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Zilebesiran in the Treatment of Hypertension: Molecular Insights, Clinical Trial Results, and Future Perspectives

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ABSTRACT

Introduction: Hypertension is considered the main modifiable risk factor associated with cardiovascular diseases and early death on an international level. Ineffective results are often connected with daily drug intake and poor adherence to drug therapy. Zilebesiran, a novel experimental siRNA, acts by blocking angiotensinogen (AGT) production in the liver. The effect of zilebesiran gives a new approach for blood pressure control. To conduct a review of the zilebesiran drug, its pharmacology, effectiveness, safety, and application prospects in the treatment of hypertension based on clinical trials. *Methods*: This literature review was conducted via a PubMed search, including clinical trials (Phase I and Phase II), KARDIA-1, KARDIA-2, and KARDIA-3, up to April 2026. *Results*: Clinical trials show that a single subcutaneous dose of zilebesiran leads to a dose-dependent reduction in serum angiotensinogen (>90%) and a significant, sustained decrease in 24-hour ambulatory systolic blood pressure for up to six months. In studies, KARDIA zilebesiran was effective alone or when co-administered with indapamide and amlodipine. There were adverse effects like mild injection site pain and hyperkalemia. *Conclusions*: Zilebesiran can help to improve treatment adherenc in patients who have hypertension. The long-term safety profile and the effect on cardiovascular events are still under investigation in larger trials.

Keywords: hypertension; zilebesiran; siRNA; angiotensinogen; RAAS; long-acting agent

1. INTRODUCTION

The premature death globally is caused by hypertension. The number of deaths caused by high systolic blood pressure is 10.5 million. At the same time, 223 million disability-adjusted life years (DALYs) have been recorded in 2023 (Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators, 2025). Although many drugs have proven effective in controlling blood pressure, global treatment falls short of meeting blood pressure standards. Only 23% of women and 18% of men have met

the goal of less than 140/90 mmHg (NCD Risk Factor Collaboration, 2021). For those patients who have resistant hypertension, meaning that their uncontrolled high blood pressure remains high even though they are on three or more drugs for blood pressure, this accounts for 19.7% of cases. These types of patients will have a particularly grim prognosis since the risk of cardiovascular diseases will be at least 50% higher than for people whose blood pressure levels are within normal range (Azizi et al., 2026; Jones et al., 2025). A decrease of 10 mmHg in systolic blood pressure levels results in a 13% reduction in mortality (Addison et al., 2023; Ogunniyi et al., 2021). The disparity between the effectiveness of the available treatments and their successful use for blood pressure reduction can be attributed to non-adherence to drugs and treatment inertia.

Currently, there are five major classes of antihypertensive drugs, namely ACE inhibitors, ARB, beta blockers, CCB, and diuretics, which have been rendered ineffective due to inefficacy and difficulty in tolerance as well as the necessity for once-a-day administration (Siddiqui et al., 2025). Alarmingly, treatment adherence drops to approximately 50% among patients by the end of the first year (Webb, 2024). Non-adherence is the main reason the goals of hypertension treatments are not achieved, which is common in both young and elderly patients (Dudzicz-Gojowy & Adamczak, 2025).

Zilebesiran is a novel medication that inhibits the synthesis of angiotensinogen in the liver. Angiotensinogen is an essential compound in the process of synthesis of various angiotensin peptides in the renin-angiotensin-aldosterone system (Verma et al., 2026). It is injected twice a year and constitutes a great discovery in treating hypertension. The drug eliminates the need for daily medication, a practice that is likely to increase patient adherence (Dudzicz-Gojowy & Adamczak, 2025).

