Review

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Advancing hypertension management: the role of zilebesiran as an siRNA therapeutic agent

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Abstract

Elevated blood pressure poses a significant global health challenge, affecting over 1.28 billion adults worldwide, with a staggering 46% unaware of their condition. Despite its pervasive impact and association with cardiovascular disease, hypertension remains inadequately controlled, highlighting the urgent need for innovative treatment approaches. This review explores the potential of small interfering RNA (siRNA) therapeutics, focusing on zilebesiran, as a promising strategy for hypertension management. SiRNA therapy represents a groundbreaking approach to selectively modulate protein production, offering targeted intervention in the pathophysiological mechanisms underlying hypertension. Zilebesiran, a siRNA, targets hepatic angiotensinogen (AGT) synthesis through interaction with the asialoglycoprotein receptor, ultimately reducing angiotensin II levels and reducing blood pressure. Zilebesiran demonstrates remarkable pharmacokinetic properties, with sustained efficacy observed after single-dose administration. Clinical trials evaluating zilebesiran have shown significant reductions in blood pressure, with effects lasting up to 24 weeks post-administration. Moreover, combination therapy with angiotensin receptor blockers has demonstrated enhanced efficacy, highlighting the potential for synergistic effects in hypertension management. Importantly, zilebesiran exhibits a favorable safety profile, with manageable adverse events, primarily injection site reactions. Zilebesiran represents a transformative therapy in hypertension management, offering targeted and potent blood pressure reduction with favorable safety and dosing characteristics. Its emergence highlights the ongoing evolution of cardiovascular pharmacology and underscores the importance of innovative approaches to address the global burden of hypertension. Moving forward, concerted efforts in research and clinical practice are necessary to realize the benefits of zilebesiran into hypertension management protocols, ultimately advancing cardiovascular health worldwide.

Keywords: zilebesiran, hypertension, angiotensinogen, small interfering RNA

Introduction

In the intricate network of the cardiovascular system, high blood pressure silently causes chaos, earning hypertension the nickname "silent killer"[1]. This condition often remains undetected, without overt symptoms, yet its impact is profound and pervasive. An estimated 1.28 billion adults worldwide, primarily in low- and middle-income countries, suffer from hypertension, with a staggering 46% unaware of their condition. Each year, hypertension claims over 10 million lives globally[2], cementing its status as the foremost risk factor for cardiovascular disease (CVD)[3]. In the United States alone, nearly 36 million adults battle uncontrolled hypertension[4], amplifying the urgency of effective management strategies. Hypertension stands as a primary risk factor for numerous cardiovascular ailments acquired throughout life[5], including coronary artery disease (CAD) and sudden cardiac death[6]. Despite its prevalence and profound impact, hypertension remains both common and preventable, with less than a quarter of affected individuals achieving adequate blood pressure control worldwide[7]. According to WHO, hypertension is defined as a blood pressure reading of 140/90 mmHg or higher[2], and hypertension poses a formidable challenge to global health, demanding innovative solutions to mitigate its silent yet devastating consequences.

HIGHLIGHTS

- Zilebesiran uses siRNA to specifically inhibit hepatic angiotensinogen, effectively lowering blood pressure.
- A single dose can sustain significant blood pressure reductions for up to 24 weeks.
- Adverse events are mostly limited to injection site reactions, making it safer than many traditional antihypertensives.
- Infrequent dosing (potentially twice a year) may enhance patient compliance with hypertension treatment.

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Effective management of hypertension often begins with lifestyle modifications, emphasizing weight loss, a balanced diet low in sodium and high in potassium, regular physical activity, and moderation or cessation of alcohol consumption. These lifestyle changes offer initial blood pressure reduction and synergize with pharmacological interventions to enhance their efficacy[8,9]. While various classes of antihypertensive drugs[10], including diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, and calcium channel blockers (CCBs) are available, each comes with its own set of potential side effects. Common complaints include frequent micturition and headaches associated with CCBs, excessive micturition and dizziness with diuretics, and dry, irritating cough with ACE inhibitors[11]. Adverse reactions often lead to therapy discontinuation and substitution in a significant percentage of patients. Furthermore, inadequate blood pressure control may stem from factors such as poor patient adherence and the "renin-angiotensin system (RAS) escape phenomenon,"[12] wherein prolonged use of RAS-blocking antihypertensive therapies triggers compensatory renin elevation[13,14], resulting in a rebound increase in Angiotensin II levels and a subsequent rise in blood pressure-[15], despite initial suppression. Understanding these complexities is crucial for optimizing hypertension management and improving patient outcomes.

