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Zilebesiran — the first siRNA-based drug in hypertensiology: why is it needed, and will it change the treatment approach of hypertension?

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Abstract

Arterial hypertension is the most common cardiovascular risk factor in the world. The prevalence of hypertension has doubled over the last 30 years. Despite the availability of many antihypertensive drugs, including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs), the level of uncontrolled blood pressure (BP) in hypertensive patients remains very high, which contributes to the lack of optimization of cardiovascular risk. Antihypertensive treatment had cardioprotective effects [each reduction in systolic BP by 5 mm Hg reduced the risk of cardiovascular events in both primary and secondary cardiovascular disease (CVD) prevention by 9% and 11%, respectively]. The reasons for the lack of BP control are lack of adherence and persistence in treatment, as well as therapeutic inertia. Therefore, new therapeutic options are being sought to improve BP control. Zilebesiran, the first drug based on small interference RNA (siRNA) technology for the treatment of hypertension, is currently being tested in phase II clinical trials (KARDIA-1 and KARDIA-2). The results of the phase 1 study showed that zilebesiran in a single dose allowed for a sustained reduction in systolic BP by 22 mm Hg and diastolic BP by 10 mm Hg for as long as 6 months. This effect is related to this drug's unique mechanism of action — silencing of the angiotensinogen (AGT) gene in the liver. Zilebesiran reduces serum AGT

levels by > 90%. In clinical trials, this drug had a satisfactory safety profile and was well tolerated by patients. The use of drugs that need to be taken less frequently contributed to a significant improvement in compliance with medical recommendations in patients with lipid disorders. Therefore, it is expected that using zilebesiran only twice a year would improve compliance with medical recommendations (adherence and persistence) and contribute to improved BP control in patients with hypertension.

This article summarizes information on the mechanism of action, effectiveness, and safety of zilebesiran and presents the most important arguments indicating the need to introduce this drug into clinical practice.

Key words: renin–angiotensin–aldosteron system; angiotensinogen; AGT; zilebesiran; ALN-AGT01; siRNA

Epidemiology of hypertension — current data

Arterial hypertension has for years been the most common risk factor for cardiovascular disease (CVD), which in turn is the main cause of premature death in the world [1, 2]. An analysis of 104 million people showed that the number of people aged 30–79 years with hypertension doubled from 1990 to 2019, from 331 [95% credible interval (CI): 306–359) million women and 317 (95% CI: 292–344) million men in 1990 to 626 (95% CI: 584–668) million women and 652 (95% CI: 604–698) million men in 2019 [3]. This brings the number of patients with hypertension to 1.3 billion worldwide. In 2019, 10.8 million deaths were related to high systolic blood pressure (BP), accounting for over 19% of all deaths [4]. The prevalence of hypertension is high in Poland. A study by Małyszko et al., including 5834 participants examined during May Measurement Month 2017 (MMM2017), showed that 35.3% suffered from hypertension [5]. Such a high prevalence of hypertension results from its virtually asymptomatic onset, very low awareness of its risk factors, and progressive civilization changes (among others, increasing exposure to air pollution, environmental noise, poor quality food, and excessive body weight) [6, 7].

Antihypertensive treatment and cardiovascular risk

Antihypertensive treatment significantly contributes to improving CVD prognosis. A meta-analysis of 48 randomized clinical trials, including 344716 participants, showed that each 5 mmHg reduction in systolic BP was associated with a reduction in the risk of cardiovascular events, both in primary and secondary CVD prevention, by 9% and 11%, respectively [hazard ratio (HR) = 0.91; 95% CI: 0.89–0.94 and HR = 0.89; 0.86–0.92] [8]. Moreover, a meta-

