REVIEW PAPER

BEYOND THE DAILY PILL: ZILEBESIRAN, THE FUTURE OF BLOOD PRESSURE CONTROL?

Dr. Shivaraj D R[1*], Dr. R S Meghasri[1], Dr. Nagarjuna D[1], Varshini J[2], Bharathgowda H G[2], Gowatami L[2]

[1]*Assistant Professor, Department of Pharmacy Practice, Akshaya Institute of Pharmacy, Tumkur, Karnataka, India*

[2]*Final year B Pharm, Department of Pharmacy Practice, Akshaya Institute of Pharmacy, Tumkur, Karnataka, India*

Corresponding author: Dr Shivaraj D R, Shivaraj.dr27@gmail.com, ORCID: 0000-0002-9284-4360

ABSTRACT

High blood pressure is a major cause of heart disease worldwide, leading to over 10 million deaths each year. Many people find it hard to control their blood pressure because they don't stick to their medication or find it too complicated to take pills every day. This review looks at zilebesiran, a new type of treatment called small-interfering RNA (siRNA) therapy, designed to help with these problems. Zilebesiran targets a gene in liver cells and uses a special delivery system to make sure it reaches the liver. It works by stopping the production of a protein called angiotensinogen, which is important for blood pressure regulation. This drug blocks a system in the body that controls blood pressure, providing long-lasting effects. Unlike other treatments, zilebesiran can lower blood pressure for up to six months with just one injection. Studies have shown that an 800 mg dose can reduce blood pressure by about 22.5 mmHg after six months. The treatment is generally safe, with mild side effects like injection site reactions and headaches. Ongoing studies are looking at how it works with other treatments and in high-risk patients. Zilebesiran offers a new approach to managing high blood pressure, moving from daily pills to an injection every six months.

Keywords: Zilebesiran, Hypertension, siRNA, Angiotensinogen, RAAS

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INTRODUCTION

Existing interventions targeting high blood pressure primarily seem to be based on the medicines that reduce blood pressure and on lifestyle modifications. These strategies have already resulted in a significant reduced blood pressure level, slower rate of organ damage, and better condition of the heart and blood vessels. Since the cardiovascular risk (CVR) associated with hypertension (HTN) is strictly and directly related to BP values, the lack of their full normalization can also take part in the phenomenon.[1]

High blood pressure is a “silent killer” since it creates problems in the complicated system of the heart and blood vessels. The condition usually passes unnoticed since it has no apparent signs but its impacts are profound and far-reaching. Each year, hypertension claims over 10 million lives globally, cementing its status as the foremost risk factor for cardiovascular disease (CVD).[2]

Hypertension is another severe chronic health conditions which befalls approximately a third of individuals aged 30-79 years all over the world. .[3] Heart and blood vessel problems are significantly caused by (cardiovascular disease; CVD) high blood pressure. It has been the largest threat that contributes to disease globally. High blood pressure is found in one in every three grown-ups all around the globe. Its figure has increased two-fold within the last two decades and is projected to increase further.[4]

Hypertension remains the single largest risk factor contributing to death and disability-adjusted life years globally, resulting in 9.4 million deaths and the loss of over 200 million healthy life-years annually.[5]

This review looks at novel methods of how to treat high blood pressure with special emphasis on siRNA drugs. As we navigate the complexities of hypertension management, we delve into the prospects of siRNA therapy.[2]

Angiotensinogen (AGT) is the protein present in the blood and is produced by the liver predominantly. It is an essential component of the RAAS system and all the angiotensin peptides. RAAS can be prevented by blocking the production of AGT with the help of antisense Oligonucleotides or small interfering RNAs (siRNAs). This then reduces blood pressure.[3]

Cell therapies RNA interference (RNAi) Therapeutic agents are the emergence of a novel approach to gene silencing in the form of messenger RNA (mRNA) destruction that encode the disease-causing protein. Due to the long-lasting effect and fewer doses of RNAi, it may assist individuals to adhere to treatment strategies, reduce excessive medication intake, and achieve other objectives of heart-related treatment unmet at the moment. RNAi drugs are based on the small interfering RNA (siRNA) molecules, which bind to a complex known as the RISC, which then cleaves the complementary mRNA. Examples of the kind of medicines produced through this technology are approved medicines against rare diseases like hereditary transthyretin amyloidosis and this demonstrates that such technology can indeed work with people. An example of RNAi drug is zilebesiran which inhibits angiotensinogen to reduce blood pressure.[6]

Zilebesiran is administered under skin after every 12-24 weeks. It is long-lasting and is capable of maintaining low blood pressure weeks. Preliminary research indicates that it enters into the body and performs. It promptly prevents angiotensinogen, and prevents it in 12 weeks up to 24 weeks in a single injection.[7]

Zilebesiran is an interfering RNA small drug (siRNA) that binds to AGT gene. It is at phase II clinical trials and is able to reduce blood pressure up to six months when administered under the

skin in one injection. This demonstrates that siRNAs of AGT may be an effective method of treating hypertension. Although Zilebesiran is already effective and safe, we believe that there will be an increasing number of patients with high blood pressure that want a number of siRNA available sometime in the future. SiRNAs have not yet delivered their entire potential thus we would like to make AGT-targeting siRNAs even more useful.[3]

