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Reimagining Blood Pressure Management: The Role of Zilebesiran in Targeting Angiotensinogen

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ABSTRACT

Hypertension remains a major global health burden and a leading risk factor for cardiovascular morbidity and mortality. Despite the availability of multiple antihypertensive therapies, a significant proportion of patients fail to achieve optimal BP control due to limited efficacy, side effects, or poor adherence. Zilebesiran (siRNA)-based therapy is a novel drug emerging for the hypertension control. This drug targets hepatic angiotensinogen synthesis and lowers blood pressure for a prolonged time compared to traditional antihypertensive medications. This review analyses current clinical trial data on Zilebesiran, with a focus on its efficacy and safety profile in hypertensive patients. A comprehensive literature search was conducted across PubMed, Embase, ClinicalTrials.gov, and Cochrane Library through June 2025, identifying phase I-II randomized controlled trials. The studies show Zilebesiran is efficient in significant and sustained reductions in 24-hour ambulatory SBP, with effects lasting up to six months following a single subcutaneous dose. The treatment was well-tolerated, with the most common adverse events being mild injection site reactions. Zilebesiran represents a promising new approach for hypertension management, offering long-acting BP control and potential benefits in patients with adherence challenges. However, further large-scale trials are essential to establish long-term safety and cardiovascular outcomes in broader and higher-risk populations.

Keywords*: Zilebesiran, RNA interference therapy, Hypertension, Therapeutic adherence, KARDIA trials, blood pressure, antihypertensive therapy.*

INTRODUCTION

Hypertension remains a leading cause of cardiovascular disease and global mortality [1]. The number of adults with hypertension nearly doubled from 1990, from about 600 million to 1.3 billion in 2019. Among them, about 78% of adults with hypertension are in low- and middle-income countries [2]. Despite public health efforts and multiple drugs unable to control hypertension, there is an emerging role of small interfering RNA (siRNA)-based therapies, with a particular focus on zilebesiran, as a novel and promising strategy for managing hypertension [3]. Small interfering RNA (siRNA) therapy regulates gene expression and addresses hypertension at the molecular level. Zilebesiran, an investigational siRNA, inhibits hepatic angiotensinogen (AGT) synthesis by promoting degradation of AGT mRNA via the RNA-induced silencing complex. This reduces angiotensin II levels, leading to sustained blood pressure reduction [4,5]. Zilebesiran demonstrates favorable pharmacokinetics, with a single dose providing antihypertensive effects lasting up to 24 weeks. Combination with angiotensin receptor blockers enhances efficacy. The drug has only mild injection site reactions reported [3]. As the first siRNA targeting AGT, zilebesiran marks a significant advance in hypertension treatment, highlighting the promise of

RNA interference therapies. Ongoing clinical studies will be key to its future role in cardiovascular care [3]. Zilebesiran offers a promising and innovative approach to managing hypertension by addressing the disease at a molecular level. Given its unique mechanism of action, sustained efficacy, and favorable safety profile demonstrated in early clinical studies, a comprehensive review of zilebesiran is warranted to evaluate its potential impact on future hypertension management and cardiovascular health outcomes [3]. This article evaluates the pharmacological properties, clinical efficacy, safety profile, and therapeutic potential of zilebesiran, as an emerging treatment for hypertension.

Clinical Evaluation of Zilebesiran in hypertension: Evidence from Randomized Clinical Trials

Zilebesiran is a novel RNA interference (RNAi) therapeutic that targets hepatic AGT synthesis, leading to sustained suppression of renin angiotensin aldosterone system (RAAS) and significant reductions in blood pressure [6]. Figure 1 illustrates the chronological progression of key Zilebesiran trials. The following clinical trials have evaluated its efficacy and safety in patients with hypertension:

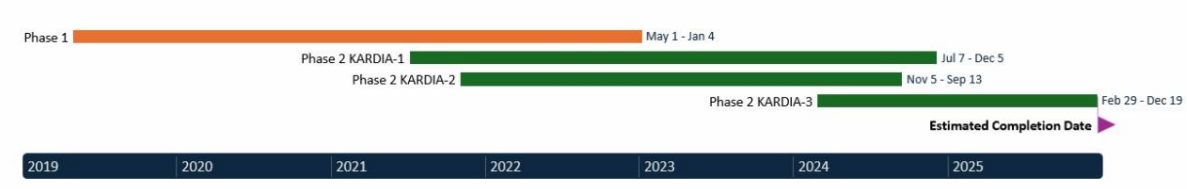

Figure 1: Timeline of Zilebesiran Clinical Trials

1. **Phase 1 Dose-Escalation Trial (ALN-AGT01)**

A phase 1, randomized, double-blind, placebo-controlled trial (NCT03934307) evaluating single ascending doses of Zilebesiran (10 to 800 mg SC) in 107 adults with treated or untreated mild hypertension (baseline 24-hour systolic blood pressure (SBP) >130-165 mmHg), with up to 24 weeks of follow up [6,7].