analysis of 51 randomized clinical trials, including 358707 participants, showed that lowering systolic BP by 5 mm Hg improved cardiovascular outcomes in virtually every age group (up to 85 years of age). Each 5 mm Hg reduction in systolic BP was associated with a reduction in the risk of major cardiovascular events in people aged < 55, 55–64, 65–74, and 75–84 by 18%, 9%, 9%, and 9%, respectively [9]. A meta-analysis of 51 randomized clinical trials, including 358636 participants (42% women), showed that reducing systolic BP by 5 mmHg reduced the risk of major cardiovascular events to a similar extent in both women and men (HR = 0.92; 95% CI: 0.89–0.95 for women and HR = 0.90; 95% CI: 0.88–0.93 for the men) [10]. Furthermore, good BP control in younger people significantly translates into better prognosis in the future. A meta-analysis of 17 studies involving 4.5 million young adults showed that compared to optimal BP (systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg), those who had normal BP (120–129 and 80–84 mm Hg), high normal BP (130–139 and 85–89 mm Hg), grade 1 hypertension (140–159 and 90–99 mm Hg), and grade 2 hypertension (≥ 160 and ≥ 100 mm Hg) had a higher risk of cardiovascular events (by 19%, 35%, 92% and 215%, respectively) [11]. The results of this meta-analysis indicate that good BP control is carried out at the earliest possible stage, i.e. in accordance with the principle “the earlier the better”. Another issue is the intensity of antihypertensive treatment. An analysis of 60,870 patients from randomized clinical trials showed that more intensive (*versus* less intensive; systolic BP higher by approximately 8 mm Hg) antihypertensive treatment was associated with a greater reduction in the risk of: stroke [odds ratio (OR) = 0.79; 95% CI: 0.67–0.93], heart failure (OR = 0.73; 95% CI: 0.55–0.96), acute coronary syndrome (OR = 0.81; 95% CI: 0.73–0.91) and cardiovascular death (OR = 0.81; 95% CI: 0.68–0.98) [12]. A meta-analysis of 19 studies, including 44989 participants, showed that more intensive antihypertensive treatment (133/76 mm Hg *vs*. 140/81 mm Hg) was associated with a more significant reduction in the risk of major cardiovascular events by 14%, acute coronary syndrome by 13%, stroke by 22%, albuminuria by 10% and retinopathy progression by 19%. More intensive antihypertensive treatment was relatively safe and did not differ in less intensively treated subjects [relative risk (RR) = 1.35; 95% CI: 0.93–1.97].

Hypotension occurred more often in those treated with more intensive antihypertensive treatment (0.3% *vs.* 0.1% per person-year) [13]. The beneficial effect of more intensive antihypertensive treatment was confirmed in other meta-analyses, including patients with and without diabetes [composite cardiovascular events or major adverse cardiovascular events (RR = 0.71; 95% CI: 0.62–0.82), CVD mortality (RR = 0.65; 95% CI : 0.49–0.86), coronary heart disease (RR = 0.75; 95% CI: 0.60–0.95), stroke (RR = 0.75; 95% CI: 0.61–0.92) and

heart failure (RR = 0.58; 95% CI: 0.41–0.82) [14] and patients with chronic kidney disease (lower risk of all-cause mortality; OR = 0.86; 95% CI: 0.76-0.97) [15] and older patients (major cardiovascular events; HR = 0.83; 95% CI: 0.74– 0.94 and stroke; HR: 0.70; 95 % CI: 0.56–0.88) [16]. More intensive antihypertensive treatment also contributes to a more significant reduction in the risk of left ventricular hypertrophy in patients with hypertension (RR = 0.66; 95% CI: 0.56-0.77) [17]. Therefore, the 2023 guidelines of the European Society of Hypertension (ESH) indicate that the target BP in most patients should be < 130/80 mm Hg. BP should not be reduced to < 120/70 mm Hg [18]. Thus, another rule of antihypertensive treatment is "the lower the better, but not lower than 120/70 mm Hg".

Antihypertensive treatment is only effective if it provides long-term BP control. Lack of adherence to antihypertensive treatment increases the risk of lack of BP control (OR = 2.15; 95% CI: 1.84–2.50), which in turn is associated with a higher risk of death from any cause and hospitalization due to CVD (various studies and meta-analysis: HR =1.57; CI: 1.40–1.76; OR = 1.38; 95% CI: 1.35–1.41; OR = 1.12; 95% CI: 1.07–1.18) [19, 20]. Therefore, antihypertensive treatment should be carried out according to the principle "the longer, the better".