Within this landscape of cardiovascular health challenges, recent advancements in pharmacotherapy have introduced a new dimension in managing not only hypertension but also a range of rare metabolic disorders. FDA-approved small interfering RNA (siRNA) agents[16], including patisiran, givosiran, lumasiran, inclisiran, nedosiran, and vutrisiran, have emerged as central players in addressing various rare conditions such as hereditary transthyretin amyloidosis (hATTR), acute hepatic porphyria (AHP), and primary hyperoxaluria type 1 (PH1). Furthermore, they contribute significantly to reducing low-density lipoprotein cholesterol (LDL-C) levels in individuals with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD).

This review explores the potential of innovative approaches in treating hypertension, explicitly focusing on the emerging class of siRNA drugs. As we navigate the complexities of hypertension management, we delve into the prospects of siRNA therapy. We shed light on its mechanisms, efficacy, and its potential to achieve the best possible outcome.

NOVEL siRNA therapeutics for hypertension: a focus on zilebesiran

SiRNA, an innovative therapeutic strategy, represents a significant advancement in drug development.[17], It offers a targeted approach to selectively modulate protein production and stands at the forefront of the groundbreaking field of RNA interference (RNAi). This cellular mechanism for gene silencing holds immense promise in medicine[18,19]. Among the emerging siRNA therapeutics, zilebesiran stands out as a pioneering agent, representing a paradigm shift in the treatment of hypertension. Zilebesiran, a first-in-class siRNA, operates by binding to the hepatic asialoglycoprotein receptor, thereby initiating a cascade of molecular events that culminate in the suppression of angiotensinogen messenger RNA[20]. Consequently, hepatic production of angiotensinogen (AGT) is diminished, leading to a reduction in the synthesis of both angiotensin I and II, ultimately resulting in blood pressure reduction. The advent of siRNA therapeutics has witnessed significant milestones, with several medications gaining FDA approval in recent years[21]. Noteworthy among these are patisiran, givosiran, lumasiran, and inclisiran, each addressing distinct medical conditions ranging from acute hepatic porphyria to hypercholesterolemia. Positioned within this landscape of innovation, zilebesiran emerges as a promising therapy, administered subcutaneously to modulate hepatic AGT synthesis for the treatment of hypertension[18]. Zilebesiran epitomizes the potential of siRNA technology to revolutionize therapeutic paradigms, offering a targeted and precise approach to address underlying pathophysiological mechanisms.

Mechanism of action

The mechanism of action of siRNA hinges on post-transcriptional gene silencing[22]. Trivalent N-acetylgalactosamine (GalNAc) ligand–conjugated siRNA emerges as a cutting-edge therapeutic approach, specifically targeting the degradation of hepatocyte-produced mRNAs with remarkable potency and specificity. This targeted approach exploits the asialoglycoprotein receptor (ASGR), the Ashwell-Morell receptor, predominantly expressed on hepatocytes[23]. The trivalent GalNAc ligand, when coupled with chemically modified siRNA, facilitates highly efficient hepatocyte uptake through interaction with the ASGR. This interaction initiates clathrin-mediated endocytosis, leading to the internalization of both the receptor and ligand, along with the siRNA cargo[24]. At the heart of this mechanism lies AGT, the most upstream precursor in the renin-angiotensin-aldosterone system (RAAS)[25], which plays a pivotal role in blood pressure regulation. Zilebesiran, a GalNAc-conjugated siRNA targeting liver-derived AGT, disrupts this cascade by inhibiting AGT production. The siRNA, delivered as duplexes, binds to hepatocyte ASGRs, facilitating its uptake into the liver. Once inside hepatocytes, the siRNA is released into the cytoplasm and engages with the RNA-induced silencing complex (RISC). This interaction triggers unraveling and strand separation, with the guide strand binding to complementary mRNA targets. Endoribonucleases then cleave the mRNA, preventing protein translation and ultimately leading to decreased AGT and angiotensin II production, resulting in reduced blood pressure[26]. The remarkable pharmacokinetic and pharmacodynamic properties of chemically modified, enhanced stabilization chemistry GalNAc-siRNAs contribute to their extended duration of activity. These properties offer the potential for infrequent dosing schedules like biannually or even annually in some cases, addressing issues of therapy non-adherence and potentially enhancing patient compliance[27]. As depicted in Figure 1, the mechanism of action of zilebesiran underscores its potential to revolutionize hypertension management through targeted gene silencing and potent blood pressure reduction.