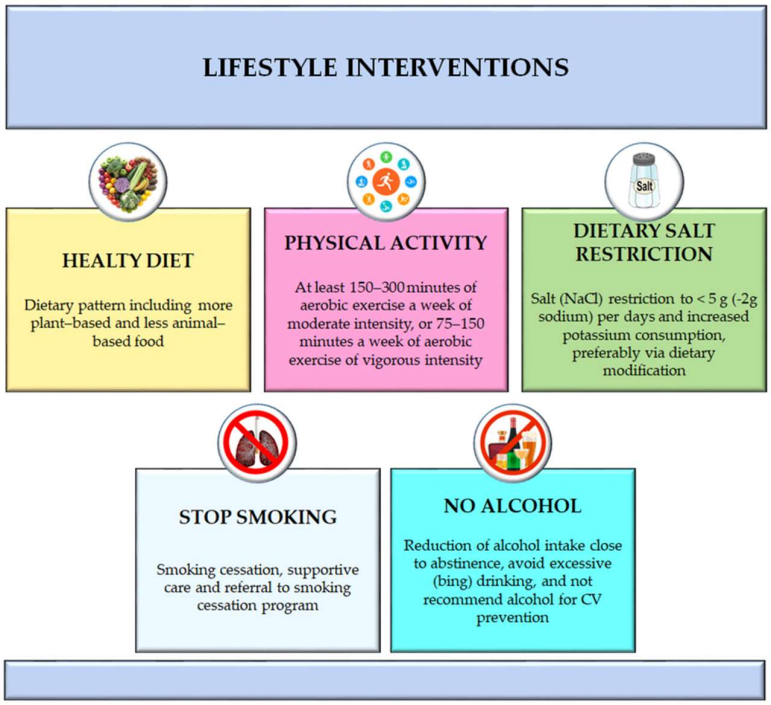


Figure: Lifestyle recommendations: current HNT guidelines summarised regarding lifestyle interventions as a healthy diet, regular physical activity, dietary salt restriction, reduction in alcohol intake, and smoking cessation.[1]

EPIDEMIOLOGY:

There were approximately twice as many high blood pressure people in the places with the highest number of people as in the places with the least number of people. In “Latin America and the Caribbean”, the respective highest numbers were reached by men. In the case of women, they were in the previously socialist economies.[8]

The lowest estimates of prevalence among men and women were in the region “other Asia and Islands”. Between 2000 and 2025, high blood pressure is projected to increase 9 percent in men and 13 percent in women around the world; the issue is primarily the changing age structure of the population.[8]

Precisely, the global population is projected to be more aged by 2025. Hypertension rates were observed as high in young people among men compared to the level between women and in old people among women compared to that of men.[8]

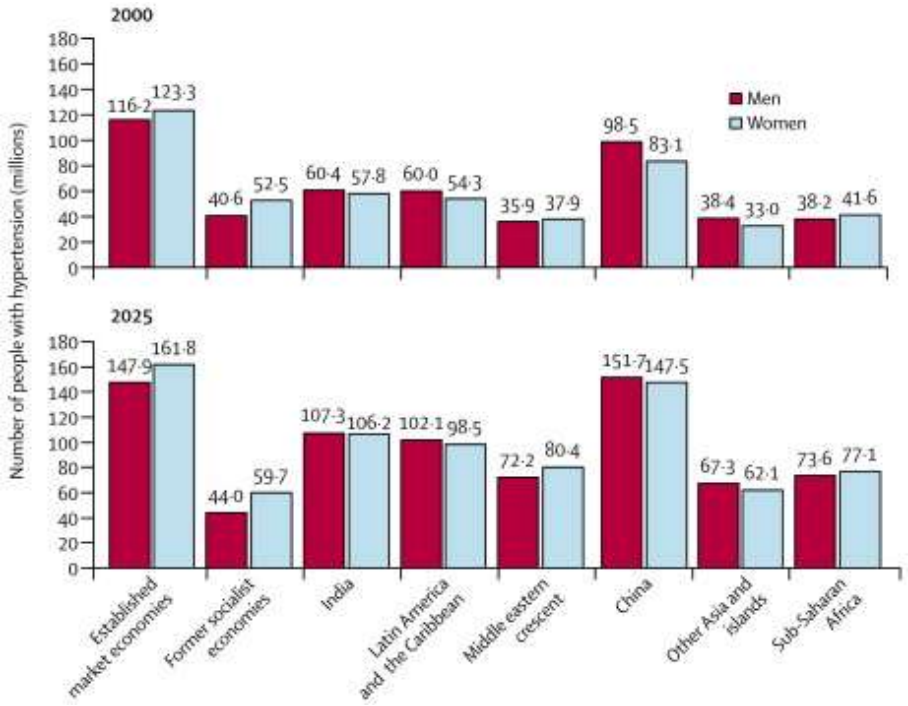


Figure 1: Number of people with hypertension aged 20 years and older by world region and sex in 2000 (upper) and 2025 (lower) In 2000, 95% CIs by region for men and women, respectively, were: established market economies (113·7–118·7 million) (121·2–125·4 million); former socialist economies (40·5–40·8 million) (52·3–52·6 million); India (52·2–68·5 million) (50·1–65·5 million);

In 2025, the 95% CIs by region for men and women, respectively, were: established market economies (144·7–151·1 million) (159·2–164·5 million); former socialist economies (43·9–44·1 million) (59·5–59·8 million); India (94·3–120·2 million) (90·9–121·6 million).[8]

MECHANISM OF ACTION

Zilebesiran is a chemically modified, double-stranded small interfering RNA (siRNA) therapeutic designed to silence the gene encoding angiotensinogen in hepatocytes.[9]

Angiotensinogen (AGT) gene targets Zilebesiran is a novel siRNA drug, the first of its kind, which attacks angiotensinogen (AGT) gene. It is an emerging blood-pressure drug which is based on turning off the AGT gene thereby preventing the production of angiotensinogen in the body thereby reducing blood pressure and angiotensinogen concentration in blood. [10]

siRNA is effective by suppressing genes post-transcription. A new form of siRNA involves trivalent N -acetylgalactosamine (GalNAc) ligand to conjugate the siRNA. It identifies and cleaves the mRNAs produced by high-potency and specificity liver cells. In this method, the asialoglycoprotein receptor (ASGR) is utilized more commonly known as the Ashwell-Morell receptor and is predominantly expressed on hepatocytes.[2]