To sum up, antihypertensive treatment carried out in accordance with the principle "the earlier, the better", "the lower, the better, but not lower than < 120/70 mm Hg" and "the longer, the better" reduces cardiovascular risk and prolongs life. It is worth noting that similar principles ["the earlier, the better", "the lower, the better", and "th*e* longer, the better"], if followed, significantly increase the effectiveness of lipid-lowering treatment [2, 21].

Adherence/persistence to antihypertensive treatment and BP control in hypertensive patients

Despite the clear evidence of the beneficial effects of antihypertensive treatment on reducing cardiovascular risk and prolonging life, the degree of BP control, persistence, and adherence to treatment are low. A meta-analysis of 27 million hypertensive patients showed that the rate of non-adherence to antihypertensive treatment was as high as 27–40% [20]. Another meta-analysis, including 13688 hypertensive patients, found that 45.2% of them and 31.2% of the hypertensive patients with comorbidities were non-adherent to medications [22]. A study of 23.8 million American adults with hypertension showed that 3-in-10 (31%) were non-adherent to antihypertensive treatment. This particularly concerned younger patients (as many as 58%) and those not using fixed-dose combination (FDC) medications (32%) [23]. One year after starting antihypertensive treatment, 23.3% and 42.3% of patients with hypertension were

non-persistent or non-adherent to treatment, respectively [24]. Lack of adherence affects women and men to a similar extent (OR = 1.04; 95% CI: 1.00–1.09) [25]. Non-adherence was suboptimal regardless of drug class [26]. All this translates into insufficient BP control in patients with hypertension. An analysis covering 104 million people from the general population showed that control rates among patients with hypertension in 2019 were 23% for women and 18% for men [3]. Uncontrolled BP in patients with hypertension increases the risk of all-cause (HR = 1.62; 95% CI: 1.35–1.95), CVD-specific (HR = 2.23; 95% CI = 1.66–2.99), heart disease-specific (HR = 2.19; 95% CI: 1.57–3.05) and cerebrovascular disease-specific (HR = 3.01; 95% CI: 1.91–4.73) mortality [27]. In younger patients with hypertension (who, as previously mentioned, are characterized by the highest percentage of lack of adherence to antihypertensive treatment), uncontrolled BP is associated with a higher risk of CVD events (HR = 1.57; 95% CI: 1.45–1.71) [28].

Another important factor that significantly influences the lack of BP control in patients with hypertension is therapeutic inertia. It is worth emphasizing that in accordance with the 2023 ESH guidelines, in most patients, it is recommended that antihypertensive treatment, from the very beginning, be based on two antihypertensive drugs, preferably in the form of a single-pill combination (SPC) [18]. The SIMPLIFY study, which included 1852 patients with hypertension and lack of BP control, showed that 44% of these patients were on monotherapy, 28% used combined treatment in the form of free-equivalent combination (FEC), and 28% used combined treatment in the form of SPC [29]. The problem of therapeutic inertia was also demonstrated in a study involving 251733 patients with hypertension. Among patients with low, moderate, and high cardiovascular risk, only 63%, 62%, and 57%, respectively, received antihypertensive treatment [30].

A number of factors influence the lack of adherence to antihypertensive treatment. The most important included lack of awareness, the greater number of antihypertensive drugs, the need to take medications daily, high treatment costs, lack of motivation, difficulties in access to health care, and fear of side effects [31, 32].

Currently, in both hypertensiology and lipidology, combined drugs in SPC form are preferred because a reduced number of pills translates into improved adherence to therapy [33, 34]. A meta-analysis of 44 studies showed that antihypertensive treatment with SPC *versus* FEC was associated with improved persistence, a lower risk of treatment discontinuation, and a greater antihypertensive effect [33]. Another meta-analysis also found that SPC improved medication adherence and clinical outcomes in patients with hypertension and/or dyslipidemia and led to a better clinical outcome than FEC under daily practice

conditions [35]. The use of antihypertensive therapy based on the SPC strategy significantly increases patient adherence and persistence to treatment [36].

