influencing the rise in blood pressure. [18,19]. Renin's main function is to split angiotensinogen into angiotensin I (Ang I), which subsequently gets transformed into angiotensin II (Ang II) with the help of the enzyme angiotensin-converting enzyme (ACE). [20]. While these medications effectively treat hypertension, their capacity to prevent end-organ damage is somewhat restricted. Additionally, blocking ACE isn't always enough, as it can lead to elevated Ang I levels and trigger pathways outside of ACE that transform Ang I into Ang II. [21]. Despite the numerous available treatments, approximately 10% to 15% of individuals with hypertension face resistant hypertension. This is characterized by blood pressure that remains unregulated even when using three or more antihypertensive medications from various categories, including a non-potassium-sparing diuretic, at recommended doses, or needing four or more drugs to manage it effectively. [22,23]. A significant number of hypertensive patients remain unmanaged due to either not following their medication regimen or experiencing adverse reactions to the prescribed antihypertensive drugs. Recent studies on drug adherence indicate that between 25% to 65% of individuals with seemingly treatment-resistant hypertension (TRH) are not adhering to their blood pressure-lowering treatments. [24-28]. Patients with hypertension who have previously experienced a stroke or transient ischemic attack should be prescribed either a thiazide diuretic, an ACE inhibitor, or an angiotensin receptor blocker for their treatment. [29,30,31]. For patients with acute coronary syndrome who still exhibit hypertension even after receiving treatment with a beta blocker in combination with an ACE inhibitor or an angiotensin receptor blocker, it is recommended to include a long-acting dihydropyridine calcium channel blocker like amlodipine or felodipine in their treatment plan. [32,33]. Patients with resistant hypertension (RH) can be accurately diagnosed by consulting specialists, most of whom can assess the condition by differentiating it from pseudo-hypertension and white-coat hypertension using 24-hour ambulatory blood pressure monitoring. Furthermore, drug absorption monitoring helps in confirming medication adherence. Once genuine RH is confirmed, after eliminating certain criteria, optimizing the drug regimen as recommended by the ESC and AHA, making lifestyle changes, and introducing

additional second-line antihypertensive drugs can lead to a notable enhancement in patient outcomes. [34]. These factors encompass ventricular hypertrophy, endothelial dysfunction, metabolic syndrome, a tendency for blood clotting, oxidative stress, inflammation, and a genetic inclination towards cardiovascular incidents. [35]. Elevated blood pressure (hypertension) stands as a primary adjustable risk element for cardiovascular ailments globally,1 leading to significant healthcare attention for its management. Recent guidelines on hypertension care have proposed more stringent treatment goals,23 drawing from studies that demonstrated advantages in reducing cardiovascular risks. [36].



Classification:

1. Diuretics:

i. Thiazides:

Eg.Hydrochlorothiazide, Chlorthalidone, Indapamide

ii. High ceiling:

Eg. Furosemide

iii. K+ Sparing:

Eg. Spironolactone, Amiloride

2. ACE inhibitors:

Eg. Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril, etc.

3. Angiotensin (ATI receptor) blockers:

Eg. Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan

4. Direct renin:

Eg. Aliskiren

5. Calcium Channel Blocker

Eg. Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.

6. ß blockers:

Eg. Propranolol, Metoprolol, Atenolol, etc.

7. β + alpha Adrenergic blockers:

Eg. Labetalol, Carvedilol

8. alpha Adrenergic blockers:

Eg. Prazosin, Terazosin, Doxazosin, Phenoxybenzamine

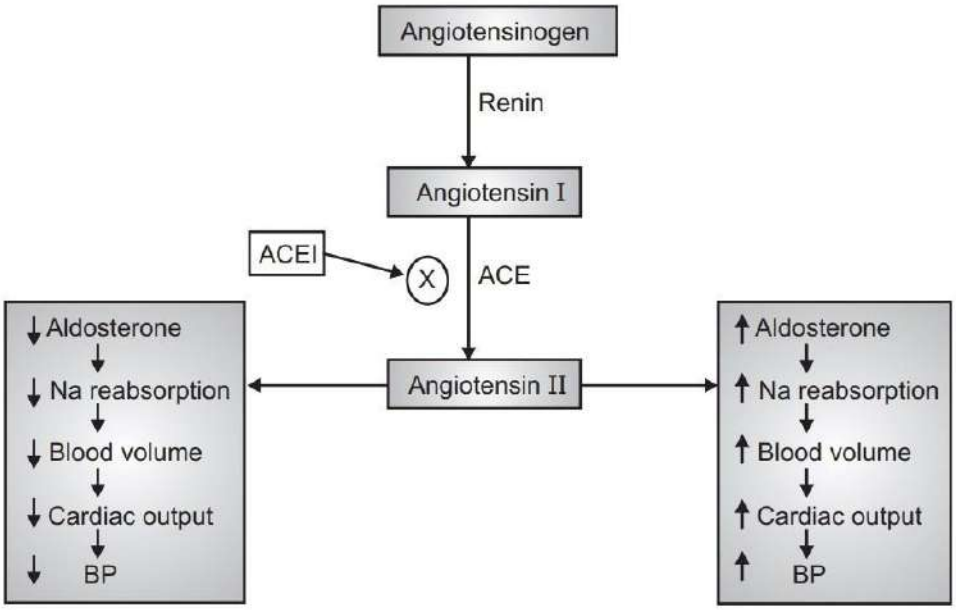
9. Central sympatholytics:

Eg. Clonidine, Methyldopa

10. Vasodilators:

Eg. Hydralazine, Minoxidil, Diazoxide, Sodium nitroprusside

Normal Mechanism of Action :



Clinical Evaluation Methods of Antihypertension 1. Randomized controlled trials :

Among the extensive meta-analyses on antihypertensive treatment randomized controlled trials (RCTs), the studies conducted by the Blood Pressure Lowering Trialists' Collaboration (BPLTTC) stand out. [43]. A thorough evaluation of BP-lowering RCTs is essential, starting with the establishment of precise criteria to distinguish these trials from the numerous others that have examined drugs categorized as antihypertensive agents. [44]. In the 68 RCTs analyzed to quantitatively assess the effectiveness of BP reduction in averting various cardiovascular events, the blood pressure reductions were achieved using medications from diverse pharmacological categories.[45].

2. Blood pressure measurement :

Oscillometric

Oscillometry is a frequently used technique for automated cuff blood pressure (BP) measurements. The concept of oscillometry dates back to 1876 and revolves around observing the fluctuations in the sphygmomanometer cuff pressure, which are induced by the oscillations in blood flow or the pulse. Several coefficient-free oscillometric algorithms have been devised to estimate blood pressure. However, it's important to note that oscillometric monitors can yield unreliable readings in individuals with heart and circulation issues, such as arteriosclerosis, arrhythmia, preeclampsia, pulsus alternans, and pulsus paradoxus. [46-51]

3. Adverse drug monitoring :

Adverse drug reactions (ADRs) rank among the primary causes of both illness and death. Typically, clinical trials evaluating new medications are relatively short-term and involve participant groups of up to 5,000 individuals. As a result, while more common dose-dependent ADRs are identified during the pre-marketing phase, rare reactions and those emerging from prolonged use often go unnoticed. For instance, one patient developed a brownish-blue discoloration of the nails after taking atenolol for three years. Another

individual, after eight years of amlodipine use, exhibited a pigmentation similar to Schamberg's purpura. Previous reports have indicated that combining amlodipine and atenolol elevates the risk of ADRs compared to using either drug alone. Our research revealed that calcium channel blockers (CCBs) were the most frequently prescribed class of medications, but beta-blockers and ACE inhibitors were linked to a higher rate of ADR occurrences. [52-55]

4. Endpoint method:

Our objective was to determine the occurrence rates of specific outcomes in patients who were randomized to receive RAAS inhibitors compared to those on control therapy. Additionally, we sought to gauge the absolute and relative decreases in these outcomes due to RAAS inhibitors. While RAAS inhibitors are often recommended for their potential to reduce (all-cause) mortality, this beneficial impact hasn't been definitively proven for hypertension treatment. Moreover, the majority of studies examining the clinical outcomes of RAAS inhibitors in the context of hypertension were not sufficiently powered to address this specific outcome. [56-58]