Participants receiving moderate-to-higher doses experienced meaningful reductions in ambulatory systolic and diastolic blood pressure that were sustained over several months. The treatment also resulted in marked suppression of circulating AGT, confirming target engagement. Zilebesiran exhibited an excellent safety profile in this Phase 1 study. Adverse events were primarily mild to moderate injection site reactions, headache, and upper respiratory tract infection. A few serious events were reported but were determined to be unrelated to the study drug. Importantly, no dose-limiting toxicities, hypotension, renal dysfunction, or no deaths or unplanned hospitalizations were observed [6].

2. **KARDIA-1 trial**

KARDIA-1 trial (NCT04936035) was a phase 2, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of Zilebesiran in patients with uncontrolled hypertension, defined as 24-hour SBP between 135-160 mmHg off all antihypertensive medications. Participants were randomized to receive a single subcutaneous dose of Zilebesiran (150 mg, 300 mg, or 600 mg) or to placebo, and were followed for 6 months [8,9].

The trial demonstrated a clear dose-response trend, with higher doses producing more pronounced reductions in both blood pressure (BP) and serum angiotensinogen levels [8]. This supports the mechanism of action of Zilebesiran, which relies on hepatic silencing of the angiotensinogen gene to suppress the renin angiotensin aldosterone system upstream, thereby reducing vasoconstriction and fluid retention [3].

Zilebesiran was generally well tolerated across all dose groups in this trial. All drug-related adverse events were mild to moderate in severity. Although a small number of participants experienced adverse effects such as hypotension, hyperkalemia, or changes in renal function, these events were usually mild, transient, and comparable in frequency to the placebo group. No treatment related deaths were reported [8].

3. **KARDIA-2 trial**

KARDIA-2 trial (NCT05103332) was a phase 2, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of Zilebesiran when added to standard background antihypertensive medications. Unlike KARDIA-1, which assessed Zilebesiran as monotherapy, this trial investigated its use as adjunctive therapy in patients with untreated hypertension or uncontrolled hypertension despite being on first-line antihypertensive [10,11]. Participants underwent a run-in phase where they were stabilized on one of the three background therapies– Amlodipine, Indapamide, or Olmesartan– before being randomized to receive either a single subcutaneous dose of Zilebesiran or placebo.

Across all background therapy groups, the addition of Zilebesiran led to greater reductions in systolic blood pressure compared to placebo. The magnitude of this effect varied somewhat depending on the background drug, but in each group,

the reductions were clinically meaningful. These findings demonstrate that Zilebesiran can provide additive antihypertensive benefits even when used alongside commonly prescribed oral medications.

Across all cohorts, the overall safety profile of Zilebesiran was acceptable, but certain adverse events occurred more frequently than with placebo, including, hyperkalemia, hypotension, minor decline in kidney function. However, most of these events were mild and resolved without medical intervention. No treatment-related deaths or permanent discontinuations due to serious adverse events were reported [10]. Efficacy outcomes from these trials are summarized in Table 1.

Table 1: Efficacy Outcomes of Zilebesiran Across Clinical

Trial	ClinicalTrials.gov ID	Dose(s)	Systolic Blood Pressure Reduction
Phase 1 Dose-Escalation Trial	NCT03934307	10 – 800 mg SC	>10 mmHg for ≥ 200 mg reduction
KARDIA-1	NCT04936035	150, 300, 600 mg SC	~ 14-17 mmHg reductions across doses
KARDIA-2	NCT05103332	600 mg SC + background therapy	Ranged from ~4 to ~12 mmHg reduction across different cohort

Note: Values are approximate summaries of published findings [6,8,10]

KARDIA-2 reinforces the therapeutic promise of Zilebesiran not only as a standalone agent but also as part of a multidrug approach to managing hypertension.

4. **KARDIA-3 Trial**

The KARDIA-3 trial (NCT06272487) is an ongoing Phase 2 randomised, double-blind, placebo-controlled study designed to evaluate Zilebesiran as an add-on to standard therapy in patients with uncontrolled hypertension who are at high cardiovascular risk. Key secondary endpoints include changes in 24-hour ambulatory BP, diastolic BP, and safety/tolerability through 6 months of follow-up [12]. This trial will provide curial data on Zilebesiran's efficacy and safety in a difficult-to-treat, high-risk hypertension population that was under-represented in earlier phases. If Zilebesiran shows efficacy and safety in this population, it could have meaningful implications for its role as a long acting adjunctive therapy in resistant hypertension or among patients at high risk for cardiovascular events.