The influence of the frequency of drug intake on adherence and therapy persistence has also been demonstrated in lipidology (the level of achieving therapeutic goals, as in hypertensionology, is low) [2, 21]. A study that included 86,5732 patients using statins, 34,490 patients using ezetimibe, and 1940 patients using proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9I) showed that after 36 months, compliance rates remained at 20.6% for statins and 22.3% for ezetimibe and 50.9% for PCSK9I [37]. Unlike statins and ezetimibe, which should be used daily, PCSK9I is taken twice a month. Modern drugs are now available in lipidology, which can take every six months (inclisiran, olpasiran). In the future, the anti-PCSK9 vaccine will likely require administration only once a year, and removal of the *PCSK9* gene using the CRISPR-Cas9 method will be a once-in-a-lifetime intervention [2, 38].

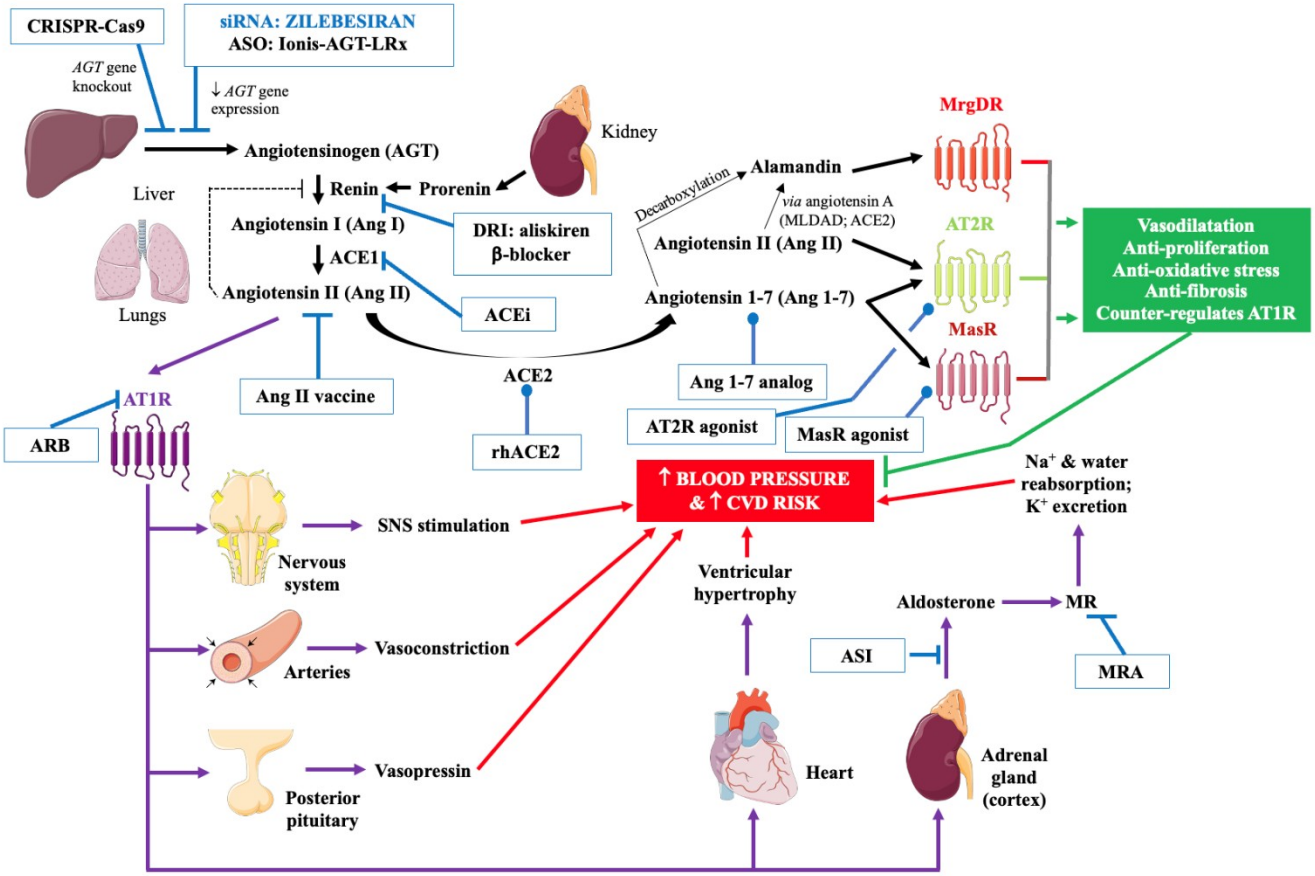
This trend in lipidology, with some delay, moved to hypertensiology in the form of zilebesiran (formerly ALN-AGT01), which interferes with the expression of the angiotensinogen gene in the liver.