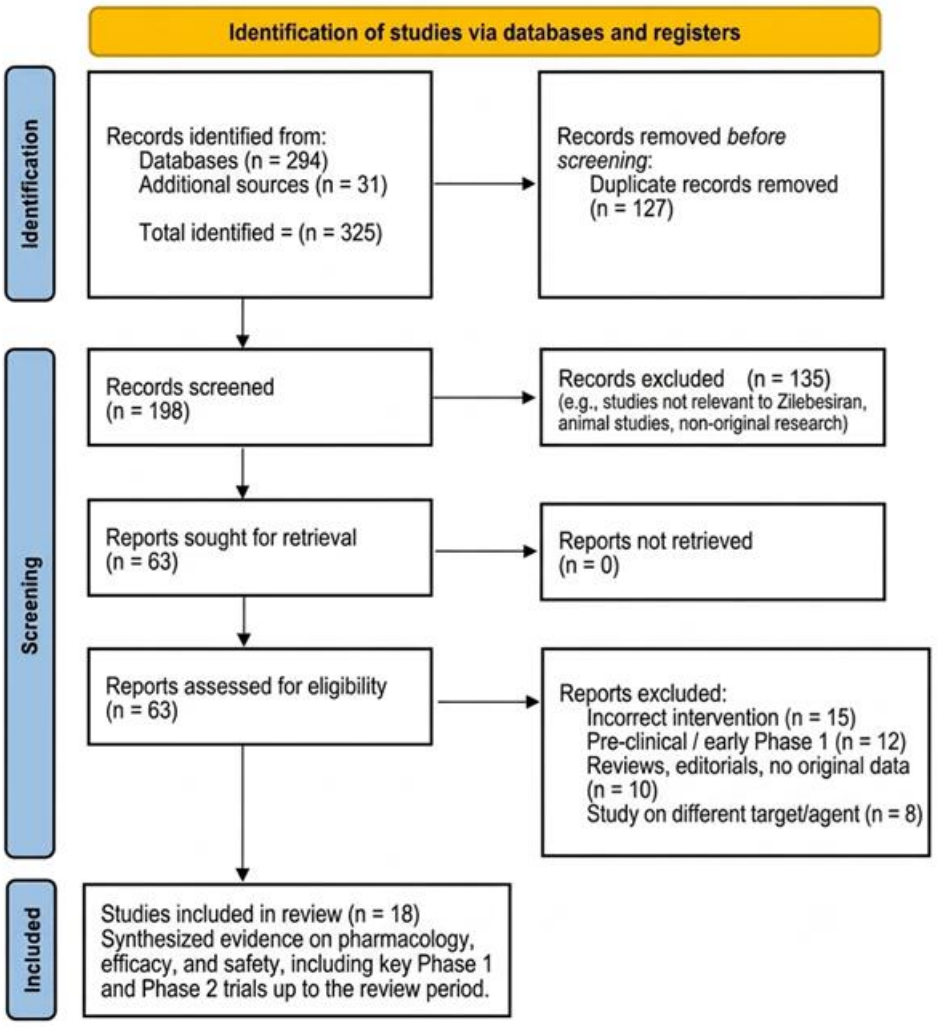

Figure 1. PRISMA flow diagram

2. REVIEW METHODS

A literature review was conducted in the PubMed database publications up to 2026. Our review included clinical trials, systematic reviews, and meta-analyses on zilebesiran, an siRNA therapy, in patients with hypertension. Exclusion criteria: lack of full text, publications in languages other than English, and descriptive studies without data on the efficacy of the therapy. During the selection, we made based on titles, abstracts, and full texts. The results were grouped by type of therapy. The article screening process followed the PRISMA guidelines (Figure 1).

3. RESULTS & DISCUSSION

Small interfering RNA

The small interfering RNA is a type of double-stranded RNA in which one of the strands acts as the non-guide (or passenger) strand, while the other acts as the guide (or antisense) strand. (Surma & Oparil, 2024; Verma et al., 2026). Each strand consists of 21 to 23 nucleotides that operate through the natural process of RNA interference (Katzmann et al., 2020; Ranasinghe et al., 2023). The guide strand is the one that detects and binds to a specific mRNA sequence, called the target. Gene silencing involves targeting the mRNA and degrading it to prevent the formation of disease-causing proteins. The guide strand becomes integrated into the RNA-induced silencing complex (RISC), where the Argonaute 2 (Ago2) endonuclease -the catalytically active component of RISC-cleaves the target mRNA (Liu et al., 2004; Ranasinghe et al., 2023; Alshaer et al., 2021; Masi et al., 2024).

