Review Article

Zilebesiran, a Small Interfering RNA agent as a potential novel antihypertensive treatment with cardiorenal protective effects: An overview of recent clinical trials

Herwindo Ahmad,[1] Refli Hasan,[1] Naomi Niari Dalimunthe,[1]Rahmad Isnanta,[2] T. Realsyah,[1] Zainal Safri[2]

Departments of Internal Medicine, Division of Cardiovascular Medicine, Faculty of Medicine, [1]Universitas Sumatera Utara, [2]Adam Malik General Hospital, Medan, Indonesia

Hypertension is the primary risk factor for kidney and cardiovascular disease. Effective control of hypertension is important as reduction of blood pressure may effectively mitigate cardiovascular risks. The prevalence of uncontrolled hypertension persists, despite the widespread availability of antihypertensive medications. Poor adherence to medications is attributed to inadequate blood pressure control with current treatments. Zilebesiran, an investigational RNA interference therapeutic agent, targets hepatic angiotensinogen synthesis to provide sustained blood pressure reduction. It provides long-lasting pharmacological effects, requiring only twice a year or quarterly subcutaneous injection. Therefore, it is feasible to tackle the inadequate patient compliance with this drug. This review discusses its potential clinical impact, efficacy, and safety profile based on recent studies.

Keywords: Cardiorenal protection, siRNA, hypertension, antihypertensive agents.

INTRODUCTION

Hypertension is a chronic medical condition that is well linked as the primary risk factor for cardiovascular and renal disease.[1] The diagnosis of hypertension is made when the office measured blood pressure is equal to or greater than 140 mmHg systolic blood pressure, and/or 90 mmHg diastolic blood pressure, consistently after repeated measurements.[2] Uncontrolled hypertension is a worldwide health issue that contributed greatly to cardiovascular disease mortality.[1] Having an effective control on hypertension is crucial in mitigating cardiovascular risks.[3] According to results from a large-scale review of randomized trials, every 5 mmHg drop in systolic blood pressure will decrease the risk of cardiovascular events by 10%.[4]

The primary therapeutic strategies for hypertension management involve pharmacological treatments and lifestyle interventions. The renin-angiotensin-aldosterone system (RAAS) inhibitors, calcium channel blockers, and diuretics are three primary antihypertensive drugs, from which various single-pill combinations have been expanded.[5] The prevalence of uncontrolled hypertension persists, despite the widespread availability of numerous antihypertensive medications. Failure of physicians to start or intensify antihypertensive therapy and poor patient adherence to daily oral drugs may be attributed to inadequate blood pressure control with current antihypertensive treatments.[6]

Numerous studies have sought to identify alternative therapeutic approaches to overcome challenges arising from uncontrolled hypertension. A novel therapeutic agent, zilebesiran may presents as a potential life-altering remedy for sustained blood pressure reduction with only twice-yearly or quarterly subcutaneous administration.[7] Nevertheless, the available evidence regarding its efficacy and safety is limited. This review is to provide a comprehensive overview of zilebesiran, including its mechanism of action as siRNA, recent evidence on its benefits and safety, and future potential as a new antihypertensive therapy.

MECHANISM OF ACTION

Zilebesiran is a small interfering RNA (siRNA) that consists of a double-stranded RNA. It has a high affinity for binding with the hepatic asialoglycoprotein receptor (ASGPR), as it is conjugated to a N-acetylgalactosamine (GalNAc) ligand.[8] The main target of Zilebesiran is to efficiently lower the concentrations of hepatic angiotensinogen messenger RNA (mRNA), resulting in a subsequent decrease in the synthesis of liver angiotensinogen (AGT).

Following its first entry into hepatocytes by endocytosis, ASGPR is transported back to the cell membrane, whereas zilebesiran interacts with the cytoplasmic RNA-induced silencing complex (RISC). The antisense strand, which is a guide strand, remains intact while the non-guided strand is released. The reverse RNA interference complex cleaves the complementary target mRNA of the guide strand, namely the AGT mRNA, leading to the suppression of the target gene responsible for AGT pro-

duction.[9]

Angiotensinogen serves as the sole precursor for all angiotensin peptides.[10] Hence, the implementation of its approach to limit the RAAS holds promise in impeding the compensatory activation of angiotensin, which is associated with the suppression of angiotensin-converting enzymes or the blocking of angiotensin receptors.[11]

The use of hepatocyte-targeted administration has the capacity to sustain the level of extrahepatic angiotensinogen production, therefore reducing the likelihood of unintended consequences in either the kidney or other organs. Preclinical studies employing a GalNAc-conjugated angiotensinogen siRNA provide evidence for the liver-specific efficacy of this method.