The renin–angiotensin–aldosterone system (RAAS) — the main cause of hypertension and its complications

The renin–angiotensin–aldosterone system (RAAS) is a key regulator of BP. Its upregulation increases BP by altering vascular tone, blood volume, electrolyte balance, and aldosterone synthesis, leading to tissue remodeling and end-organ damage [39, 40]. During the Sars-CoV-2 pandemic, RAAS gained particular interest because angiotensin-converting enzyme type 2 (ACE2) turned out to be a receptor for SARS-CoV-2 [41–43]. The primary effector of RAAS is angiotensin II (Ang II), cleaved from angiotensin I (Ang I) by ACE, which in turn results from renin-mediated cleavage of angiotensinogen (AGT) produced in the liver. Drugs targeting RAAS are effective in lowering BP and reducing the risk of CVD, and prolonging life [44, 45]. A meta-analysis including 158998 patients from randomized clinical trials showed that the use of ACEI was associated with a 10% reduction in all-cause mortality (HR = 0.90; 95% CI: 0.84–0.97) [44]. Another meta-analysis, covering over 12000 patients, showed that ACEi reduced total deaths (OR = 0.85; 95% CI: 0.78-0.93) and cardiovascular deaths (OR = 0.77; 95% CI: 0.69-0.87) [45]. The RAAS inhibitors, mainly ACEI, are the gold standard in the treatment of hypertension [18]. Due to this, and the previously mentioned issue of improving adherence through less frequent drugs administration, an exciting novel

mechanism for targeting hypertension is the silencing of the *AGT* gene in the liver through an RNA technology-based drug (requiring administration less frequently than classic antihypertensive drugs) effectively reducing the production of Ang I and Ang II and reducing signaling, in mediated by Ang II type 1 (AT1R) and Ang II type 2 (AT2R) receptors. Figure 1 shows the regulation of BP by classical and novel pathways of the RAAS and pharmacological strategies (available and in the experimental/clinical research phase) aimed at beneficial modulation of the activity of this system.

Figure 1. Regulation of blood pressure by the renin-angiotensin-aldosteron system. Based on information from [39, 40, 46, 47]. CRISPR-Cas9 — clustered regularly interspaced short palindromic repeats; siRNA - small interfering RNA; ASO — antisense oligonucleotide; AGT — angiotensinogen; ACE1 — angiotensin-converting enzyme type 1; DRI — direct renin inhibitor; ACEI — angiotensin-converting enzyme inhibitor; AT1R — angiotensin II type 1 receptor; ARB — angiotensin receptor blocker; ACE2 — angiotensin-converting enzyme type 2; rhACE2 — recombinant human ACE2; SNS — sympathetic nervous system; MrgDR — Mas-related G-protein coupled receptor type D; AT2R — angiotensin II type 2 receptor; MasR — Mas receptor; MLDAD — mononuclear leukocyte-derived aspartate decarboxylase; CVD — cardiovascular disease; ASI — aldosterone synthase inhibitor; ACE — angiotensin-converting enzyme; Ang — angiotensin; ASI — aldosterone synthase inhibitor; ASO — antisense oligonucleotide; MR — mineralocorticoid receptor; MRA — mineralocorticoid receptor antagonist


