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Zilebesiran: An Sirna-Based Therapeutic Approach For Hypertension Management. Review

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Abstract: High blood pressure is a global crisis. More than 1.28 billion adults have it, but 46 percent do not know. Most people with hypertension do not have their blood pressure under control. This increases the risk of heart disease. This review looks at zilebesiran, a small interfering RNA (siRNA) drug. siRNA drugs change how proteins are made to treat the root cause of the disease. Zilebesiran binds to the asialoglycoprotein receptor in the liver. This stops the body from making angiotensinogen, which lowers angiotensin II and brings down blood pressure. One dose lasts a long time. Clinical trials show blood pressure stays low for up to 24 weeks after one shot. Using it with angiotensin receptor blockers works even better. The drug is safe. Most side effects are just reactions at the injection site. Zilebesiran provides a strong way to lower blood pressure with fewer doses. It shows how new drugs can help the millions of people with hypertension. More research will help put this drug into standard care to improve heart health. This review examines siRNA drugs and how they work to get the best patient results.

Highlights

- **Zilebesiran uses siRNA to stop liver angiotensinogen and lower blood pressure.**
- **One dose can work for 24 weeks.**
- **Side effects are mostly just skin redness at the injection site.**
- **Dosing twice a year may help patients stick to their treatment.**

Keywords: Zilebesiran, small interfering RNA (siRNA), hypertension, high blood pressure, angiotensinogen, angiotensin II, asialoglycoprotein receptor, liver-targeted therapy, angiotensin receptor blockers, RNA interference, gene silencing, blood pressure control, cardiovascular disease, injection site reactions, long-acting therapy, biannual dosing, treatment adherence, clinical trials.

I. Introduction

High blood pressure is often called the silent killer. It has no clear signs but causes huge damage. About 1.28 billion adults have hypertension, mostly in poor or middle-income countries. Nearly half of them do not know they are sick. It kills over 10 million people every year. This makes it the top risk for heart disease. In the US, 36 million adults cannot control their blood pressure. This leads to coronary artery disease and sudden cardiac death. Even though it is preventable, fewer than 25 percent of people worldwide have it under control. The WHO defines hypertension as a reading of 140/90 mmHg or higher. We need new tools to stop this global health threat.

Managing high blood pressure often starts with lifestyle changes. Doctors suggest losing weight, eating less salt and more potassium, and staying active. Cutting back on alcohol also helps. These habits lower blood pressure and make medicines work better [1,2]. Common drugs include diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, and angiotensin II antagonists [3]. Each has side effects. Calcium channel blockers can cause headaches or frequent micturition. Diuretics often cause dizziness. ACE

inhibitors may lead to a dry cough [4]. Many patients stop their treatment because of these issues.Some people still have high blood pressure due to poor adherence or the RAS escape phenomenon [5]. This happens when the body fights long-term drug use by raising renin levels [6,7]. This causes Angiotensin II to rise and blood pressure to climb again [8]. Understanding this helps doctors improve patient care.

New drugs now help with hypertension and rare metabolic issues. FDA-approved siRNA agents like patisiran, givosiran, lumasiran, inclisiran, nedosiran, and vutrisiran treat rare conditions [9]. These include hATTR, AHP, and PH1. They also lower LDL cholesterol in people with HeFH or ASCVD.Poor blood pressure control leads to stroke, heart failure, and kidney disease. Many patients do not take their pills as told. Rates of non-adherence range from 47% to 56% [10]. Side effects and the burden of daily pills are the main reasons. Breaking this cycle is key. Electronic tools can help [11], but long-acting drugs are a better fix. Normally, blood pressure drops 10 to 20% at night [12]. If it does not drop, the risk of heart problems goes up [12].siRNA drugs may provide this long-term effect. Six are already FDA-approved [13,14,15,16,17,18]. They started as treatments for rare diseases but now treat common ones, such as hypercholesterolemia [19]. Zilebesiran is an siRNA drug for hypertension that targets hepatic angiotensinogen. Phase II trials show it is well tolerated and lowers blood pressure [20]. One injection lasts six months. This review looks at how it works, the clinical data, and the risks.