Efficacy of zilebesiran in hypertensive patient

The efficacy of Zilebesiran in hypertensive patients has been significantly supported by several trials (Table 1).

In the first multi-part, phase 1 randomized controlled trial[28], patients diagnosed with hypertension were randomly assigned in a 2:1 ratio (Table 2). They received either a single subcutaneous

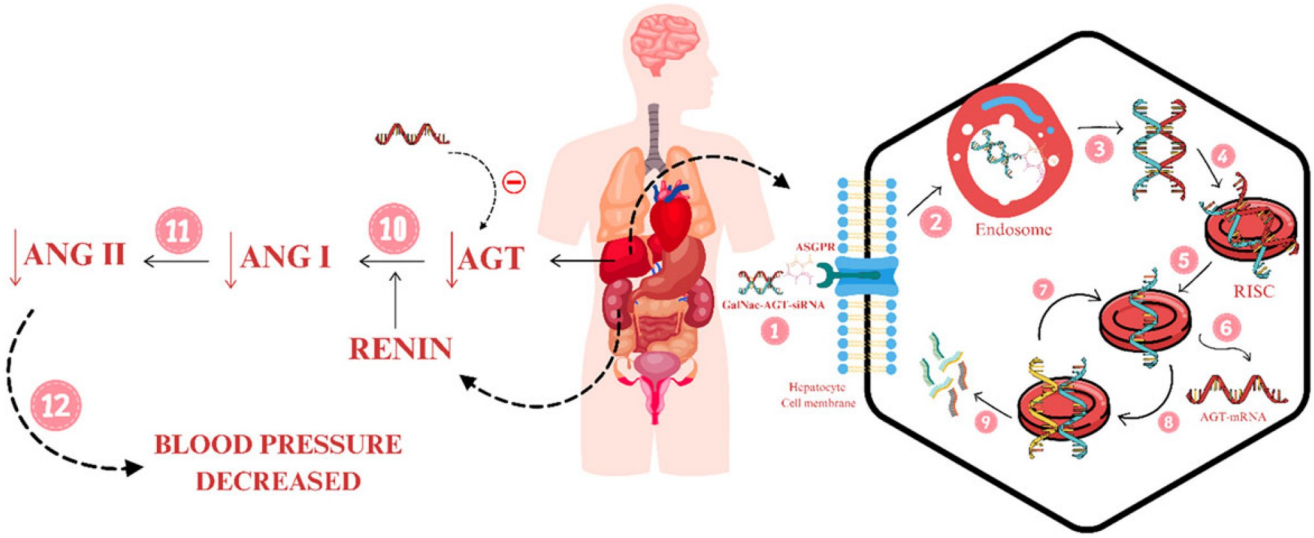

Figure 1 Mechanism of action of zilebesiran. (1) Zilebesiran (GalNac-AGT-siRNA) binds to ASGPR on hepatocytes. (2) It enters an endosome. (3) AGT-siRNA is released as endosomal escape. (4) AGT-siRNA Binds RISC. (5) siRNA unwinds and strands separate. (6) Guide strand forms and Hybridizes with AGT-mRNA. (7) RISC Recycling. (8) Cleavage of AGT-mRNA. (9) AGT-mRNA degraded. (10) Decreased angiotensinogen. (11) Decreased angiotensin II. (12) Blood pressure lowered. AGT, angiotensinogen; RISC, RNA-induced silencing complex.

dose of zilebesiran ranging from 10 to 800 mg or a placebo. The trial comprised of three parts:

Part A: Patients were monitored for 24 weeks after administering zilebesiran or placebo. Significant reductions in both systolic and diastolic blood pressure (>10 mmHg and >5 mmHg, respectively) were observed by week 8, as assessed by 24-hour ambulatory blood pressure monitoring (ABPM). These reductions were sustained throughout the 24-week period[28].