Zilebesiran, once injected under the skin, enters liver cells by receptor-mediated uptake very rapidly. The siRNA enters the cytoplasm and gets attached to the RNA-silencing complex located in the cell. The siRNA guide strand is complementary to the AGT mRNA and leads to the mRNA being cut preventing the expression of angiotensinogen protein.[9]

Angiotensin I and II concentrations in blood decrease when zilebesiran decreases the amount of angiotensinogen produced by the liver. Renin converts to angiotensin I, which is known as angiotensinogen, and thus reducing its amount reduces the entire RAAS pathway. There are two theoretical advantages of this strategy of preventing RAAS by blocking at the top rather than typical RAAS blockers.[9]

Since angiotensinogen produces all angiotensin peptides, it is possible to reduce angiotensinogen and suppress RAAS activity and prevent the angiotensin II “break-out” that occasionally occurs with ACEIs or ARBs medications. Angiotensin I and II remain low even when the level of renin increases due to treatment but there is no angiotensinogen that the body can use either for angiotensin I or II formation.[9]

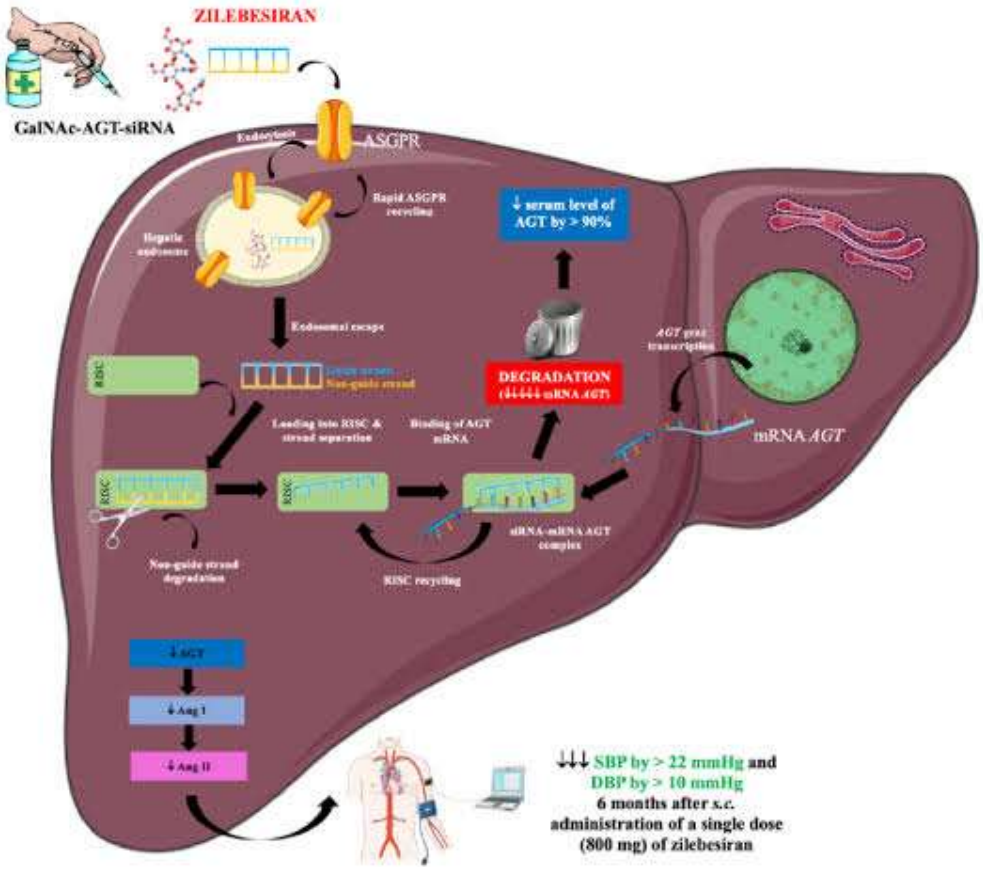


Figure 2: Zilebesiran – Mechanism of Action [9]

Second, this liver- targetable drug usually does not affect angiotensinogen in other locations than the liver, i.e., in the kidneys or fat tissue.

It functions in the liver alone, and thus could reducing the side effects in other organs like the kidneys. The drug in animal studies essentially inhibited the production of angiotensinogen in the liver, and had no apparent effect on the kidneys. This drug does not disrupt the bradykinin unlike the ACE inhibitors hence it is unlikely to cause the cough and swelling experienced with these drugs. Zilebesiran provides a solid and long-lasting method of lowering blood pressure by striking the primary premature phase of the blood-pressure machinery.[9]

Pharmacokinetics:

Zilebesiran is also designed to remain active in the liver over an extended period. Once injected into the skin, the siRNA attains its peak level in the bloodstream soon after which it gets into the liver cells efficiently. Unmodified normal siRNA is degraded by enzymes at a very rapid rate (in minutes). Zilebesiran employs special chemistry (+) changes, which ensure longevity by safeguarding them.

The GalNAc ligand conjugated with the drug holds nearly all of the dose concentration in the liver and therefore only a negligible amount is distributed throughout the body.

Phase 1 study non-compartmental analyses revealed that the exposure of the drug and dose increased in a directly proportional manner between 10 mg and 800 mg in the phase 1 study. In practice, there was an increase in the blood and liver level as the higher the dosage the higher the level but the drug was not accumulating at an unexpected rate. Repeat dosing: In a phase 1 - sub-study (Part D), subjects with obesity were dosed with 800 mg/12 weeks. The effects and the drug exposure were comparable to that after a single dosage which showed no changes in repeated dosing on the drug behavior even in individuals with varying body mass index.[9]

Pharmacodynamics:

Zilebesiran reduces the angiotensinogen in the blood strongly and long-lastingly, and this also reduces blood pressure. In a phase1 trial, it reduced angiotensinogen levels by greater than (>90%) percent using a dose of (≥100mg) or higher in a few weeks. Actually, the median decrease remained greater than 90% in week 3 to week 12 following one dose of 100mg or above.