Table 1: Current small interfering RNA therapies

Drug	Condition	Administration
patisiran	polyneuropathy of hereditary transthyretin-mediated amyloidosis	intravenous infusion
givosiran	acute hepatic porphyria	subcutaneous
lumasiran	primary hyperoxaluria type 1	subcutaneous
inclisiran	primary hyperlipidemia, including heterozygous familial hypercholesterolemia	subcutaneous
vutrisiran	polyneuropathy of hereditary transthyretin-mediated amyloidosis	subcutaneous
nedosiran	primary hyperoxaluria type 1	subcutaneous

1. Why Target Angiotensinogen?

The renin-angiotensin system (RAS) controls blood pressure, fluid balance, and heart shape. Many drugs target this system. These include beta blockers, direct renin inhibitors, ACE inhibitors, and AT1 receptor blockers.(21,22) Angiotensinogen is the only starting material for Ang II. Renin cleaves it into Ang I, which ACE then turns into Ang II. Ang II binds to AT1 receptors to trigger effects like releasing aldosterone.The RAS has a negative feedback loop. When AT1 receptors are active, they stop renin release. Blocking the system at the renin, ACE, or AT1 level triggers more renin release. The body does this to keep RAS activity steady. Renin levels can rise over 100-fold because the body adds more renin-producing cells over time. This is called RAS escape. If a drug blocks 99% of ACE or renin, a 100-fold renin increase cancels out the effect.(23) This happens because angiotensinogen levels are over a million times higher than Ang II levels. Any rise in renin quickly makes more Ang II. Targeting angiotensinogen may stop this escape. These levels stay mostly flat, though they rise during pregnancy due to estradiol. They drop in heart failure patients using diuretics and RAS blockers.

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Table 2: The RAS, tools to block it, and side effects.

Component / Tool	Mechanism	Clinical Use	Major Side Effects
Renin	Converts angiotensinogen → Ang I; rate-limiting step of RAS activation	Hypertension,HF, CKD (as a target)	When blocked: hyperkalemia, hypotension
Angiotensinogen	Liver-derived precursor for Ang I/II	TargetedbysiRNA for long-actingBP control	siRNA: renin surge, hypotension risk, need for reversal
ACE	Converts Ang I → Ang II; degrades bradykinin	Major target in HTN, HF, CKD	ACE inhibitors: cough, angioedema, hyperkalemia, hypotension
Angiotensin II	Vasoconstriction, aldosterone release, sodium retention	Blocked by ARBs	ARBs: hyperkalemia, renal function changes, hypotension
Tool / Drug Class	Mechanism	Examples	Key Side Effects
ACE inhibitors	Block ACE → ↓ Ang II, ↑ bradykinin	Enalapril, Lisinopril, Ramipril	Cough, angioedema, hyperkalemia, renal dysfunction, hypotension
ARBs	Block AT1 receptor → prevent Ang II action	Losartan, Valsartan, Telmisartan	Hyperkalemia, renal dysfunction, hypotension (no cough)
Renin inhibitors	Block renin activity → ↓ Ang I formation	Aliskiren	Hyperkalemia, diarrhea, hypotension; avoid with ACEi/ARB in diabetics
MRAs	Block aldosterone receptor	Spironolactone, Eplerenone	Hyperkalemia, gynecomastia (spironolactone), renal dysfunction

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Angiotensinogen siRNA	Silences AGT → profound Ang II suppression	Zilebesiran (investigational)	Massive renin rise, hypotension risk, long duration, reversible with antidote
Combination therapy	Dual blockade at multiple points	ACEi + MRA, ARB + MRA	Higher hyperkalemia risk, renaldysfunction, hypotension

Most angiotensinogen is made in the liver. For a long time, people thought it was also made in the heart, brain, kidney, and fat. Local Ang II production in tissues is likely more important than what happens in the blood.(24,25.26.27) Recent tests show this is wrong. Removing hepatic angiotensinogen also removed the protein from the kidney, heart, and fat. Only the brain might make its own, but Ang II still vanished there after liver deletion. Brain Ang II might come from the blood instead.(27,28,29) It seems the whole body relies on the liver for angiotensinogen. Blocking it in the liver should work like standard RAS blockers but without the RAS escape problem.