The RISC guide strand is catalytic because it recycles to destroy additional RNA molecules after demolishing one RNA molecule. This explains the persistence of pharmacodynamic activity seen in siRNA-based medications (Katzmann et al., 2020). This technology has found its way into clinics and applications in different clinical conditions. The RNAi therapy inclisiran silences PCSK9 mRNA, decreasing LDL cholesterol by about 50% when administered biannually (Nurmohamed et al., 2021).

Mechanism of action

Zilebesiran is an siRNA conjugated to a trivalent N-acetylgalactosamine (GalNAc); the siRNA-GalNAc conjugate selectively binds to the asialoglycoprotein receptor (ASGPR). This receptor is primarily expressed in the liver. The hepatocytes show abundant expression of these receptors, with more than half a million copies present per cell. On the other hand, very little receptor expression is observed in non-hepatic tissues (Sayer et al., 2025; Touyz, 2023). When zilebesiran binds to ASGPR, it is taken up by hepatocytes via clathrin-mediated endocytosis. The ASGPR receptor detaches from the siRNA within the acidic endosome and is recycled back to the cell membrane for further uptake (Katzmann et al., 2020). The amount of siRNA that enters the cytoplasm is less than 1%, but the gradual release of siRNA from endosomes accounts for the prolonged therapeutic effect, which lasts for several weeks or even months (Desai et al., 2023; Sayer et al., 2025). Inside the cell, siRNA enters the cytoplasm, where it acts on an RNA-induced silencing complex (RISC). The unwinding process happens after that. In addition, the guide siRNA interacts with angiotensinogen (AGT) mRNA, whereby the Ago2 endonuclease in the RISC cleaves the mRNA, as a result, it prevents the synthesis of AGT protein (Liu et al., 2004; Siddiqui et al., 2025).

Angiotensinogen is the main precursor of all angiotensin peptides in the renin-angiotensin-aldosterone system (RAAS) (Verma et al., 2026). Inhibiting AGT synthesis at this upstream level causes zilebesiran to reduce circulating levels of all downstream angiotensin peptides - including angiotensin I and angiotensin II- thereby lowering blood pressure (Desai et al., 2023). GalNAc-conjugated siRNA is taken up almost exclusively by hepatocytes, angiotensinogen synthesis in other organs- notably the kidney- remains intact, thereby preserving local tissue RAAS functions. This organ-selective silencing has been confirmed in preclinical models. Hepatic AGT mRNA was lowered to near-undetectable levels with no measurable change in renal AGT transcript abundance (Verma et al., 2026).

Pharmacokinetics and Pharmacodynamics

Zilebesiran is dose-proportional when administered subcutaneously over a dose range of 10-800 mg, according to the research findings (Verma et al., 2026). There is sustained action at pharmacological doses of 200 mg or more for lasting up to 24 weeks, indicating potential dosing regimens of once per quarter and twice per year (Bakris et al., 2024; Verma et al., 2026). The disassociation of ASGPR from the GalNAc conjugate under acid conditions within the endosomes makes it possible to recycle it to the cell membrane surface. Less than one percent of siRNA leaks into the cytoplasm from endosomes (Katzmann et al., 2020). In phase 1, there was a negative correlation between the administered dose and the difference in serum AGT at 8 weeks (r = -0.56; 95% CI, -0.69 to -0.39) (Desai et al., 2023). The serum concentration of angiotensinogen decreased by over 90% from week 3 to 12 weeks in doses above 100 mg and at 800

mg. In the KARDIA-1 study, zilebesiran was administered at doses of 300 mg or 600 mg, with >90% suppression kept-up for 6 months (Bakris et al., 2024).