5. Pharmacokinetic and pharmacodynamic studies

Pharmacokinetic modeling involves using mathematical methods to understand the dynamic processes that encompass the release, absorption, distribution, protein and tissue binding, metabolism, and excretion of a drug. Key pharmacokinetic parameters highlighted in the Food and Drug Administration's guidance for pediatric antihypertensive studies include the area under the concentration-time curve (AUC), peak plasma or serum concentration (Cmax), and the time to reach peak concentration (Tmax). On the other hand, pharmacodynamics delves into the relationship between a drug's concentration at its action site and the observable effects it produces on biological systems. The magnitude and duration of these effects are influenced by various factors, encompassing the drug's inherent properties and characteristics of the biological system it interacts with. When assessing antihypertensive drugs, short-term therapeutic efficacy is typically evaluated based on blood pressure (BP) changes. This could be as simple as observing the shift in systolic or diastolic BP following the administration of a standard drug dose. However, more intricate measures to gauge short to mid-term therapeutic outcomes might involve comparing BP changes in groups receiving a placebo versus the active drug or analyzing the variance in BP levels between these groups over time. [59-62]

6. Patient-Reported Outcomes:

The primary aim of this study was to assess the outcomes of a pharmacist-led intervention on adherence for hypertensive patients receiving treatment at hospital outpatient clinics, focusing on both process outcomes and feedback from patients and pharmacists. Additionally, the study aimed to compare two adherence assessment tools: a questionnaire employed in the intervention and a measure based on prescription data. Among individuals aged 50 and above, isolated systolic hypertension stands out as the predominant form of high blood pressure. Furthermore, systolic blood pressure (BP) becomes a more crucial determinant than diastolic BP in contributing to conditions such as coronary artery disease, stroke, and renal disorders. Studies have indicated that for participants aged between 40 and 69 years, every increase of 20 mmHg in BP beyond 115 mmHg was associated with a doubling in the risk of cardiovascular events, including mortality. For those aged between 80 and 89 years, this elevated risk was heightened by over a third. [63-67].

Clinical Practice Guidelines for the Management of Hypertension in the Community :

While earlier guidelines from the National High Blood Pressure Education Program (NHBPEP) advocated for regular blood pressure (BP) checks in children and adolescents during every healthcare visit, the 2017 AAP Clinical Practice Guidelines (CPG) suggest that such screenings should only be conducted during annual preventive care check-ups. However, exceptions are made for patients with underlying conditions that elevate the risk of hypertension, such as obesity, diabetes mellitus, heart disease, or kidney disease. Such a recommendation acknowledges the controversy on routine screening of BP in childhood to some extent [68] Confirmation of the diagnosis of hypertension in children and adolescents with repeatedly elevated office BP readings; Confirmation of suspected white-coat hypertension. Assessing the blood pressure (BP) patterns and determining the risk of hypertensive target organ damage (TOD) in children and adolescents with high-risk conditions, like chronic kidney disease (CKD), is crucial. Additionally, monitoring the effectiveness of treatments and identifying potential cases of masked hypertension in children and adolescents diagnosed with CKD is essential for comprehensive care..[69] Data regarding the prevalence of high blood pressure (BP) in children primarily comes from the National Health and Nutrition Examination Survey (NHANES). Often, these statistics rely on a single session of BP measurements. These surveys suggest a rising trend in the prevalence of elevated BP and hypertension among children. [70,71] Boys consistently exhibit higher rates of high blood pressure (BP) at 15%–19%, compared to girls who have rates between 7%–12%. Additionally, the prevalence of high BP is more pronounced in Hispanic and non-Hispanic African American children compared to their non-Hispanic white counterparts. Furthermore, this disparity is more evident among adolescents than in younger children. [72] Regrettably, comprehensive studies focusing on BP awareness or control in young individuals are lacking. However, an examination of prescription data from a nationwide drug provider revealed a notable rise in prescriptions for high BP among youth between 2004 and 2007.[73]Risk factors for the development of nephropathy in people with type 1 diabetes include increasing age, duration of diabetes, male gender and hyperglycaemia.[74 The effectiveness of ACEIs has been explored in individuals who have normal blood pressure (normotensive) and normal levels of albumin in their urine (normoalbuminuric). The findings suggest minimal protective benefits against the onset of diabetic nephropathy. Notably, several of these studies employed blood pressure criteria that would currently be deemed elevated. In a notable multicentre European research, 530 individuals with type 1 diabetes and blood pressure readings below 155/90 mmHg were studied. [75] The existence of this category underscores the idea that blood pressure and vascular risk exist on a spectrum rather than being a binary, all-or-nothing issue. For individuals in this borderline category, the likelihood of progressing to hypertension is significantly elevated unless there are interventions. Lifestyle modifications become crucial, including dietary changes to reduce calorie and salt intake, moderating alcohol consumption, quitting smoking, and promoting consistent physical activity. All three sources align on these recommendations. [76] The treatment guidelines, grounded in extensive clinical trials, exhibit consistency across various groups for specific conditions like heart failure, ischemic heart disease, diabetes mellitus, chronic kidney disease, concurrent cardiovascular ailments, left ventricular hypertrophy, and a pronounced cardiovascular risk profile. However, discrepancies emerge when selecting the initial medication. [77] For Home BP Measurement (HBPM), patients should receive guidance on the