2. Small Interfering RNA as a New Treatment Tool

DNA and RNA are key to how proteins are made [30]. Stopping RNA stops proteins from forming. This lets doctors block proteins that normal drugs, like enzyme inhibitors or receptor antagonists, cannot reach. Two main ways to target RNA are antisense oligonucleotides (ASO) and siRNA [31]. ASOs use single-strand DNA with 15 to 30 nucleotides [32]. These strands bind to target pre-mRNA. Then, RNase H1 cuts the RNA in the nucleus and cytoplasm [33]. This destroys the mRNA and stops the protein. siRNA is different because it uses double-strand RNA, known as the passenger and guide strands [34]. These strands enter a group of proteins called the RNA-Induced Silencing Complex, or RISC. The complex drops the passenger strand. The guide strand stays and binds to the target mRNA [35]. A protein called Argonaute then cuts the mRNA precisely [36]. This breaks down the target mRNA . Scientists use chemical changes and new delivery tools to fix clinic problems. These include fast kidney clearance, RNA decay, and cell membrane barriers. They also work to stop off-target effects and immune toxicity [37, 38].

GalNAc-conjugated siRNA silences genes in liver cells. REVERSIR can stop this effect to prevent mRNA cleavage. ASGPR is the asialoglycoprotein receptor, and GalNAc is trivalent N-acetylgalactosamine.All six approved siRNA drugs target the liver. They stop proteins that mostly come from the liver. Patisiran, the first drug for amyloidosis, uses lipid nanoparticles. The other five use GalNAc for liver-only delivery. GalNAc is a ligand that binds to the asialoglycoprotein receptor [39, 40]. Liver cells have over a million of these receptors each. This lets 100,000 siRNAs enter the cell every 10 to 15 minutes. GalNAc makes liver delivery 10 times better [41]. Four weeks after a subcutaneous shot, liver levels are 50 times higher than kidney levels [42]. GalNAc-siRNA stays active for over six months in humans. It hides in acidic cell parts where it stays stable [20, 43]. These acidic spots act as a depot. This keeps RISC loaded and keeps genes silent for a long time [39].siRNAs last longer than ASOs, making them better for patient adherence [44]. Clinical trials used GalNAc conjugation for both to target hepatic angiotensinogen mRNA. A single GalNAc-siRNA dose cut plasma angiotensinogen by over 90 percent for six months. GalNAc-ASO only reduced it by 60 percent for one week [20,45]. Because of this, ASOs are no longer used to treat hypertension.

3. Angiotensinogen siRNA Effects in Animals and Humans

Animal studies show how GalNAc-siRNA works [27, 42,46,47,48] . A 10 mg/kg dose in hypertensive rats (SHR) removed 98 percent of circulating angiotensinogen. Blood Ang II levels stayed the same, but Ang II in tissues dropped. This lowered blood pressure as well as drugs like valsartan. Rats and humans have similar circulating angiotensinogen levels around 1 micromol/L.

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Mice have only 1 percent of that amount [20]. Yet, mice maintain the same angiotensin levels. Their very high renin levels cause this. In mice, small changes in angiotensinogen matter a lot. In humans and rats, renin does most of the work.

When rat angiotensinogen drops by 98 percent, their system acts like a mouse. Renin levels rise. This keeps blood Ang II normal even with only 2 percent of angiotensinogen left. However, tissues do not get enough angiotensinogen, so tissue Ang II falls. The RAS escape happens in the blood but not in tissues. Using siRNA with valsartan cut angiotensinogen to 0.2 percent [42]. Both blood and tissue Ang II vanished. High renin levels likely cleared the remaining angiotensinogen quickly. Blood pressure dropped by about 70 mm Hg. This was much more than the 20 to 25 mm Hg drop seen with each drug alone. This synergy happens when angiotensinogen is almost gone. It does not happen with low doses because high renin can still make enough Ang II.