Several investigations suggest that the system is almost completely effective in decreasing the expression of liver AGT mRNA, without interfering the expression of renal AGT mRNA. Furthermore, the initial clinical trials involving GalNAc-conjugated antisense oligonucleotides that specifically target angiotensinogen provide additional evidence for these effects.[7] The long-lasting and persistent pharmacological effects of GalNAc–siRNAs offer the potential to achieve a sustained decrease in ambulatory blood pressure up to several months. By administering Zilebesiran subcutaneously twice a year or quarterly, it is possible to address the issue of inadequate patient adherence to antihypertensive therapy.[11]

EFFICACY AND SAFETY

A total of 5 clinical trials reported the efficacy and safety of zilebesiran in managing hypertension. All the five studies included were randomized and blinded, with a total of 1438 patients with resistant hypertension. Three studies evaluated zilebesiran as monotherapy for hypertension, comparing zilebesiran with placebo.[7,12,13] Notable reductions in ambulatory systolic blood pressure were showed in all dose regimens of single dose zilebesiran.[7,13]

Study by Taubel et al, showed zilebesiran effectively reduced blood pressure in patients with resistant hypertension and obesity as comorbidity.[12] Study by Saxena et al, evaluated zilebesiran as additional therapy. Results demonstrated zilebesiran significantly reduced blood pressure in addition to either diuretic, ARB, or ACE-i.[14] Zilebesiran demonstrated a significant effect in lowering blood pressure, either as monotherapy or additional therapy in a broad population with favourable safety profile (Table 1).

Table 1: Summary of Zilebesiran research investigations.

Study	Participants	Interventions of study	Findings
Desai et al, 2023.[7] Phase-1 study	107 participants with hypertension	Zilebesiran 10-800 mg SC compared to placebo	Single-dose zilebesiran (≥200 mg) was associated to reduction of systolic blood pressure >10 mmHg and diastolic blood pressure >5 by week 8 and remained until week 24. No serious adverse events were reported.
Taubel et al, 2023.[12] Phase-1 study	12 participants with hypertension and BMI >35 - 50 kg/m2	Zilebesiran 800 mg SC + oral placebo compared to Irbesartan 150 mg oral + subcutaneous placebo	Similar effectivity and safety of zilebesiran in broader population, namely obese patients. Mild headaches were the AEs reported.
Bakris et al, 2024.[13] KARDIA-1 (Phase-2 study)	377 participants with SBP 135-160 mmHg	Zilebesiran 150, 300, or 600mg SC every 6 months or 300mg SC every 3 months compared to placebo	Notable reductions in ambulatory systolic blood pressure were showed in all dosage regimens of zilebesiran compared to placebo. No significant adverse event reported.
Saxena et al, 2024.[14] KARDIA-2 (Phase-2 study)	672 participants with uncontrolled hypertension	Zilebesiran 600 mg SC as additional therapy to either olmesartan 20 or 40 mg, amlodipine 5 mg, or indapamide 2.5 mg compared to placebo	• Zilebesiran and indapamide decreases 12 mmHg SBP. • Zilebesiran and amlodipine decreases 9.7 mmHg SBP. • Zilebesiran and Olmesartan decreases 4 mmHg SBP. No serious adverse events in all groups.

Tabel 2: Series of novel antihypertensive agents.

	Administration	Potential Advantages	Limitations
Zilebesiran[7,12-14]	Subcutaneous injection, every 3-6 months	• Impressive effect on 24-hours BP control • Durability over months • Minimal first dose hypotension risk • No serious adverse events • Potentially benefits patient with renal and cardiovascular diseases	• May not be used in hypertensive emergencies
ETRAs[27,28]	Oral, once daily	• Safe administration in patients with chronic kidney disease (CKD) • Minimal risk of hyperkalemia	• Granted approval solely for pulmonary hypertension • May cause volume retention and necessitate the simultaneous use of a diuretic
ASIs[32-35]	Oral, once daily	• May benefit patients with hyperaldosteronism • Minimal effect in cortisol level	• Significant risk of increasing potassium level • May elicit poor adherence to therapy
IONIS-AGT-L_{Rx}[36,37]	Subcutaneous injection, weekly	• Potentially benefits in hypertension and heart failure	• Requiring further studies as the current studies were small in sample size