appropriate device to use. It's essential to advise against the use of finger and wrist monitors due to their lack of accuracy, with the exception being wrist monitors, which might be deemed acceptable for obese individuals with notably large arm circumferences. When utilizing HBPM, patients should be instructed that for every blood pressure reading, they need to take two consecutive measurements, with at least a 1-minute interval between them, while seated.The blood pressure should be recorded twice daily, ideally in the morning and evening, and the recording continues for 4 to 7 days. The measurements taken on the first day should be discarded and the average value of all the remaining measurements should be used to confirm a diagnosis of hypertension. Patients with an average BP more than 135/85 mmHg measured at home are generally considered to be hypertensive.[78]

Risk factors :

1. History of CVD (myocardial infarction),
2. Heart failure [HF],
3. Stroke, Transient ischemic attacks [TIA],
4. Diabetes,
5. Dyslipidemia,
6. Chronic kidney disease [CKD],
7. Smoking status,
8. Diet,
9. Alcohol intake,
10. Physical activity,
11. Psychosocial aspects,
12. History of depression.

Family history of hypertension, premature CVD, (familial) hypercholesterolemia, diabetes. Fasting serum glucose levels should be reduced below 126 mg/dL (7 mmol/L) or HbA1c below 7% (53 mmol/mol) [79] BP exhibits seasonal variation with lower levels at higher temperatures and higher at lower temperatures. Similar fluctuations in blood pressure occur when individuals transition from cold to hot climates or vice versa. A meta-analysis revealed an average drop in BP during the summer by 5/3 mm Hg (systolic/diastolic). These BP variations are more pronounced in individuals undergoing hypertension treatment. Hence, it's essential to factor in these changes when observing symptoms that might indicate excessive treatment due to temperature fluctuations or noticing an increase in BP during colder temperatures.BP below the recommended goal should be considered for possible downtitration, particularly if there are symptoms suggesting overtreatment.[80] Healthy lifestyle choices can prevent or delay the onset of high BP and can reduce cardiovascular risk.[81] If a patient, managed with three or more antihypertensive medications at their optimal (or maximally tolerated) doses, including a diuretic, records a seated office BP reading of >140/90 mm Hg, several potential causes need to be considered before labeling it as resistant hypertension. First and foremost, exclude factors like incorrect BP measurement techniques, the white coat effect, nonadherence to medication, and inappropriate antihypertensive drug choices. Additionally, investigate the possibility of substances or medications that could be elevating the BP. Refine the existing treatment plan by emphasizing health behavior modifications and prioritizing diuretic-based therapy. Ensure patients are on the highest tolerable doses of diuretics. When selecting a diuretic, favor thiazide-like diuretics over traditional thiazides. For individuals with an eGFR less than 30 ml/min/1.73m^2 or those displaying clinical signs of volume overload, consider initiating loop diuretics. [82] Hypertension during pregnancy is a significant concern, impacting 5%–10% of pregnancies globally. Maternal complications can encompass placental abruption, stroke, and multi-organ failure involving the liver and kidneys. There's also a risk of disseminated intravascular coagulation. For the fetus, potential risks include intrauterine growth restriction, premature birth, and intrauterine demise. The

conditions associated with hypertension in pregnancy include pre-existing hypertension, gestational hypertension, and preeclampsia. [83,84]

Clinical studies of antihypertensive drug :