CRISPR-Cas9
siRNA: ZILEBESIRAN
ASO: Ionis-AGT-LRx
AGT gene knockout
↓AGT gene expression
Liver
Angiotensinogen (AGT)
Kidney
Renin
Prorenin
Angiotensin I (Ang I)
DRI: aliskiren
β-blocker
ACE1
Angiotensin II (Ang II)
Lungs
ACEi
Ang II vaccine
ACE2
rhACE2
AT1R
ARB
Decarboxylation
Alamandin
via angiotensin A (MLDAD; ACE2)
Angiotensin II (Ang II)
Angiotensin 1-7 (Ang 1-7)
MrgDR
AT2R
MasR
Vasodilatation
Anti-proliferation
Anti-oxidative stress
Anti-fibrosis
Counter-regulates AT1R
Ang 1-7 analog
AT2R agonist
MasR agonist
↑ BLOOD PRESSURE & ↑ CVD RISK
Na+ & water reabsorption; K+ excretion
SNS stimulation
Nervous system
Ventricular hypertrophy
Aldosterone
MR
MRA
ASI
Vasoconstriction
Arteries
Heart
Adrenal gland (cortex)
Vasopressin
Posterior pituitary

Zilebesiran — mechanism of action

Zilebesiran is the first drug based on small interfering RNA (siRNA) technology for the treatment of hypertension [40, 48–51] (Fig. 2).

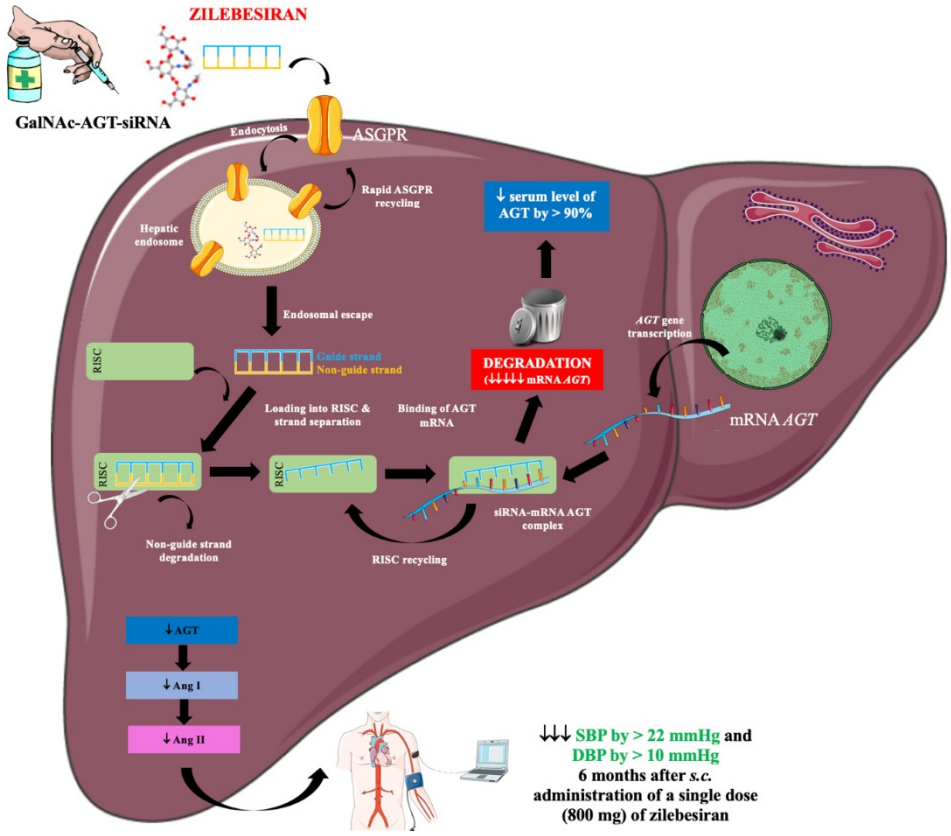


Figure 2. Zilebesiran — mechanism of action. Modification based on [51] — with permission. GalNAc — N-acetylgalactosamine; ASGPR — asialoglycoprotein receptor; AGT — angiotensinogen; RISC — RNA-induced silencing complex; Ang I — angiotensin I; Ang II — angiotensin II