Clinical Trial Results

Phase I clinical trial enrolled 107 participants with hypertension. In part A, single subcutaneous doses from 10 mg to 800 mg were tested in a double-blind, controlled, placebo study; patients were randomized to receive zilebesiran or placebo at a 2:1 ratio. Part B focused on figuring out the effect of a dietary intervention on sodium intake by examining the 800 mg dose under two conditions: a low-salt diet at 0.23 g/day and a high-salt diet at 5.75 g/day. Under Part E, patients with systolic BP ≥ 120 mm Hg received an additional dose of irbesartan 300 mg once a day for 2 weeks during week 6 (Verma et al., 2026). The participants were administered one dose of the drug through an escalating subcutaneous injection of zilebesiran, which varied between 10 mg and 800 mg. The observation period was 24 weeks post-drug administration. During the 8th week, subjects who received doses of 200 mg or higher demonstrated antihypertensive effects. This was attributed to a drop in SBP >10 mm Hg and DBP>5 mm Hg. There was no variation in the blood pressure throughout the day. It had similar effects both during the daytime and at night. In conclusion, the above information indicates that the drug is highly effective at lowering blood pressure, regardless of day-to-day fluctuations (Desai et al., 2023). Sodium intake in the diet affected the blood pressure-lowering ability. High intake of sodium significantly reduced the antihypertensive effect of zilebesiran.

On the other hand, the use of both drugs enhanced the decrease in blood pressure. The values for systolic and diastolic blood pressure reductions were -6.3 mm Hg and -3.0 mm Hg, respectively (Desai et al., 2023). Zilebesiran had a good safety profile as injection site reactions were noted in only five subjects, and there were no complications. Also, hypotension, hyperkalemia, and kidney-related side effects were not present (Verma et al., 2026). KARDIA-1 was a randomized, double-blinded, placebo-controlled, and Phase 2 trial. In this trial, there were 394 subjects with mild to moderate high blood pressure who were randomized into one of four zilebesiran dose groups of 150 mg, 300 mg, 300 mg in three months, and 600 mg in six months or placebo in each six-monthly visit. Of the 394 subjects, 377 patients who received zilebesiran or placebo were included in the study. Before randomization, all subjects were required to discontinue any antihypertensive medications, which resulted in increased blood pressure in the placebo group (Bakris et al., 2024). Both 300 mg doses (once every 3 months or every 6 months) had been exposed to only one dose when compared at the 3-month assessment period. These were combined in the main efficacy analysis at that time.

As shown in Table 1, at 3 months, the changes in systolic BP in the treatment groups were -7.3 mm Hg in the 150 mg once every six months dosage group, -10 mm Hg in the 300 mg every 3 months and 6 months dosages, and -8.9 mm Hg in the 600 mg once every six months group. The least squares mean difference between the placebo and the drug treatment groups after three months is -14.1 mm Hg for the 150 mg dose, -16.7 mm Hg for the 300 mg dose, and -15.7 mm Hg for the 600 mg dose, which was taken every six months. The drop in blood pressure was maintained for 24 hours (Bakris et al., 2024). It can be noted that zilebesiran significantly reduced 24-hour systolic blood pressure by 10 mm Hg, with no safety concerns. In 6 months, there were more adverse events in the zilebesiran treatment group (60.9%) than in the control group (50.7%).

The main adverse events observed were injection site reactions (6.3%) and hyperkalemia (5.3%). Participants who received zilebesiran after every quarter rather than after every half-yearly period have more often injection site reactions. Hypotension occurred in 4.3% of participants receiving zilebesiran compared to 1.3% receiving placebo. 1.3% of participants receiving zilebesiran had signs of renal dysfunction, which were classified as non-serious. (Bakris et al., 2024). The KARDIA-2 phase 2 originally listed 1491 patients who were treated with one of three standard blood pressure medications (indapamide 2.5mg, amlodipine 5 mg, or olmesartan 40mg) for at least 4 weeks. After this initial treatment period, 663 patients with continued inadequate blood pressure control were randomized 1:1 to receive zilebesiran 600 mg or placebo as a single subcutaneous dose. All patients remained on their baseline antihypertensive therapy (Desai et al., 2025). Table 2 shows results from the study showing that all 3 drug classes had a statistically significant decrease in 24-hour systolic blood pressure with zilebesiran compared with placebo. The reductions of SBP with indapamide were (-12.1 mmHg) and on amlodipine (-9.7 mmHg), whereas for those on olmesartan, it was (4.5 mmHg) as shown in Table 2. Blood pressure reductions were maintained among patients receiving zilebesiran for 6 months, regardless of whether they were on indapamide or amlodipine (Desai et al., 2025).