Human Studies :-

The effect on blood pressure of lean fish as the protein source, has been evaluated and documented in two dietary intervention studies. Erkkila et al. [85] randomized 33 medicated patients with coronary heart disease into three groups eating lean fish, fatty fish or lean meat as protein sources four times a week during eight weeks. After the intervention period, both systolic and diastolic blood pressure was reduced in the group eating lean fish. Ramel et al. [86] In a study exploring the dose-response relationship of consuming cod meals weekly, 126 healthy overweight participants were randomly assigned to one of three groups: no cod, cod thrice weekly, or cod five times weekly, all while adhering to a calorie-restricted diet for eight weeks. However, the findings from the blood pressure assessments were inconsistent and thus deemed unreliable. Double-blind, placebo-controlled trials are typically considered the benchmark for assessing the impacts of various substances. In a related study, 34 overweight adults were provided with either fish protein capsules or placebo tablets over an eight-week period. [87]. Participants consumed the supplement at a dosage of 3 g daily for the initial four weeks, which was then increased to 6 g daily for subsequent weeks. Despite the increased dosage, there was no observed impact on blood pressure. In a parallel study of a comparable nature, researchers examined the influence of a salmon peptide on blood pressure levels. [88]. In a study involving 52 individuals with mild hypertension, participants were divided into three groups. Each group consumed a daily beverage (50 mL) containing either 1 g, 0.3 g, or no salmon peptide for a duration of four weeks. Results indicated that the group consuming 1 g of salmon peptide experienced a significant reduction in systolic blood pressure, dropping from 140 mmHg to 135 mmHg. This finding was reported by Kawasaki et al. [89] Kawasaki et al. conducted a study to assess the impact of a specific peptide on 29 individuals who had high-normal blood pressure or mild essential hypertension. These participants were divided into two groups for a crossover, placebo-controlled trial. The findings revealed that the dipeptide drink led to a notable reduction in blood pressure within the dipeptide group. In contrast, the placebo group showed no significant changes. It's worth noting that findings related to blood pressure from one fish species might not directly apply to others, especially given that compounds like taurine, known for their blood pressure-lowering effects, can vary across species. [90]. Taurine content varies greatly between fish species [91], however, compared to other foods, it is generally high in marine foods.

FUTURE PERSPECTIVE

The future trajectory of antihypertensive drug evaluation is poised for significant advancements, especially with the rapid evolution of personalized medicine, targeted therapeutic interventions, and an in-depth comprehension of genetic variables that influence blood pressure dynamics. Innovations like wearable technologies and continuous monitoring systems are expected to revolutionize the assessment of treatment outcomes. As we delve deeper into the realms of genetics and individualized patient profiles, the focus may shift towards novel therapeutic targets, refined drug delivery techniques, and synergistic combinations of existing treatments. The confluence of digital health tools, genetic insights, and artificial intelligence is anticipated to amplify treatment efficacy while minimizing adverse effects. The evolution of clinical assessment methodologies for antihypertensive drugs could gravitate towards a more inclusive approach,

harnessing real-world data from diverse demographics and capitalizing on sophisticated analytical tools. The integration of wearable tech and mobile applications promises a holistic, real-time understanding of treatment responses. Furthermore, the dawn of precision medicine, anchored in genetic and biomarker insights, holds promise for tailoring antihypertensive regimens to individual needs, optimizing therapeutic outcomes. The potential for adaptive clinical trials, bolstered by the prowess of AI and machine learning, is poised to refine study designs, expediting drug discovery endeavors while upholding rigorous evidence standards. In essence, the horizon appears bright with prospects of ushering in patient-centric, data-enriched, and adaptive paradigms in the clinical assessment and management of hypertension.

CONCLUSION :

In summary, the landscape of hypertension management has witnessed remarkable advancements with the development and evaluation of a diverse array of antihypertensive drugs. Through rigorous research, pivotal clinical trials, and continuous evaluation, these medications have demonstrated efficacy in reducing blood pressure and mitigating cardiovascular risks, thereby improving patient outcomes and quality of life. The review underscores the importance of a multifaceted approach to hypertension management, emphasizing the need for individualized therapy tailored to patient-specific factors, including age, comorbidities, and renal or hepatic function. The comparative analysis of various drug classes provides valuable insights into their distinct mechanisms of action, efficacy profiles, and safety considerations, enabling clinicians to make informed decisions in selecting appropriate therapeutic regimens. In conclusion, while considerable progress has been made in the field of hypertension management, ongoing research, rigorous evaluation, and collaborative efforts among clinicians, researchers, and healthcare stakeholders remain paramount. By fostering a holistic understanding of the current evidence and emerging trends, this review seeks to guide and inspire future advancements in the quest to effectively manage hypertension and improve cardiovascular health on a global scale

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HOW TO CITE: Vishavjeet Pisal*,Tejaswini Kamble,Pritam Salokhe,Sachin Navale,Nilesh Chougule, Research advance in clinical evaluation of antihypertensive Drug , Int. J. of Pharm. Sci., 2024, Vol 2, Issue 1, 526-540. https://doi.org/10.5281/zenodo.10557184