Zilebesiran consists of double-stranded RNA (non-guide strand and guide strand) conjugated with N-acetylgalactosamine (GalNAc). Conjugation with GalNAc causes zilebesiran to be selectively taken up by hepatocytes because the asialoglycoprotein receptor (ASGPR) that interacts with GalNAc is located only on the surface of these cells. After zilebesiran enters the hepatocytes by endocytosis, ASGPR is recirculated to the cell membrane, while the drug escapes from the endosome and then binds to the RNA-induced silencing complex (RISC) in the cytoplasm, which contains a functional core of endonucleases. The anti-sense strand is

recognized as a “guide strand” and is retained, while the “nonguided” strand is released. The RISC-complex cleaves the guide strand’s complementary target mRNA (in this case, AGT mRNA), which silences its target gene (AGT) [40, 48–51]. The same mechanism of action is used by modern drugs used in lipidology, including olpasiran, zerlasiran, lepodisiran [silencing the apolipoprotein (a) — *LPA* gene], and inklisiran (silencing the *PCSK9* gene) [2].

Standard RAAS inhibitor (ACEi or ARB) medications cause a compensatory rise in renin (and Ang I in case of ACEi use) with long-term use because of loss of negative feedback mediated by Ang II (RAAS escape) (Fig. 1). Near complete depletion of AGT by zilebesiran therapy could potentially prevent RAAS escape [48].

Zilebesiran — safety and efficacy: results of clinical trials

In a randomized phase I clinical trial by Huang et al., the effectiveness and safety of various doses of zilebesiran *versus* placebo were assessed in a group of 60 mild to moderate hypertension patients. Patients were randomized to a single dose of zilebesiran (10 mg, 25 mg, 50 mg, 100 mg, or 200 mg) or placebo subcutaneously. After 8 weeks of observation, serum AGT levels decreased > 90% at the 100 and 200 mg doses of zilebesiran (Fig. 3). This effect lasted for 12 weeks. Single doses of 100 mg or 200 mg of zilebesiran reduced mean 24-hour systolic BP by 10 mm Hg at week 8 after administration. No symptomatic hypotension, treatment-related severe adverse events, or clinically significant elevations in blood creatinine or potassium were seen [52].