In highest dose (800mg) over 90 percent (>90%) of the angiotensinogen in the blood remained at a low concentration during 24 weeks on that dose. The duration of effect was due to the long persistence of a siRNA in the liver cells and long-lasting continued disrupting of AGT mRNA by the RNA-induced silencing complex.[9]

Accordingly, doses of zilebesiran of effective dose clinical significance brought about a measurable difference in RAAS biomarkers: at doses ≥200mg and above, both plasma renin activity and angiotensin I, angiotensin II and aldosterone levels showed marked effect and evidence of downstream RAAS inhibition was noted (Interestingly, at higher dosages 200mg, plasma renin concentration can rise because of attenuation of the inhibitory effect of angiotensin II; however, the overall angiotensin production will.[9]

The extent of angiotensinogen silencing is correlated with the amount of BP drop with zilebesiran. In the phase 1, increased dose led to a greater decrease in 24 -hour ambulatory blood pressure, and the dose was strongly inversely correlated with the decrease in systolic pressure (r = -0.4). Similarly, the decrease in systolic BP, increased as the blood levels of angiotensinogen reduced.[9]

Two hundred and above doses reduced blood pressure significantly. At 8 weeks, individuals receiving ≥200mg showed systolic blood pressure reduction >10mm Hg and diastolic >5mm Hg compared to baseline. The reduction occurred within 1-4 weeks and remained stable at 12-24 weeks with increased dose.

To give one example, individuals taking 800 mg of the drug had an average systolic blood pressure decrease of approximately ~22.5mm Hg after 24 weeks, and their diastolic pressure decreased by almost ~10.8mm Hg.1. These prolonged changes indicate that the drug remains active in the body over a considerable period of time.

One of the aspects of zilebesiran is its interaction with salt in the diet and with other blood-pressure medications that inhibit the RAAS system. In a small study that randomized the amount of salt that people consumed, those consuming large amounts of salt had a significantly smaller reduction in blood pressure on zilebesiran, whereas those consuming less salt had a greater reduction.[9]

This finding aligns with blood pressure knowledge: excess salt causes fluid retention and poor blood pressure control. Blood pressure reduction with irbesartan combined with zilebesiran exceeds reduction from zilebesiran alone, showing dual system targeting is more effective. The results guide physicians' use of zilebesiran and suggest patients limit salt intake while safely using other medications affecting the same system.[9]

Preclinical Studies:

The preclinical trials have indicated the reduction of blood pressure in rodents using zilebesiran providing insights on how it might work on humans. Both the angiotensin II or norepinephrine can reverse the drop in blood pressure that the AGT -targeted siRNA causes in a short period of time and by consuming more salt can decrease the drop in blood pressure that the AGT -targeted siRNA causes. This comprehensive knowledge on the mechanism of action of zilebesiran and the fact that its action is reversible makes this agent a very easy therapeutic agent in high blood pressure.[10]

In 2011, REVERSIR (RVR) was developed as a tool using DNA to prevent siRNA activity. This enabled switching zilebesiran's effect on/off in lab animals, allowing angiotensinogen reproduction when needed. AGT siRNA (10 mg/kg) reversed zilebesiran's blood-pressure-lowering effect in hypertensive rats under 1, 10 or 20 mg/kg of AGT siRNA, with normal blood pressure restored within 4-7 days.[10]

RVR doses of 10 and 20 mg/kg restored AGT and renin values to normal and a repeat dose of zilebesiran after AGT-RVR restored blood pressure proportionally to the initial dose of RVR.

Anti-AGT siRNA: Blood Pressure Lowering and Organ Protection in Preclinical Disease models.

One preclinical research by Merck studied an siRNA in lipid nanoparticles, which was to inhibit the AGT gene. It was administered at the rate of 3mg/kg as an injection into the blood of male spontaneously hypertensive rats.

Treatment resulted in rapid reduction of liver AGT mRNA and blood AGT levels with the treatment effect lasting approximately 1 week. Blood pressure significantly decreased reaching the lowest level on day 4 following the treatment (154 ± 4 mmHg vs. 188 ± 2 mmHg in the control group). The liver and kidney tests remained normal and no evidence of injury was detected.[10]

Another preclinical study was conducted by Alnylam. They experimented on an AGT-conjugated siRNA in spontaneously hypertensive rats (SHR; systolic blood pressure ≥ 150 mmHg) and above. They also experimented it using normal rats with a (systolic blood pressure 110–125 mmHg). They administered the siRNA and the combination of siRNA and captopril or valsartan.

SiRNA therapy reduced mean arterial pressure by −14 mmHg, captopril by −23 mmHg, and valsartan by 10mmHg, while valsartan-siRNA combination achieved −68 mmHg reduction. Valsartan monotherapy reduced plasma AGT by 97-99% and suppressed angiotensin-III. The combination also decreased heart enlargement by reducing NT-pro BNP levels without affecting kidney activity.[10]

A study comparing oral captopril with RNA-based GalNAc siRNA R0797070 in hypertensive rats showed R0797070 caused greater cardiac changes, reducing heart weight by 10 and left ventricular cell size by 17. These findings suggest zilebesiran may provide better cardiac protection through blood pressure reduction. While preeclamptic rats showed no fetal damage in lab tests, concerns remain about effects on other organs. Haase et al. tested liver-targeted siRNA therapy for AGT on pregnant rats to treat preeclampsia.[10]

Transgenic rats carrying human AGT and renin genes stimulated the mother and placental renin angiotensin aldosterone system. The RUPP model decreased uterine blood circulation and caused inflammation. In both models, siRNA reduced blood pressure and urinary proteins, improved fetal growth, and preserved fetal-placental health.