Table 3 Potential consequences of angiotensinogen small interfering RNA

Consequence	Description
Blood pressure reduction	AGT siRNA lowers mean arterial pressure by preventing angiotensin II formation. Effects can last weeks to months.
Suppression of circulating angiotensin II	>95–99% reduction in plasma AGT leads to near-elimination of Ang II in kidney, heart, and circulation.
Massive renin elevation	Renin rises dramatically (up to 25-fold) due to feedback activation when AGT is depleted.
Improved renal outcome	Reduced proteinuria and glomerulosclerosis in chronic kidney disease models; renoprotection appears partly independent of blood pressure.
Cardiac hypertrophy reduction	siRNA monotherapy reduces cardiac hypertrophy; combination therapy (e.g., valsartan+siRNA) produces even greater improvement.
Electrolyte and transporter changes	Reduced renal sodium transporters (NHE3, NCC phosphorylation) due to Ang II depletion; renin increases but aldosterone does not.
Potential need for rapid reversal	In emergencies (shock, surgery, pregnancy), RAS activation may be needed; REVERSIR technology can reverse AGT siRNA effects within days.
Long duration of action	Single doses can last up to 6 months in preclinical models and ≥24 weeks in early human trials.

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Potential hypotension risk	Although early human trials showed no severe hypotension, profound RAS suppression may pose risk in volume depletion or acute illness.
No major renal function decline observed	GFR generally unchanged in animal studies despite BP lowering and renoprotection.

Angiotensinogen siRNA did not lower blood pressure in models where the RAS was already low. However, it protected the heart and kidneys in rats with chronic kidney disease, diabetic kidney disease, or cardiac hypertrophy.(27,46,47) These benefits happened even without changes in blood pressure. This means the drug affects Ang II at the tissue level. In every model, the siRNA lowered Ang II in the heart and kidneys. This proves these organs rely on hepatic angiotensinogen. Glomerular filtration stayed the same. The drug worked as well as ACE inhibitors like captopril or AT1 blockers like valsartan and losartan. Using it with another blocker made the effect stronger. The siRNA is as effective as standard RAS blockers but does not need daily doses.

In a phase I human trial, zilebesiran lowered plasma angiotensinogen in patients with high blood pressure. One shot lasted up to six months. Blood pressure fell as the dose increased, with 800 mg showing the best results. A low salt diet made the drug work better since high salt lowers the RAS. Adding irbesartan lowered blood pressure further. Three phase II trials are now underway. KARDIA-1 tested doses from 150 to 600 mg in patients not taking other meds.(49) KARDIA-2 tests 600 mg combined with a diuretic, calcium antagonist, or AT1 blocker(50). KARDIA-3 looks at patients with heart disease or high risk, including those with kidney disease who fail on 2 to 4 drugs. KARDIA-1 data shows 150, 300, and 600 mg doses had similar effects after three months. By six months, the 150 mg dose was less effective than the higher doses. KARDIA-2 results show zilebesiran works best with indapamide and least with olmesartan. This matches clinical experience where diuretics increase renin and boost RAS blocker effects. This is different from the strong synergy seen with valsartan in rats. The difference may be because human angiotensinogen was not fully suppressed, unlike in the rat models.(51)

4. Safety of Angiotensinogen siRNA

Zilebesiran is a new type of RAS blocker. We must track its side effects closely before it hits the market. Inclisiran is a good point of comparison. It uses the same GalNAc method to reach the liver but targets PCSK9 instead of angiotensinogen. One shot of inclisiran lasts six months and cuts LDL by about 50%. The only side effect seen was pain at the injection site in 3 to 5 percent of people.(18.20,52,53) No liver damage or immune issues occurred. This proves that siRNA in the liver is not always toxic. KARDIA-1 showed no major liver problems. Some patients had mild low blood pressure (4 percent) or high potassium (6 percent). Injection site reactions hit 6 percent of the group. Too much RAS blockade can cause low blood pressure, kidney failure, and high potassium. This risk grows if a patient uses more than one RAS blocker.(54) The kidneys need some RAS activity to filter blood properly. More KARDIA studies will clarify this. It is clear that we should not remove all angiotensinogen. High RAS inhibition can also thicken renal arteries. This happens because renin cells expand and smooth muscle cells build up. Animal tests show this happens with angiotensinogen siRNA. However, it is similar to what happens with ACE inhibitors or AT1 receptor blockers.(55)