Part B: This phase investigated the impact of an 800 mg dose of zilebesiran on blood pressure under varying dietary salt conditions, namely low- or high-salt diets. The study revealed a diminished blood pressure-lowering effect with a high-salt diet compared to a low-salt diet[28].

Part E: Explored the effects of combining an 800 mg dose of zilebesiran with the angiotensin receptor blocker irbesartan. The combination therapy demonstrated an enhanced reduction in blood pressure compared to zilebesiran alone[28].

Overall, single doses of zilebesiran at or above 200 mg significantly reduced blood pressure levels, with reductions maintained throughout the day and sustained over the 24-week monitoring period. Additionally, serum AGT levels were markedly reduced by over 90% with 200 mg or higher doses, persisting from week 3 to 12 of the trial.

The potential of zilebesiran as an antihypertensive therapy is also being investigated through the phase 2 KARDIA-1 (NCT04936035)[30] and KARDIA-2 (NCT05103332)[29] trials.

In KARDIA-1, the efficacy and safety of zilebesiran monotherapy was evaluated in 378 adults with mild-to-moderate arterial hypertension, irrespective of whether they were untreated or receiving stable treatment with one or more antihypertensive drugs. Over a 12-month double-blind period and subsequent extension phase, participants were randomized into one of five treatment arms: subcutaneous administration of 150 mg or 300 mg every 6 months, 300 mg or 600 mg every 3 months, or placebo. Notably, the trial successfully achieved its primary endpoint on 7 September 2023, demonstrating a clinically significant reduction in mean 24-h systolic blood pressure (SBP) after 3 months ($P < 0.0001$) with both doses of zilebesiran compared to placebo. Additionally, KARDIA-1 revealed significant reductions in mean 24-h SBP after 6 months and in office SBP after 3 and

Table 1

Clinical trials evaluating the safety and efficacy of zilebesiran.

Study name.	Outcomes	Results
Desai A. S[28]. (phase I)	Pharmacokinetics and pharmacodynamics of single doses of zilebesiran (10–800 mg), and changes in baseline systolic and diastolic BP.	Single doses of zilebesiran (≥200 mg) lowered SBP by >10 mmHg and diastolic BP by >5 mmHg by week 8, with effects lasting to week 24. Mild ISRs reported
KARDIA I[2] (phase II)	Evaluated the efficacy of various doses of zilebesiran in patients with hypertension	Change in ambulatory SBP: –11.1 mmHg for zilebesiran 150 mg every 6 months, –14.5 mmHg for 300 mg every 6 months, –4.1 mmHg for 300 mg every 3 months, and –14.2 mmHg for 600 mg every 6 months ($P < 0.05$ for each group).
KARDIA II[29] (phase II)	Evaluated the efficacy of various doses of zilebesiran in patients with hypertension	Expected in 2024

ISR, in-stent restenosis.

Table 2

Basic demographic details of patients.

	Part A		Part B		Part E	
Characteristic	**Zilebesiran**	**Placebo**	**Zilebesiran**	**Placebo**	**Zilebesiran + Irbesaratan**	**Placebo zilebesiran**
Total No. patients	56	28	8	4	3	5
Mean age (years)	53	52.9	59	50	55.2	54
Blood pressure						
Systolic	139.2	140.6	139	148.5	147	133
Diastolic	85.8	87.9	86.4	99	89	85.8
BMI	28.6	29.3	29	29.3	28.3	29.7

6 months compared to placebo, underscoring the potent and lasting inhibition of AGT by zilebesiran[30].

Meanwhile, the ongoing KARDIA-2 trial seeks to assess the role of zilebesiran in combination with another antihypertensive drug in mild-to-moderate hypertension, with results anticipated in early 2024[29]. The clinically significant reduction in SBP, coupled with the potential for achieving consistent blood pressure control with only two injections per year, offers promise for addressing issues of therapeutic adherence and resolving many cases of uncontrolled hypertension arising from blood pressure variability or nocturnal blood pressure dysregulation.