Further research is required to find out the possibility of zilebesiran to cross the placenta and produce the same beneficial effects on fetal development. Notably, zilebesiran is primarily taken to liver cells thus avoiding involvement of other tissues such as the kidneys and the fat in the production of AGT. This is so much more applicable to individuals that are obese, since the tissues secret a lot of AGT. [10]

CLINICAL TRIAL EVIDENCE

Phase 1 Trials: The first study of zilebesiran in humans was a phase 1 trial with multiple parts. In part A, 84 individuals with mild or moderate hypertension were divided into groups. Two-thirds received a single injection of zilebesiran (doses 10-800 mg), while one-third got placebo, with 24-week follow-up. Part B compared 800 mg effects between low and high salt intake, while Part E tested 800 mg combined with irbesartan.[9]

The endpoints included safety, drug tolerability and reduction of serum AGT, drug behavior and blood pressure changes. Zilebesiran showed dose-effectiveness with greater blood pressure reductions at ≥200mg. At 8 weeks after a 200mg dose, 24-hour ambulatory systolic and diastolic blood pressure decreased >10mm Hg and >5mm Hg from baseline. These reductions persisted for 24 weeks due to its long-acting activity. The mean systolic and diastolic blood pressure changes were 22.5 mmHg and 10.8 mmHg at 6 months with 800mg dose. [9]

BP decreased during day and night, denoting proper control. The salt study showed failure to reduce salt suppresses drug effectiveness, as BP remains high despite medication, indicating lifestyle's role. Part E showed irbesartan with zilebesiran decreased BP more significantly than zilebesiran alone. Phase1 findings demonstrated AGT silencing with siRNA reduces BP for months with a single dose.[9]

Phase 2 Trials: A phase 2 randomized, double-blind, placebo-controlled trial (KARDIA-1) included 394 adults with mild-to-moderate hypertension. Patients discontinued blood-pressure medications and received either subcutaneous zilebesiran or placebo. Doses were: 150 mg or 300 mg or 600 mg every 6 months, or 300 mg every 3 months. The primary endpoint was change in 24-hour systolic blood pressure at 3 months via ambulatory monitoring.[9]

KARDIA-111 showed zilebesiran reduced blood pressure across doses. At 3 months, zilebesiran patients had reduced 24hour systolic BP versus placebo. The least squares mean differences against placebo for 150mg, 300mg, and 600mg doses were -14.1mmHg, -16.7mmHg and -15.7mmHg respectively ($P < 0.001$).[9]

The blood pressure reduction mirrors that of standard BP medication, demonstrating zilebesiran's significant clinical effect. This reduction persisted throughout the six-month duration, with BP remaining lower in drug-taking groups despite reduced dosing frequency. Most patients taking the drug achieved their target blood pressure, unlike the placebo group where BP increased. Additional phase 2 studies are ongoing.[9]

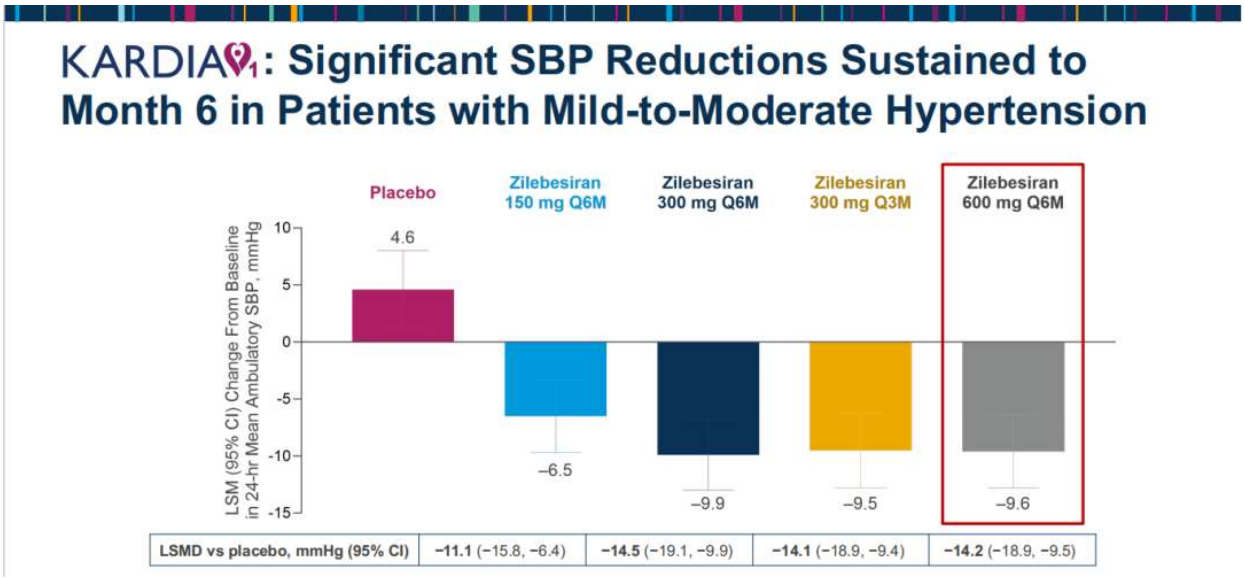
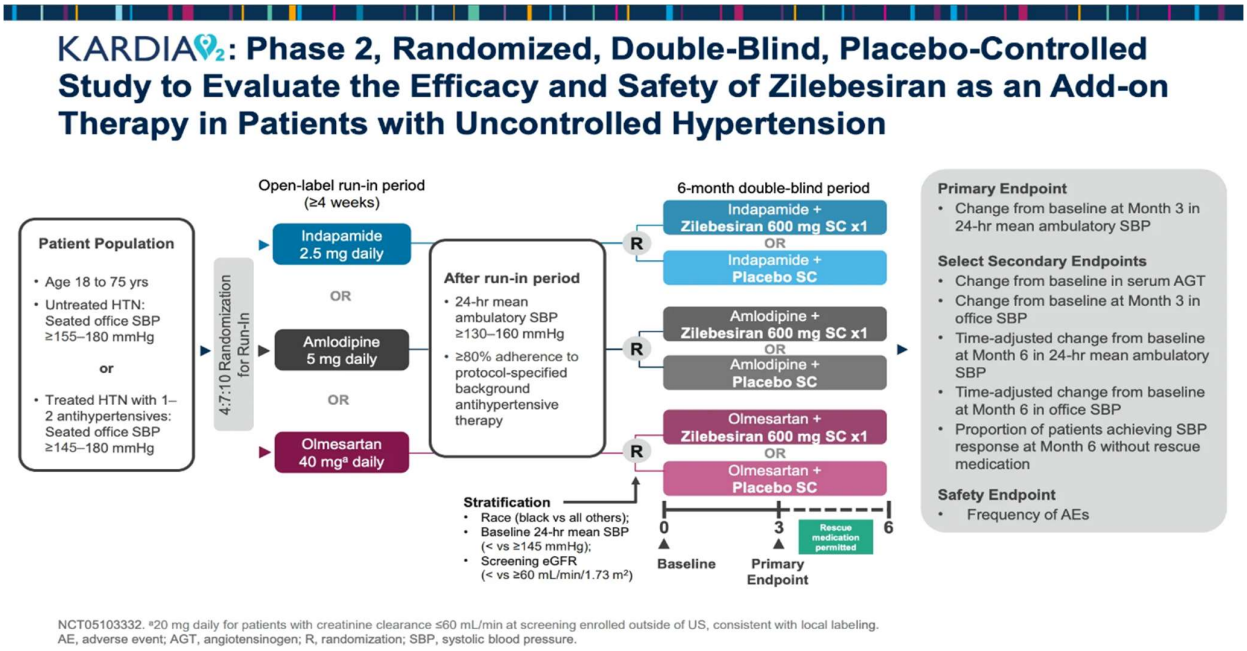