5. **Planned Phase 3 Cardiovascular Outcomes Trial**

In parallel with KARDIA-3, a Phase 3 outcomes trial of Zilebesiran is being planned to determine whether long-term blood pressure lowering with this agent can improve major cardiovascular outcomes in high-risk hypertension [13].

Real-World Potential and Safety Considerations for Zilebesiran for Hypertension Management

Zilebesiran represents a novel paradigm in antihypertensive treatment, diverging from traditional pharmacotherapy by targeting hepatic angiotensinogen synthesis using RNAi technology [14]. Early-phase trials have demonstrated sustained 24-hour blood pressure reductions lasting up to six months after a single subcutaneous (SC) dose, making it a promising option for both monotherapy and adjunctive use. Its most compelling real-world advantages lie in its potential to address poor adherence, one of the greatest obstacles in hypertension management [15]. While traditional antihypertensives require daily dosing, making suboptimal adherence a persistent challenge that contributes to poor blood pressure control, Zilebesiran's biannual subcutaneous dosing is designed to overcome this barrier, delivering continuous 24-hour BP suppression without the need for daily patient effort.

Zilebesiran may also benefit patients with resistant hypertension, which affects approximately 10-15% of hypertensive individuals and is associated with elevated cardiovascular risk. These patients often require complex regimens of multiple agents, further compounding adherence issues [16,17]. The ongoing KARDIA-3 trial will clarify its role in this population [12].

Despite its strong clinical promise, Zilebesiran's prolonged action and sustained RAAS suppression necessitate vigilant safety monitoring to optimize benefits and minimize risks. In clinical practice, periodic laboratory parameters should be monitored in patients taking Zilebesiran to detect potential complications before they become clinically significant. Existing trials have emphasized monitoring renal and hepatic function with serum creatinine, estimated glomerular filtration rate (eGFR), and liver enzymes [6,8,10]. Electrolytes and hemoglobin were also monitored as part of safety labs [6,8,10]. While RAAS biomarkers, namely serum angiotensinogen and aldosterone levels, were assessed as endpoints [6,5], they are unlikely to be clinically useful. Considering the potential risk of hyperkalemia and worsening renal function in RAAS blockers [6,8,10], routine monitoring with a comprehensive metabolic panel (CMP) and eGFR is a reasonable

strategy. Although hepatic safety was demonstrated in trials [6,8,10], monitoring of liver enzymes may be considered given the drug's hepatic selectivity. A summary of adverse effects from early-phase clinical trials is shown in Table 2.

Table 2: Adverse events reported in Zilebesiran group across clinical trials

	Adverse Event	Phase 1 Dose Escalation	KARDIA-1 (Phase 2)	KARDIA-2 (Phase 2)
1	Injection Site Reaction	~6.3%	~6.3%	Not separately specified (~16.9% non-serious AEs overall)
2	Hyperkalemia	~ 5%	~ 5%	5.5%
3	Hypotension	~ 4–8%	~ 4–8%	4.3%
4	Headache	> 5%	> 5%	Not reported
5	Acute Kidney Injury	~ 1%	~ 1%	~4.9%
6	Hepatic Adverse events	~ 3%	~ 3%	Not specified
7	Serious Adverse Events	~3.6%	~3.6%	Not specified (stated as "low rates")
8	Mortality	0.3% (1 unrelated death)	0.3% (not related to treatment)	0%

Note: Data represent approximate values summarized from [6,8,10]

BP monitoring remains essential to detect both insufficient BP reduction and excessive lowering, which may increase the risk of falls, syncope, or hypoperfusion events, particularly in older patients or those with coronary artery disease. Home BP monitoring can complement clinic readings to provide continuous feedback, allowing earlier intervention if BP falls outside the target range. Physicians need to plan for early follow-up after initial dosing to ensure the patient tolerates the drug, then transition to longer interval surveillance aligned with its dosing schedule. Given the long duration of action, establishing clear protocols for monitoring at set intervals will help mitigate risk while maintaining therapeutic benefit.