Zilebesiran's superiority: a comparative analysis in hypertension therapy

The ASGR-mediated delivery system for GalNAc-siRNA conjugates stands out as a state-of-the-art modalities in the therapeutic development of investigational oligonucleotides, offering promising clinical candidates[31]. A hallmark of GalNAc-siRNA conjugates is their remarkable durability of silencing, persisting for several months after a single-dose administration in both preclinical species and humans[32]. This prolonged duration of activity is mechanistically attributed to the enhanced metabolic stability of chemically modified siRNA molecules within hepatocyte acidic intracellular compartments, such as the endolysosomal system[33].

Unlike some conventional drugs that may not maintain efficacy for 24 h due to pharmacokinetic and pharmacodynamic characteristics or suboptimal dosing[34], zilebesiran shows potential as a breakthrough therapy. With a published phase 1 study and anticipated phase 2 results in 2024, zilebesiran emerges as the first siRNA therapy for essential hypertension. Promisingly, it offers the convenience of just two injections per year, akin to inclisiran for anti-PCSK9 therapy[35].

Safety and tolerability are paramount considerations, and KARDIA-1 demonstrated favorable outcomes. Notably, serious adverse events were less frequent in zilebesiran-treated patients than those receiving placebo. Reported adverse events, including injection site reactions, hyperkalemia, and hypertension, were generally manageable[30].

Moreover, in anticipation of the potential need for a reversal of zilebesiran's effects, a rapid and potent reversal mechanism has been developed using GalNAc-conjugated single-stranded oligonucleotides; this oligonucleotide is rapidly taken up by the liver and blocks the siRNA activity of zilebesiran. This innovation represents unprecedented progress in clinical cardiovascular pharmacology, safeguarding against adverse events such as severe hypotension or hypovolemia[36]. Furthermore, preclinical studies have elucidated reversible mechanisms of zilebesiran-induced blood pressure reduction in rodent models, offering insights into potential management strategies in clinical settings. AGT siRNA-mediated blood pressure lowering can be rapidly reversed by administration of angiotensin II or norepinephrine, or gradually reversed by interventions like fludrocortisone or high-salt intake. This comprehensive understanding of zilebesiran's mechanism of action and reversible effects further underscores its potential as a transformative therapy in hypertension management[36].

Safety profile and future considerations

An in-depth analysis of the clinical landscape of zilebesiran necessitates a comprehensive review of the spectrum of adverse events and considerations associated with its therapeutic application. Comparative analyses against other siRNA therapeutics such as lumasiran and givosiran unveil distinct patterns of adverse reactions. Notably, injection site reactions are prevalent with lumasiran administration[37], whereas givosiran is associated with adverse events like fatigue, nausea, and chronic kidney disease[38]. Patisiran, another siRNA therapeutic, commonly elicits mild-to-moderate infusion-related reactions[39]. However, amidst these comparisons lies the unique profile of zilebesiran, where injection site reactions stand out as the primary adverse event. It is essential to note that zilebesiran has shown low rates of related adverse events. Mild reactions at the injection site were the most common, with no clinically relevant changes observed in kidney or liver function, as highlighted by Bakris *et al.*[30] Furthermore, observations from the trial revealed sustained reductions in serum AGT levels and blood pressure following single subcutaneous doses of zilebesiran, extending up to 24 weeks[28]. Comparatively, numerous large-scale clinical trials and meta-analyses have underscored the efficacy of RAS blockers[40–43], such as ACE inhibitors and ARBs, in reducing blood pressure and improving cardiovascular outcomes. However, adverse events associated with RAS blockers, such as angioedema and dry cough[44,45], have led to treatment discontinuation in some cases. Moreover, RAS blockers pose an increased risk for adverse events, particularly hyperkalemia and worsening renal function[46], necessitating careful monitoring of these effects with Zilebesiran in the latest trials. In the Desai and colleagues clinical trial, while notable adverse events were documented, including ischemic optic neuropathy, prostate cancer requiring surgery, and acute anemia, there were no instances of death or unplanned hospitalizations. Furthermore, no interventions were necessary for hypotension,