POTENTIAL BENEFITSIN RENAL AND CARDIOVASCULAR DISEASE

The RAAS) is an intricate system which ensure the perfusion to vital organs by regulating blood pressure. The dysregulation of RAAS may lead to organ damage including fibrosis of the kidney, heart and vascular wall resulting in higher cardiovascular and kidney failure risk.[15,16] Pharmacological interventions targeting RAAS have effectively halted the advancement of renal disease and decreased cardiovascular mortality.[17] Nevertheless, excessive inhibitory effects of RAAS through the combination of RAAS inhibitors, such as ACE inhibitors (ACEi) and Angiotensin Receptor Blockers (ARB) appears to have a detrimental effect, as it leads to collapse in renal autoregulation and greater side effects such as hyperkalemia and acute kidney injury.[18] ACEi or ARB, elicit a compensatory rise in renin and Ang I levels after prolonged usage due to the disruption of negative feedback facilitated by Ang II, resulting in RAAS escape. The findings of a new RAASi target, small-interference RNA (siRNA), offers a promising remedy by efficiently eliminating AGT, hence preventing the RAAS escape phenomena.[19]

A study demonstrated that Zilebesiran has renal and cardiovascular protection effects.[17] The model chosen in this study were 5/6th nephrectomy rat with hypertension, cardiac enlargement, and characteristics of CKD including reduced GFR, proteinuria, glomerulosclerosis, and kidney fibrosis.[20] Angiotensinogen siRNA reduced plasma angiotensinogen and Ang II in renal and cardiac. Consistent with its liver selectivity, AGT siRNA did not impact the expression of renal AGT. However, it significantly reduced Ang I, Ang II, and renal AGT levels. Linear regression analysis demonstrated that siRNA may have advantageous effects in chronic renal disease and cardiac hypertrophy.[21]

Aside from its impact on blood pressure, angiotensin II stimulates the progression of atherosclerosis. High blood pressure and atherosclerosis rely on Ang II in mice who are fed a high-saturated fat diet and lacking low density lipoprotein (LDL) receptor.[22] An alternative pharmaceutical strategy using antisense, siRNA has emerged as a potential avenue for directly targeting AGT in the prevention of hypertension and atherosclerosis.[23] Mice with reduced AGT expression manifested reduced body weight gain, hepatic steatosis, atherosclerosis, and systolic blood pressure. Therefore, siRNA that supress the expre-

ssion of AGT may be advantageous to the cardiovascular system.[24]

ZILEBESIRAN RATHER THAN OTHER NOVEL ANTIHYPERTENSIVE TREATMENT

In the present day, a series of novel agents have emerged, specifically targeting new mechanisms of blood pressure regulation. Non-steroidal mineralocorticoid receptor antagonists (nsMRA), endothelin receptor antagonists (ETRA), aldosterone synthase inhibitors (ASI), and small interfering ribonucleic acid (siRNA) are among the drug classes.

Author Contributions:
Conception and design: Herwindo Ahmad, Refli Hasan, Naomi Niari Dalimunthe, Rahmad Isnanta.
Collection and assembly of data: Herwindo Ahmad, T Realsyah, Zainal Safri.
Analysis and interpretation of the data: Herwindo Ahmad, Refli Hasan, Naomi Niari Dalimunthe, Rahmad Isnanta, T Realsyah, Zainal Safri.
Drafting of the article: Herwindo Ahmad, Refli Hasan, Naomi Niari Dalimunthe T Realsyah, Zainal Safri.
Critical revision of the article for important intellectual content: Herwindo Ahmad, Rahmad Isnanta, T Realsyah, Zainal Safri.
Final approval and guarantor of the article: Herwindo Ahmad.
Corresponding Author Email: Herwindo Ahmad: ahmadherwindo@usu.ac.id
Conflict of Interest: None declared.
Source of Funding: None disclosed.
Rec. Date: Mar 26, 2025 Revision Rec. Apr 25, 2025 Date: Accept Date: May 4, 2025.