Figure 3: KARDIA -1 about phase -2 clinical trials.[11]

The KARDIA-2 trial is a study that combines zilebesiran with standard blood pressure medications in a large group of over 600 patients. It will indicate whether zilebesiran is effective on top of, or is able to substitute for, well-known medications such as diuretics, ACE blockers, ARBs or calcium channel blockers.

Another trial is known as KARDIA-3 and is observing individuals with higher blood pressure, but with a high chance of heart disease and those who take multiple drugs.



NCT05103332. [a]20 mg daily for patients with creatinine clearance ≤60 mL/min at screening enrolled outside of US, consistent with local labeling.
AE, adverse event; AGT, angiotensinogen; R, randomization; SBP, systolic blood pressure.

Figure 4: KARDIA -2 about phase -2 clinical trials.[11]

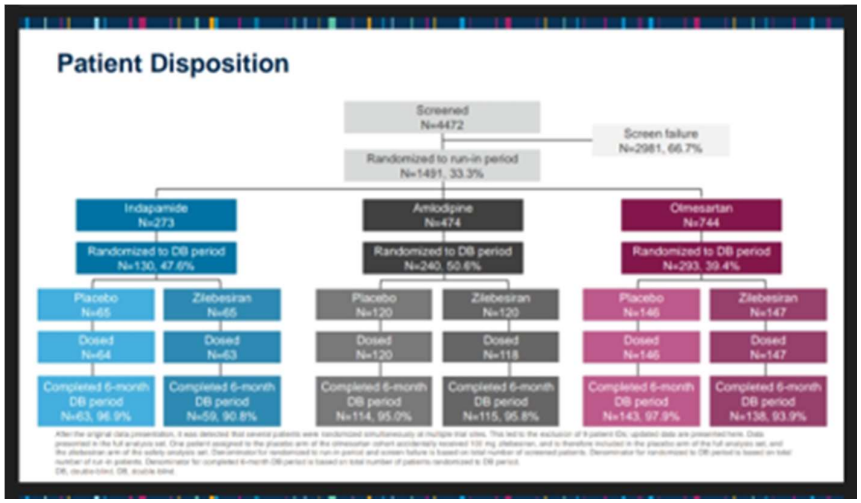


Figure 5: KARDIA -2 about phase -2 clinical trials.[11]

In KARDIA-3, physicians are prescribing zilebesiran with 2-4 other blood-pressure drugs to 400 individuals to assess its effectiveness in reducing blood pressure resistant to other treatments. Phase 2 trials will help determine optimal use of zilebesiran, whether alone or combined with other medications for patients with difficult-to-treat hypertension.[9]

KARDIA-3 (NCT06272487) investigates zilebesiran's safety and effectiveness in patients with or at risk of heart/blood vessel disease. The study includes patients with critical kidney disease and those whose high blood pressure remains uncontrolled despite taking multiple blood pressure medications.[12]

Efficacy of Zilebesiran:[6]