hyperkalemia, or worsening of renal function, and there were no clinically significant changes in serum levels of potassium, sodium, or creatinine, nor the estimated glomerular filtration rate[28]. However, it is important to recognize that due to the study's size and duration, uncommon serious adverse events may not have been fully assessed. In the context of comorbidities such as type 2 diabetes and chronic kidney disease, the safety profile of zilebesiran warrants further exploration. The potential for off-target effects remains a consideration with siRNA therapeutics, as they selectively target specific genetic sequences. While there is a theoretical risk of unintended effects on other genes, leading to unforeseen side effects. The need for assessment of allergic symptoms and potential inflammatory side effects stemming from the liver accumulation of siRNA is crucial. Although, observations regarding liver-targeted PCSK9 siRNA (inclisiran) over a 6-month period did not reveal such concerns[47]. Furthermore, given the known risks associated with RAS inhibition during pregnancy, including renal hypoperfusion and fetal ischemia, RAS blockers are typically contraindicated in pregnant individuals[48]. Zilebesiran's action of blocking RAAS pathway raises concerns surrounding renal hypoperfusion and ischemia in fetus in pregnant individuals. Although the preclinical studies in rat models of preeclampsia have not detected deleterious effects on offspring[49], but the concerns regarding potential off-target effects remain. Therefore, further trials are essential to assess whether zilebesiran has the potential to cross the placenta and exert any such effects on fetal development. Furthermore, zilebesiran's hepatocyte-targeted delivery system preserves extrahepatic AGT expression, limiting potential effects on kidney and adipose tissues that are believed to be a relevant source of AGT, especially in the obese[50]. The AGT gene is indeed expressed in the human kidney cortex, medulla and visceral adipose tissue in a differential manner, influenced by genetic variants[51]. So the theoretical risk of unintended consequences stemming from the specificity of siRNA therapeutics underscores the need for meticulous monitoring.

Conclusion

In conclusion, the emergence of zilebesiran as an innovative siRNA therapy represents a significant advancement in hypertension management. Zilebesiran offers a promising approach for achieving substantial and enduring blood pressure reduction by targeting hepatic AGT synthesis. The favorable safety profile observed in clinical trials and the potential for infrequent dosing schedules underscores its potential as a transformative therapy in cardiovascular pharmacology. However, as with any emerging therapeutic approach, careful consideration of potential adverse events and implications, including off-target effects and considerations for special populations such as pregnant individuals, is essential. Furthermore, ongoing research and vigilance are necessary to unlock the full potential of zilebesiran and ensure its safe and effective integration into hypertension management protocols, ultimately advancing the goal of optimal cardiovascular health for all.

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Ethical approval not require for this article type.

Consent

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Data availability statement

Data analyzed in the study is original data from institution and cannot be shared openly to protect study participant privacy.

Provenance and peer review

Not applicable.

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References

[1] Murillo-Godínez G. A silent killer: the primary hypertension non complicated. RevistaMedica Del InstitutoMexicano Del Seguro Social 2011;49:233–5.
[2] World Health Organization. Hypertension 2023 https://www.who.int/news-room/fact-sheets/detail/hypertension
[3] Oparil S, Acelajado MC, Bakris GL, *et al*. Hypertension. Nat Rev Dis Primers 2019;4:1–48.
[4] Centers for Disease Control and Prevention (CDC) Vital signs: Awareness and Treatment of Uncontrolled Hypertension Among Adults—United States, 2003-2010. MMWR Morb Mortal Wkly Rep 2012;61:703–9.
[5] Kjeldsen SE. Hypertension and cardiovascular risk: General aspects. Pharmacol Res 2018;129:95–9.
[6] Von Brandis P, Kjeldsen SE, Gjesdal K. Sudden cardiac death in hypertension. Tidsskrift for Den Norske Laegeforening: Tidsskrift for PraktiskMedicin, NyRaekke 1997;117:2337–40.
[7] Zhou B, Carrillo-Larco RM, Danaei G, *et al*. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 2021;398:957–80.