REFERENCES

1. Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension 2020;75:285-92.
2. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension 2020;75:1334–57.
3. Khalil H, Zeltser R. Antihypertensive Medications. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554579/
4. Rahimi K, Bidel Z, Nazarzadeh M, Copland E, Canoy D, Ramakrishnan R, et al. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. Lancet 2021;397:1625–36.
5. Ma J, Chen X. Advances in pathogenesis and treatment of essential hypertension. Front Cardiovasc Med 2022;9: 1003852.
6. Burnier M, Egan BM. Adherence in Hypertension. Circ Res 2019;124:1124-40.
7. Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, et al. Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension. N Engl J Med 2023;389:228-38.
8. Addison ML, Ranasinghe P, Webb DJ. Emerging insights and prospects for therapeutic application of siRNA targeting angiotensinogen in hypertension. Exp Rev Clin Pharmacol 2023;16:1025–33.
9. Ranasinghe P, Addison ML, Webb DJ. Small Interfering RNA Therapeutics in Hypertension: A Viewpoint on Vasopressor and Vasopressor-Sparing Strategies for Counteracting Blood Pressure Lowering by Angiotensinogen-Targeting Small Interfering RNA. J Am Heart Assoc 2022;11: e027694.
10. Addison ML, Ranasinghe P, Webb DJ. Novel Pharmacological Approaches in the Treatment of Hypertension: A Focus on RNA-Based Therapeutics. Hypertension 2023; 80:2243-54.
11. Kahlon T, Carlisle S, Otero Mostacero D, Williams N, Trainor P, DeFilippis AP. Angiotensinogen: more than its downstream products: evidence from population studies and novel therapeutics. JACC Heart Fail 2022;10:699-713.
12. Taubel J, Desai AS, Lasko M, Zee T, Stiglitz D, Rhyee S, et al. Safety and Tolerability of Zilebesiran, An RNA Interference Therapeutic Targeting Hepatic Angiotensinogen Synthesis, In Obese Patients with Hypertension. Hypertension 2023;80:A116.
13. Bakris GL, Saxena M, Gupta A, Chalhoub F, Lee J, Stiglitz D, et al. KARDIA-1 Study Group. RNA Interference with Zilebesiran for Mild to Moderate Hypertension: The KARDIA-1 Randomized Clinical Trial. JAMA 2024;331: 740-9.
14. Saxena M, Aswad A, Badariene J, Kazi F, Karns AD, Neutel JM, et al. Zilebesiran as add-on therapy in patients with hypertension inadequately controlled with a standard antihypertensive medication: efficacy and safety results from the kardia-2 study. J Hypertens 2024;42:e115.
15. Cruz-López EO, Ye D, Wu C, Lu HS, Uijl E, Mirabito Colafella KM, et al. Angiotensinogen Suppression: A New Tool to Treat Cardiovascular and Renal Disease. Hypertension 2022;79:2115-126.
16. Singhania N, Bansal S, Mohandas S, Nimmatoori DP, Ejaz AA, Singhania G. Role of renin–angiotensin–aldosterone system inhibitors in heart failure and chronic kidney disease. Drug Context 2020;9:1-9.
17. Mullick AE, Yeh ST, Graham MJ, Engelhardt JA, Prakash TP, Crooke RM. Blood Pressure Lowering and Safety Improvements with Liver Angiotensinogen Inhibition in Models of Hypertension and Kidney Injury. Hypertension 2017;70:566-76.
18. Ksiazek SH, Hu L, Andò S, Pirklbauer M, Säemann MD, Ruotolo C, et al. Renin–Angiotensin–Aldosterone System: From History to Practice of a Secular Topic. Int J Mol Sci 2024;25:4035-9.
19. Morgan ES, Tami Y, Hu K, Brambatti M, Mullick AE, Geary RS, et al. Antisense Inhibition of Angiotensinogen With IONIS-AGT-L_{Rx}: Results of Phase 1 and Phase 2 Studies. JACC Basic Transl Sci 2021;6:485-96.
20. Bovée DM, Cuevas CA, Zietse R, Danser AHJ, Mirabito Colafella KM, Hoorn EJ. Salt-sensitive hypertension in

chronic kidney disease: distal tubular mechanisms. Am J Physiol Renal Physiol 2020;319:729–45.
21. Bovée DM, Ren L, Uijl E, Clahsen-Van Groningen MC, Van Veghel R, Garrelds IM, et al. Renoprotective Effects of Small Interfering RNA Targeting Liver Angiotensinogen in Experimental Chronic Kidney Disease. Hypertension 2021;77:1600–12.
22. St. Paul A, Corbett CB, Okune R, Autieri MV. Angiotensin II, Hypercholesterolemia, and Vascular Smooth Muscle Cells: A Perfect Trio for Vascular Pathology. Int J Mol Sci 2020;21:4525-9.
23. Wu CH, Mohammadmoradi S, Chen JZ, Sawada H, Daugherty A, Lu HS. Renin-angiotensin system and cardiovascular functions. Arterioscler Thromb Vasc Biol 2018;38:108–16.
24. Lu H, Wu C, Howatt DA, Balakrishnan A, Moorleghen JJ, Chen X, et al. Angiotensinogen exerts effects independent of angiotensin II. Arter Thromb Vasc Biol 2016;36:256-65.