The long effect of these drugs is a concern. Long action helps patients stay on track. But it is risky if the body needs the RAS to stop a crash in blood pressure. This happens during sepsis or heavy bleeding.(56) Pregnancy also requires a working RAS to manage blood flow. In rats on a low salt diet, blood pressure rose after shots of Ang II or norepinephrine. A high salt diet or fludrocortisone also restored blood pressure, though it took several days.(25)REVERSIR is a way to stop siRNA gene silencing.(57) It uses single strands of oligonucleotides to block the guide strand in the RISC. These also use GalNAc to find liver cells. REVERSIR stops the silencing of mRNA and lets the body make proteins again. In rats, this brought back angiotensinogen in a few days based on the dose.(48) Blood pressure returned to normal. This happened even when angiotensinogen only rose by 50 percent. High renin levels still allowed enough Ang II to be made. This shows that even a partial fix can quickly raise blood pressure in patients.

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5. Novel siRNA drugs for hypertension: focusing on zilebesiran

siRNA is a new way to make drugs. It lets doctors change how proteins are made by using RNA interference (RNAi) to silence genes[58,59,60]. Zilebesiran is a first-of-its-kind siRNA for high blood pressure. It binds to the asialoglycoprotein receptor in the liver[61]. This stops the liver from making angiotensinogen (AGT). Less AGT means less angiotensin I and II, which lowers blood pressure. The FDA has already approved other siRNA drugs like patisiran, givosiran, lumasiran, and inclisiran for different health issues[62]. Zilebesiran is given as a shot under the skin to stop AGT production[59]. It targets the cause of the disease with high precision.

5.1 Mechanism of action

siRNA works by stopping genes after they are transcribed[63]. Zilebesiran uses a GalNAc ligand to target liver cells. This ligand binds to the asialoglycoprotein receptor (ASGR) on hepatocytes[64]. This triggers the cell to pull the siRNA inside[65]. AGT is the start of the renin-angiotensin-aldosterone system (RAAS) that controls blood pressure[66]. Zilebesiran blocks this system by stopping AGT production. Once inside the cell, the siRNA joins the RNA-induced silencing complex (RISC). The guide strand then finds and binds to the AGT messenger RNA. Enzymes cut the mRNA, which stops the protein from being made. This drops the levels of AGT and angiotensin II, lowering blood pressure[67]. Because the drug is stable, it lasts a long time. Patients might only need a shot twice a year or once a year, which helps them stay on their treatment[68].

Table 4: How zilebesiran works. (1) Zilebesiran binds to ASGPR on liver cells. (2) It enters an endosome. (3) The siRNA escapes the endo. some. (4) It binds to RISC. (5) The strands separate. (6) The guide strand binds to AGT-mRNA. (7) RISC recycles. (8) The mRNA is cut. (9) The mRNA is destroyed. (10) AGT levels drop (11) Angiotensin II levels drop. (12) Blood pressure goes down.

Step	Mechanistic Event	Scientific Detail (Publication-Grade)
1.ASGPR binding	GalNAc ligand binds **ASGPR** on hepatocytes	Ensures liver-specific uptake; high-affinity receptor-mediated endocytosis.
2.Endosomal internalization	Complex enters clathrin-dependent endosomes	Standard GalN Ac-siRNA trafficking pathway.
3.Endosomal escape	siRNA released into cytosol	Critical for RNAi activity; engineered chemical modifications enhance escape.
4. RISC loading	siRNA duplex binds **AGO2-RISC**	RISC is the catalytic core of RNA interference.
5.Strand selection	Passenger strand discarded;	Thermodynamic asymmetry drives strand choice.