Limitations

While preliminary data is promising, it is important to note the lack of data regarding long-term outcomes and outcomes in high-risk demographics. Aliskiren is a direct renin inhibitor FDA-approved in 2007 following strong data from trials suggesting its efficacy and safety [18-22]. However, later studies found notable frequency of serious adverse events in certain demographics [23,24], as well as a lack of long-term cardiovascular benefit [24,25], thereby changing the way Aliskiren is prescribed. The history of Aliskiren underscores the importance of obtaining long-term data, particularly in the context of evaluating safety of RAAS inhibitors.

Early clinical trials of Zilebesiran had treatment and follow-up periods limited to approximately six months, with assessments generally extending to six months after last dose [6,8,10]. As a result, long-term effects of the drug beyond the 6-month follow-up period could not be ascertained. Furthermore, participants from existing studies were enrolled based on specific selection criteria, such that the studied population cannot be generalized to represent broader populations. Existing clinical trials have primarily evaluated populations with mild-to-moderate hypertension, excluding individuals with significant comorbidities, such as diabetes and history of cardiovascular events [6,8,10]. As a result, prevalent high-risk demographics are not represented. The ongoing KARDIA-3 trial is expected to provide insight into the efficacy and safety of Zilebesiran in higher-risk demographics [12].

Future direction

Zilebesiran, if approved, is poised to become a valuable addition to hypertension management, particularly for adults with mild to moderate hypertension who struggle to achieve adequate blood pressure control with standard oral medications or face adherence challenges. As a subcutaneous RNA interference therapy that targets hepatic angiotensinogen, zilebesiran has shown promising results in phase 2 trials (KARDIA-1 and KARDIA-2), delivering sustained blood pressure reductions for up to six months [6,10]. Rather than replacing established first-line therapies such as thiazide diuretics, Angiotensin-converting enzyme inhibitors (ACE inhibitors), Angiotensin II receptor blockers (ARBs), or calcium channel blockers, zilebesiran would likely serve as an adjunctive treatment, particularly beneficial for patients with resistant hypertension or poor medication adherence. Its long-acting profile may offer significant advantages for high-risk populations, including individuals with cognitive impairment, limited access to healthcare, or complex medication regimens. By inhibiting the RAAS upstream, zilebesiran provides consistent 24-hour blood pressure control, which may help reduce end organ damage and long-term cardiovascular risks, although further studies are needed to confirm these outcomes [6,8,26]. There is also potential for its use in patients with comorbid conditions such as chronic kidney disease or type 2 diabetes, especially in combination therapy [6,8,26]. The convenience of monthly or less frequent dosing carries meaningful public health implications. Nonadherence remains a major contributor to uncontrolled hypertension worldwide, and long-acting injectables like zilebesiran can ease pill burden and reduce missed doses, thereby improving overall control and minimizing variability between clinical visits. However, the long duration of action necessitates careful safety monitoring for adverse

effects like hyperkalemia, hypotension, and acute kidney injury [8,27]. In urgent situations requiring rapid RAAS reactivation, its prolonged effect may complicate clinical management. Furthermore, cost and infrastructure requirements could present barriers to widespread implementation, especially in resource-limited settings [4,28].

CONCLUSION

Zilebesiran is a promising new antihypertensive. As an siRNA-based gene modulator, the drug has demonstrated excellent blood pressure control by precluding synthesis of hepatic AGT, thereby achieving RAAS blockade. Early clinical trials consistently demonstrate meaningful and durable reductions in blood pressure, both as monotherapy and in combination with standard antihypertensives, alongside a generally favorable safety profile. Its biannual dosing offers a potential solution to the persistent challenge of poor adherence, and its efficacy in resistant hypertension could address an important unmet need in cardiovascular care.

However, translating trial results into clinical practice will require vigilane. The drug's long duration means that adverse effects– such as hyperkalemia, hypotension, acute kidney injury– could persist for weeks or months, limiting rapid reversibility. Dose adjustments are not immediately feasible once drug is administered, underscoring the need for careful patient selection, structured laboratory surveillance, and clear clinical protocols. While Zilebesiran's long-acting profile and favourable safety data from early trials highlights its potential as a novel strategy in the management of hypertension, large-scale trials are necessary to ascertain its full potential of Zilebesiran as an antihypertensive. Further research is needed to evaluate its effect on broader populations, as well as to establish a favourable long-term safety profile.

List of Abbreviations

- AGT: angiotensinogen
- RNAi: RNA interference
- RAAS: renin angiotensin aldosterone system
- SBP: systolic blood pressure
- eGFR: estimated glomerular filtration rate
- ACE inhibitors: Angiotensin-converting enzyme inhibitors
- CMP: comprehensive metabolic panel
- ARBs: Angiotensin II receptor blockers
- SC: subcutaneous
- BP: Blood Pressure

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