[8] Carey RM, Moran AE, Whelton PK. Treatment of hypertension: a review. JAMA 2022;328:1849–61.
[9] Strilchuk L, Cincione RI, Fogacci F, *et al*. Dietary interventions in blood pressure lowering: current evidence in 2020. KardiologiaPolska 2020;78:659–66.
[10] Taddei S, Ghiadoni L, Salvetti A. Current treatment of patients with hypertension: therapeutic implications of INSIGHT. Drugs 2003;63:1435–44.
[11] Olowofela AO, Isah AO. A profile of adverse effects of antihypertensive medicines in a tertiary care clinic in Nigeria. Ann Afr Med 2017;16:114–9.
[12] Dézsi CA. Differences in the clinical effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a critical review of the evidence. Am J Cardiovasc Drugs 2014;14:167–73.
[13] Mooser V, Nussberger J, Juillerat L, *et al*. Reactive hyperreninemia is a major determinant of plasma angiotensin II during ACE inhibition. J Cardiovasc Pharmacol 1990;15:276–82.
[14] Cruz-López EO, Ye D, Wu C, *et al*. Angiotensinogen suppression: a new tool to treat cardiovascular and renal disease. Hypertension 2022;79: 2115–26.
[15] Ren L, Colafella KMM, Bovée DM, *et al*. Targeting angiotensinogen with RNA-based therapeutics. Curr Opin Nephrol Hypertens 2020; 29:180–9.
[16] Padda IS, Mahtani AU, Parmar M. Small Interfering RNA (siRNA) Based Therapy [Internet]. PubMed. StatPearls Publishing; 2022.
[17] Pushparaj Peter Natesan, Melendez AJ. Short intefering RNA (siRNA) as a novel therapeutic. Clin Exp Pharmacol Physiol 2006;33:504–10.
[18] Alnylam Pharmaceuticals. A Randomized, Double-blind, Placebo-Controlled, Dose-Ranging Multicenter Study to Evaluate the Efficacy and Safety of ALN-AGT01 in Patients With Mild-to-Moderate Hypertension. clinicaltrials.gov. 2024. [cited 2024 May 27]. https://classic.clinicaltrials.gov/ct2/show/NCT04936035
[19] Levin AA. Targeting therapeutic oligonucleotides. Phimister EG. N Engl J Med 2017;376:86–8.
[20] Uijl E, MirabitoColafella KM, Sun Y, *et al*. Strong and sustained antihypertensive effect of small interfering RNA targeting liver angiotensinogen. Hypertension 2019;73:1249–57.
[21] Traber GM, Yu AM. RNAi-based therapeutics and novel RNA bioengineering technologies. J Pharmacol Exp Ther 2022;384:133–54.
[22] Alshaer W, Zureigat H, Al Karaki A, *et al*. siRNA: Mechanism of action, challenges, and therapeutic approaches. Eur J Pharmacol 2021;905: 174178.
[23] Nair JK, Willoughby JLS, Chan A, *et al*. Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing. J Am Chem Soc 2014;136:16958–61.
[24] Foster DJ, Brown CR, Shaikh S, *et al*. Advanced siRNA designs further improve in vivo performance of GalNAc-siRNA conjugates. Mol Ther 2018;26:708–17.
[25] Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med 2010;2:247–257.
[26] Touyz RM. Silencing angiotensinogen in hypertension. N Eng J Med 2023;389:278–81.
[27] Ye D, Cruz-López EO, Tu HC, *et al*. Targeting angiotensinogen with *N*-acetylgalactosamine–conjugated small interfering RNA to reduce blood pressure. Arterioscler Thromb Vasc Biol 2023;43:2256–64.
[28] Desai AS, Webb DJ, Taubel J, *et al*. Zilebesiran, an RNA interference therapeutic agent for hypertension. N Eng J Med 2023;389:228–238.
[29] National Institutes of Health. Study NCT05103332. ClinicalTrials.gov. 2024. https://clinicaltrials.gov/study/NCT05103332
[30] Bakris GL, Saxena M, Gupta A, *et al*. RNA interference with zilebesiran for mild to moderate hypertension. JAMA 2024;50.
[31] Springer AD, Dowdy SF. GalNAc-siRNA conjugates: leading the way for delivery of RNAi therapeutics. Nucleic Acid Ther 2018;28:109–118.
[32] Zimmermann TS, Karsten V, Chan A, *et al*. Clinical proof of concept for a novel hepatocyte-targeting GalNAc-siRNA conjugate. Mol Ther 2017;25:71–8.