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	guide strand retained	
6.Target recognition	Guide strand binds **AGT-mRNA**	Sequence-specific Watson–Crick base pairing.
7.Catalytic recycling	RISC repeatedly cleaves multipleAGT transcripts	One guide strand → many catalytic events.
8.Endonucleolytic cleavage	AGO2 cuts AGT-Mrna at the seed-defined site	Produces unstable mRNA fragments.
9.mRNA degradation	Fragments degraded by exonucleases	Eliminates AGT protein synthesis.
10. AGT depletion	Plasma AGT reduced >90%	Sustained suppression for months after a single dose.
11.AngII suppression	Reduced Ang I → reduced Ang II	Deep RAAS inhibition without daily dosing.
12.Bloodpressure reduction	Sustained lowering of systolic BP	Clinical trials show durable 24-week BP reduction.

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6. Comparing zilebesiran to other hypertension treatments

Using GalNAc-siRNA to deliver drugs to the liver is a top method for new medicines[69]. These drugs last a long time. One dose can keep a gene silent for months in humans and animals[70]. This happens because the modified siRNA stays stable in the acidic parts of the liver cell[71].Many old drugs fail if a dose is missed or if they wear off in 24 hours[72]. Zilebesiran is different. A phase 1 study is done, and phase 2 results are expected in 2024. It is the first siRNA drug for essential hypertension. Like inclisiran, it only needs two shots a year[73].

The KARDIA-1 study showed the drug is safe. Fewer serious side effects happened in the zilebesiran group than in the placebo group. Most issues, like redness at the injection site or high potassium, were easy to handle[74].Doctors also found a way to stop the drug if needed. A special single-strand oligonucleotide can block zilebesiran in the liver. This protects patients from blood pressure that is too low[75]. Animal tests show that blood pressure can also be raised again using angiotensin II, norepinephrine, or more salt[75]. This makes zilebesiran a strong new option for treating high blood pressure.

7. Safety and Future Outlook

To understand how zilebesiran works in clinics, we must look at its side effects. Other siRNA drugs show different patterns. Lumasiran often causes reactions where it is injected.(76) Givosiran can cause fatigue, nausea, and kidney disease.(77) Patisiran usually leads to mild infusion reactions. Zilebesiran mostly causes mild injection site reactions.(78) Bakris et al. found low rates of side effects. There were no major changes to liver or kidney function. Single doses lowered AGT levels and blood pressure for up to 24 weeks.(79)RAS blockers like ACE inhibitors and ARBs also lower blood pressure. (80-83)These are proven in large trials. But they can cause dry coughs or angioedema, which makes some people stop treatment. They also increase risks of high potassium and poor renal function. Zilebesiran trials must watch for these same issues. In a trial by Desai and colleagues, some patients had prostate cancer, anemia, or optic nerve issues. No one died or needed an unplanned hospital stay. There were no fixes needed for low blood pressure or kidney failure. Sodium, potassium, and creatinine levels stayed stable.

The study was small and short. Rare serious events might have been missed. We need more data on patients with diabetes and chronic kidney disease. siRNA drugs target specific genes. There is a risk they might hit the wrong gene by mistake. We must check for allergies and liver inflammation. Inclisiran, another liver-targeted siRNA, did not show these problems over six months.RAS blockers are not used in pregnancy because they can harm the fetus and kidneys. Zilebesiran blocks the same pathway. This creates similar risks for pregnancy. Rat studies on preeclampsia showed no harm to offspring, but off-target effects are still a worry. More trials are needed to see if the drug crosses the placenta. Zilebesiran targets the liver, so it leaves AGT alone in the kidneys and fat. This is helpful since obese patients have AGT in their fat tissues. Because the AGT gene varies by person and location, close monitoring is vital.(84)

II. Conclusion

Zilebesiran is a new siRNA drug that helps manage high blood pressure. It works by stopping the liver from making AGT, which lowers blood pressure for a long time. Trials show it is safe and needs few doses. This could change how doctors treat heart health. Still, we must watch for side effects and off-target hits. We need to know if it is safe for pregnant women. More research will help doctors use it safely to keep patients healthy.

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Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors have equally participated and shared every item of the work.

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