The achievement of clinically significant blood pressure reductions (systolic <130 mmHg or a reduction of>20 mmHg) was much higher among patients receiving zilebesiran. Zilebesiran had a 64.2% success rate among those on indapamide, while the placebo group had just a 14% success rate. The reason for carrying out the KARDIA-3 research is that it aims at assessing the effectiveness and safety

of using zilebesiran in people with hypertension, and these individuals were on two or more drug classes to help reduce their high blood pressure due to their heart disease and the risk of heart disease (Morosan et al., 2025). Patients were randomized to a group with zilebesiran or placebo and continued their antihypertensive treatments. Antihypertensive treatment with zilebesiran led to significant and sustained reductions in systolic blood pressure relative to placebo. Zilebesiran can be considered a prospective treatment option for patients with resistant hypertension. The full results of KARDIA-3 have not yet been published (Verma et al., 2026; Morosan et al., 2025).

Table 1. Efficacy results for the KARDIA-1 trial

Name of study	Number of patients	150mg zilebesiran Q6M	300mg zilebesiran Q6M and 300mg zilebesiran Q6M	600mg zilebesiran Q6M
KARDIA-1	377	24-hour SBP was decreased by 7.3 Placebo-adjusted	24-hour SBP was decreased by 10 mmHg 10 mmHg Placebo-adjusted difference (LSM) was 16.7 mmHg	24-hour SBP was decreased by 8.9 mmHg Placebo-adjusted difference (LSM) was 15.7 mmHg

Abbreviations: 24h SBP, 24-hour ambulatory systolic blood pressure; Q3M: every 3 months; Q6M: every 6 months; LSM, least-squares mean.

Table 2. Efficacy results for the KARDIA-2 trial

Name of study	Number of patients	Indapamide 2.5mg with 600mg zilebesiran	Amlodipine 5mg with 600 mg zilebesiran	Olmesartan 40mg with 600 mg zilebesiran
KARDIA-2	1491	24-hour SBP was decreased by 12.1 mmHg Office SBP reduction was decreased by 18.5 mmHg	24-hour SBP was decreased by -9.7 mmHg Office SBP reduction was decreased by 10.2mmHg	24-hour SBP was decreased by -4.5 mmHg Office SBP reduction was decreased by 6.7mmHg

Future Perspectives

Several research areas could be key to the future clinical application of zilebesiran. Most importantly, there is an ongoing phase 3 study, ZENITH, that aims to evaluate the efficacy of this drug in preventing adverse cardiovascular outcomes by lowering blood pressure levels The emergence of the innovative REVERSIR technology, which is a pharmacological approach to reverse the effects of RNA interference-based siRNA-mediated gene silencing, might turn out to be a highly beneficial safety approach addressing the irreversibility problem in cases of sudden hemorrhage, sepsis, or hypovolemia. Besides the control of hypertension, the reduction of AGT expression might prove useful for gaining therapeutic benefits in the situation of the overactivity of the RAAS system in cases of heart failure, kidney disorders, and diabetes-related kidney disease. Animal experiments have shown that siRNA targeting the AGT gene yields effects similar to those of chemical RAAS inhibitors. In addition, the distinctive dosing regimen, either every 3 months or biannually, is likely to represent an important paradigm shift in the treatment of high blood pressure, especially among those with the least adherence to their prescribed regimens.

4. CONCLUSION

Zilebesiran represents a potentially significant advancement in the management of hypertension by suppressing angiotensinogen production in the liver through RNA interference at the most upstream point in the RAAS cascade. The primary benefits of zilebesiran

include lowering blood pressure and a good safety profile. The possibility of administering zilebesiran quarterly or twice per year can greatly improve patient adherence, and the main challenge is properly regulating blood pressure. However, many unanswered questions remain regarding the long-term safety of sustained angiotensinogen suppression. The management of patients who experience acute hemodynamic compromise during the prolonged pharmacological effect, and the appropriateness of this approach in specific populations, including pregnant women and patients with bilateral renal artery stenosis. The outcome of the ZENITH Phase III trial will be necessary to determine the drug's safety in patients with cardiovascular disease.

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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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