[33] Brown CR, Gupta S, Qin J, *et al*. Investigating the pharmacodynamic durability of GalNAc–siRNA conjugates. Nucleic Acids Res 2020;48:11827–44.
[34] Radauceanu A, Boivin JM, Bernaud C, *et al*. Differential time effect profiles of amlodipine, as compared to valsartan, revealed by ambulatory blood pressure monitoring, self blood pressure measurements and dose omission protocol. Fundam Clin Pharmacol 2004;18:483–491.
[35] Scheen AJ, Wallemacq C, Lancellotti P. Inclisiran (Leqvio®), a potent cholesterol-lowering agent by inhibiting PCSK9 using small interfering RNA-based innovative therapy. Rev Med Liege 2022;77:745–51.
[36] Uijl E, Ye D, Ren L, *et al* . Conventional vasopressor and vasopressor-sparing strategies to counteract the blood pressure–lowering effect of small interfering RNA targeting angiotensinogen. J Am Heart Assoc 202211: e026697.
[37] National Institute of Diabetes and Digestive and Kidney Diseases. Lumasiran. 2012. [cited May 27, 2024]. https://www.ncbi.nlm.nih.gov/books/NBK588653/
[38] Poli A, Schmitt C, Moulouel B, *et al*. Givosiran in acute intermittent porphyria: a personalized medicine approach. Mol Genet Metab 2022;135:206–14.
[39] Adams D, Polydefkis M, González-Duarte A, *et al*. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. Lancet Neurol 2021;20:49–59.
[40] Lin YC, Lin JW, Wu MS, *et al*. Effects of calcium channel blockers comparing to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with hypertension and chronic kidney disease stage 3 to 5 and dialysis: a systematic review and meta-analysis. *Shimosawa T*, *editor Plos One* 2017;12:e0188975.
[41] Ssentongo AE, Ssentongo P, Heilbrunn ES, *et al*. Renin–angiotensin–aldosterone system inhibitors and the risk of mortality in patients with hypertension hospitalised for COVID-19: systematic review and meta-analysis. Open Heart 2020;7:e001353.
[42] Kurdi A, Mueller T, & Weir N. (2022). An umbrella review and meta-analysis of renin–angiotensin system drugs use and COVID-19 outcomes. European Journal of Clinical Investigation, 53(1), e13862.
[43] García-Prieto AM, Verdalles Ú, de José AP, *et al*. Renin–angiotensin–aldosterone system blockers effect in chronic kidney disease progression in hypertensive elderly patients without proteinuria: PROERCAN trial. Hipertensión y Riesgo Vascular 2024;41:95–103.
[44] AMBOSS. (n.d.). Renin-angiotensin-aldosterone system inhibitors. Knowledge @ AMBOSS. https://www.amboss.com/us/knowledge/renin-angiotensin-aldosterone-system-inhibitors/
[45] Orphanet. (n.d.). Renin-angiotensin-aldosterone system-blocker-induced angioedema. [cited May 27, 2024]. https://www.orpha.net/en/disease/detail/100057
[46] Epstein BJ, Smith SM, Choksi R. Recent changes in the landscape of combination RAS blockade.2009;7:1373–84.
[47] Landmesser U, Haghikia A, Leiter LA, *et al*. Effect of inclisiran, the small-interfering RNA against proprotein convertase subtilisin/kexin type 9, on platelets, immune cells, and immunological biomarkers: a pre-specified analysis from ORION-1. Cardiovasc Res 2020;117:284–91.
[48] Ahmed B, Zoega H, Havard A. Renin-angiotensin system blockers in early pregnancy among women with chronic hypertension: getting to the heart of the risk-benefit equation. Int J Epidemiol 2018;47:683–6.
[49] Haase N, Foster D. J, Cunningham M. W, *et al* . RNA interference therapeutics targeting angiotensinogen ameliorate preeclamptic phenotype in rodent models. J Clin Invest 2020;130:2928-42.
[50] Van Harmelen V, Elizalde M, Ariapart P, *et al*. The association of human adipose angiotensinogen gene expression with abdominal fat distribution in obesity. Int J Obes 2000;24:673–8.
[51] Riccardo Sarzani, Bordicchia M, Marcucci P, *et al*. Angiotensinogen promoter variants influence gene expression in human kidney and visceral adipose tissue. J Hum Hypertens 2009;24:213–9.