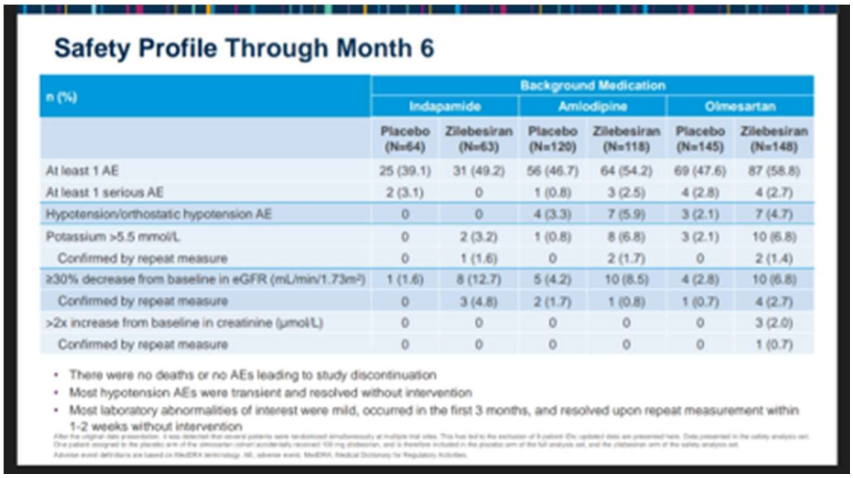
Zilebesiran reduced blood pressure in trials, showing dose-dependent effects that could result in six months of pressure reduction after one dose. It benefited individuals with unchecked high blood pressure, adding value to existing treatment. Research shows angiotensinogen-blocking decreases blood pressure and prevents blood vessel and heart changes.[6]

Safety profile and future considerations:[2]

Nevertheless, due to the small and fast study it is possible that uncommon severe side effects have not been extensively examined. Since individuals with other disorders such as type 2 diabetic and chronic kidney disease were not excluded, further safety testing of zilebesiran is required. siRNA therapies may have an impact on genes that they are not targeted to so we continue to be concerned about off-target effects.[2]

RAS blockers can slow kidney blood flow and reduce fetal oxygen, making them unsuitable during pregnancy. Zilebesiran, which inhibits RAAS pathway, may similarly affect kidney blood flow and fetal oxygen levels. Though studies found no adverse effects in preeclamptic rat embryos, concerns about potential side effects persist.[2]

Further research is needed to determine zilebesiran's placental transfer and fetal effects. As zilebesiran primarily targets liver cells, it does not affect AGT in other regions like kidneys or fats, which are important for obese individuals.[2]



Safety Profile Through Month 6

n (%)	Background Medication					
	Indapamide		Amlodipine		Olmesartan	
	Placebo (N=64)	Zilebesiran (N=63)	Placebo (N=120)	Zilebesiran (N=118)	Placebo (N=145)	Zilebesiran (N=148)
At least 1 AE	25 (39.1)	31 (49.2)	56 (46.7)	64 (54.2)	69 (47.6)	87 (58.8)
At least 1 serious AE	2 (3.1)	0	1 (0.8)	3 (2.5)	4 (2.8)	4 (2.7)
Hypotension/orthostatic hypotension AE	0	0	4 (3.3)	7 (5.9)	3 (2.1)	7 (4.7)
Potassium >5.5 mmol/L	0	2 (3.2)	1 (0.8)	8 (6.8)	3 (2.1)	10 (6.8)
Confirmed by repeat measure	0	1 (1.6)	0	2 (1.7)	0	2 (1.4)
≥30% decrease from baseline in eGFR (mL/min/1.73m²)	1 (1.6)	8 (12.7)	5 (4.2)	10 (8.5)	4 (2.8)	10 (6.8)
Confirmed by repeat measure	0	3 (4.8)	2 (1.7)	1 (0.8)	1 (0.7)	4 (2.7)
>2x increase from baseline in creatinine (µmol/L)	0	0	0	0	0	3 (2.0)
Confirmed by repeat measure	0	0	0	0	0	1 (0.7)

- There were no deaths or no AEs leading to study discontinuation
- Most hypotension AEs were transient and resolved without intervention
- Most laboratory abnormalities of interest were mild, occurred in the first 3 months, and resolved upon repeat measurement within 1-2 weeks without intervention

Figure 6: safety profile through month 6 about phase -2 clinical trials.[11]

Safety and adverse events:[13]

Overall, 58 patients (72%) were assigned to zilebesiran and 28 patients (88%): a placebo.

Side effects which had a minimum of 5 percent of the patients' included headaches, injection site reactions as well as upper respiratory tract infection; majority of these were mild or moderate. The only known adverse outcome of treatment reported to have occurred in over two patients consisted of injection-site reaction.

There were three critical adverse events, including: ischemic optic neuropathy; surgery treatment in a patient who took 200mg of zilebesiran (prostate cancer); and acute anemia as a side effect of a procedure done on the screening patient before taking the study drug (in a patient taking zilebesiran and irbesartan).[13]

The patients did not experience any deaths and unexpected hospital admissions, or treatment of low blood pressure, high potassium, or deteriorating kidney conditions. Blood potassium levels, sodium, creatinine and kidney filtration rate did not show any significant change.[13]

Future Directions:[14]

Zilebesiran shows promise for future hypertension management. Despite over 100 approved antihypertensive medications,

treatment response remains unsatisfactory. Semi-annual zilebesiran administration could improve BP through better adherence. While its safety profile appears adequate, more research in high-risk populations is needed to evaluate kidney effects, similar to RAAS inhibitors. Reversing zilebesiran's long-acting effects remains a key safety concern. Though noradrenaline and Ang II show potential as reversal agents, clinical testing is required. AGT elevation likely contraindicates use in reproductive-age women without guaranteed contraception due to RAS inhibition teratogenicity.[14]

Further research shall determine zilebesiran's effect on blood pressure in individuals with abnormal blood pressure profiles, including those with nocturnal hypertension. It will assess safety and efficacy when combined with other blood pressure medications. [14]

Zilebesiran inhibits AGT blood levels by over 90%. As proposed by Professor Bruanwald, it could be administered annually with inclisiran to prevent heart illness by targeting CVD's major risk factors. Zilebesiran may transform hypertension treatment.[14]

Limitations:[15]

This review is faced with a number of limitations. Being a narrative synthesis, it neither compounds data into figures nor can be biased due to the manner of studies selection and verification. Although using the SANRA guidelines made the methods more readable, the maintenance of a clear goal, systematic literature research, consistent interpretations, and clear references, there are still certain limits. Very early evidence of trials that are still in progress, or only recently finished, is, in some respects, premature, and variations in the design of study, what is measured by the study, and the duration of the study population substantiate comparisons between treatments. In addition, many new drugs are still shedding plenty of long-term safety, real-world effectiveness, and cost-effectiveness data, and thus we must be cautious as regards the extent to which they may actually exert a positive effect on the world.[15]

Conclusion

Zilebesiran represents a breakthrough in hypertension treatment, moving from daily oral medications to injections given twice yearly. This siRNA therapy uses RNA interference (RNAi) to inhibit hepatic angiotensinogen (AGT) production, achieving sustained blood pressure reduction for up to six months. Phase 1 and Phase 2 trials, including KARDIA-1, demonstrate strong efficacy and safety, ensuring consistent 24-hour blood pressure control. The blood pressure reduction with infrequent dosing addresses medication non-adherence, a key factor in uncontrolled hypertension worldwide. The targeted delivery to hepatocytes minimizes off-target effects in non-liver tissues, such as kidneys, offering advantages over conventional RAAS inhibitors. While ongoing studies, like KARDIA-2 and KARDIA-3, are vital to assess its role in combination therapies and high-risk groups, zilebesiran's mechanism and lasting impact signal a new era in cardiovascular treatment. This therapy could improve clinical outcomes and reduce global hypertension-related mortality and disability.

REFRENCES

1. Natale F, Franzese R, Luisi E, Mollo N, Marotta L, Solimene A, D'Elia S, Golino P, Cimmino G. The Increasing Problem of Resistant Hypertension: We'll Manage till Help Comes! Medical Sciences. 2024 Oct 4;12(4):53.
2. Siddiqui E, Siddiqui AH, Moeed A, Laique F, Najeeb H, Al Hasibuzzaman M. Advancing hypertension management: the role of zilebesiran as an siRNA therapeutic agent. Annals of Medicine and Surgery. 2025 Feb 1;87(2):577-82.
3. Huang ZA, Ji GS, Yang S, Yang Y, Wu YC, Tian ZK, Song GS. Design, pharmacology, and toxicology of a novel chemically modified siRNA targeting hepatic angiotensinogen. Molecular Therapy Nucleic Acids. 2025 Jun 10;36(2).
4. Lemine M, Almuzainy S, Aljubeh R, Alilo A. Zilebesiran and hypertension: A systematic review and meta-analysis. Journal of the Saudi Heart Association. 2024 Dec 20;36(4):420.
5. Addison ML, Ranasinghe P, Webb DJ. Novel pharmacological approaches in the treatment of hypertension: a focus on RNA-based therapeutics. Hypertension. 2023 Nov;80(11):2243-54.
6. Skibicka K, Skibicki T, Wesołowska W, Pietrzak J. RNA Interference Therapeutics in Cardiology: Focus on Zilebesiran and Olpasiran. Journal of Education, Health and Sport. 2025 Sep 21;84:65429.
7. Raza M, Riaz CZ, Chaudhry ER, Jannat M, Basit AR, Qureshi AJ, Qureshi MH, Ahmed MW, Qureshi Jr AJ. Efficacy and Safety of Zilebesiran for the Management of Hypertension: An Updated Systematic Review and Meta-Analysis of Randomised Controlled Trials. Cureus. 2025 Sep 16;17(9).
8. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. The lancet. 2005 Jan 15;365(9455):217-23.
9. Maheta D, Shah F, Biba V, Ngardig NN, Agrawal SP, Rajput J, Sager AR, Frishman WH, Aronow WS. Zilebesiran: A novel RNA interference therapeutic for hypertension. Cardiology in Review. 2025 Jun 2:10-97.
10. Morosan PA, Bobu AM, Carauleanu A, Popa R, Costea CF, Filip C, Buzduga CM, Patrascanu E, Cucu AI, Tudosa RI, Covali R. Zilebesiran as an Innovative siRNA-Based Therapeutic Approach for Hypertension: Emerging Perspectives in Cardiovascular Medicine. International Journal of Molecular Sciences. 2025 Nov 4;26(21):10717.
11. Bakris GL, Desai AS, Aswad A, Badariene J, Kazi F, Karns AD. Zilebesiran in combination with a standard-of care antihypertensive in patients with inadequately controlled hypertension: primary results from the phase 2 KARDIA-2 study. Late-Breaking Clinical Trials II. 2024 Apr.
12. Havasi A, Pagidipati N, Bakris G, Weber M, Bengus M, Daga S, Xiang Z, Zee T, Bhan I, Granger CB. KARDIA-3 study design: zilebesiran as add-on therapy in patients with high cardiovascular risk and hypertension inadequately controlled by standard of care antihypertensives. J Hypertens. 2024 May 31;42(Suppl 1):e120.
13. Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, Foster D, Huang SA, Rhyee S, Sweetser MT, Bakris GL. Zilebesiran, an RNA interference therapeutic agent for hypertension. New England Journal of Medicine. 2023 Jul 20;389(3):228-38.
14. Surma S, Oparil S. Zilebesiran—the first siRNA-based drug in hypertensiology: why is it needed, and will it change the treatment approach of hypertension? arterial hypertension. 2024; 28:1-1.
15. Varrassi G, Al Alwany AA, Borghi C, Pergolizzi JV, Mercieri M, Breve F, Myrcik D, Tran VY, Pham VP, Caruso A, Leoni ML.2025. A New Era of Disease-Modifying Pharmacotherapy in Cardiovascular Medicine.
16. Zilebesiran — the first siRNA-based drug in hypertension logy: why ... https://share.google/h1h3vkYsvwXdt3QvE