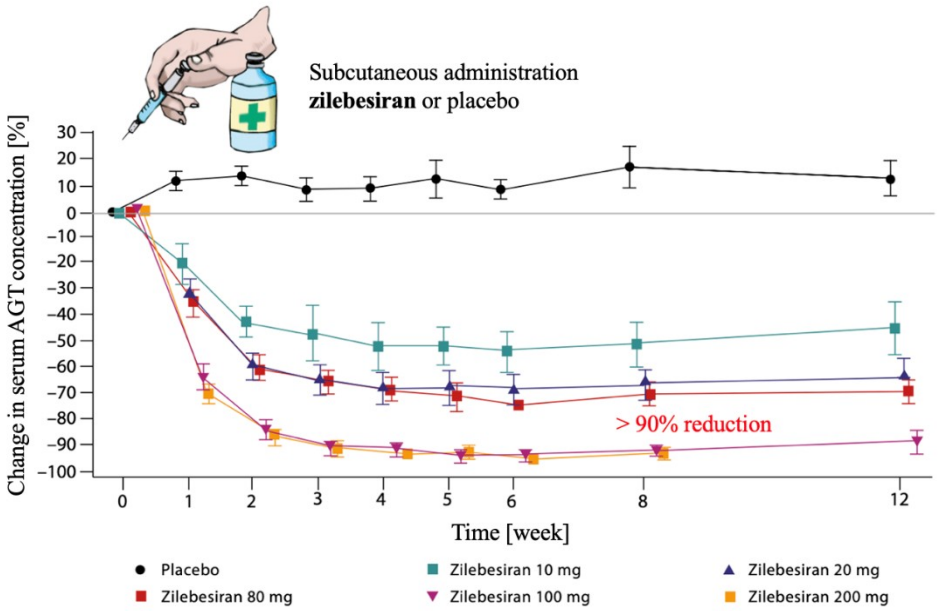


Figure 3. Effect of single ascending doses of zilebesiran on serum angiotensinogen (AGT) concentrations. Modification based on [52]

In the effect of zilebesiran *versus* ibersartan was assessed in a randomized phase I clinical trial by Taubel et al., including 20 patients with hypertension and obesity. Patients were randomized to zilebesiran 800 mg subcutaneously (day 1 and 85) and daily oral placebo or sequential subcutaneous doses of saline (day 1 and 85), and daily 150 mg oral irbesartan. After 24 weeks of observation, AGT serum levels did not change with irbesartan but were reduced by 99% with zilebesiran from week 4 to week 24. Change in systolic BP from baseline to week 24 was –27 ± 8 mm Hg with zilebesiran *versus* –19 ± 6 mm Hg with irbesartan. Zilebesiran was generally well tolerated [53].

In a randomized phase I clinical trial by Desai et al., including 107 patients with hypertension, the effectiveness and safety of zilebesiran (after washout of antihypertensive medications for at least 2 weeks) were assessed. The study was divided into several parts. In part A, patients were randomized to a single escalating dose of zilebesiran (10, 25, 50, 100, 200, 400, or 800 mg) or placebo and were followed for 24 weeks. Part B analyzed the 800-mg dose of zilebesiran on BP under low- or high-salt diet conditions, and Part E the effect of that dose when coadministered with irbesartan. Major results regarding the safety and efficacy of zilebesiran in the three therapeutic scenarios studied are presented in Table 1 [54].

Table 1. Summary of key safety outcomes and changes in angiotensinogen (AGT) and blood pressure (BP) in the phase 1 randomized controlled trial (RCT) with zilebesiran. Based on information from [54]

Part/key outcomes	**Part A**		**Part B**		**Part E**	
	Placebo (n = 28)	**Zilebesiran (n = 56)**	**Placebo (n = 4)**	**Zilebesiran (n = 8)**	**Zilebesiran (n = 6)**	**Zilebesiran + irbesartan (n = 10)**
AEs	24 (85.5)	42 (75)	4 (100)	3 (37.5)	6 (100)	7 (70)
SAEs	1 (3.6)	1 (1.8)	0	0	0	1 (10)
Hypotension	0	0	0	0	0	0
Hyperkalemi	0	0	0	0	0	0

a						
Renal AEs	0	0	0	0	0	0
Hepatic AEs	0	1 (1.8)	1 (25)	0	0	0
ISR	0	5 (8.9)	0	0	0	0
AGT reduction	> 90% with doses ≥ 100 mg (week 3–12) > 90% with 800 mg (week 3–24)		> 90% (week 3–12)		> 90% (week 3–12) No effect of irbesartan on AGT levels	
24 h SBP reduction	≥ –10 mm Hg with ≥200 mg (week 8–24) −22.5 mm Hg with 800 mg (week 24)		−9.1 after 1-week low Na diet (baseline) −18.8 after 1-week low Na diet at week 6 after 800 mg		−21.8 with 800mg at week 6 and 8 (n = 6) −7.7 with 800 mg at week 6 (*n* = 10) −14 with dual therapy at week 8	

AEs — adverse events; SAE — serious adverse events; ISR — injection site reaction; AGT — angiotensinogen; SBP — systolic blood pressure

Overall, 5 patients experienced mild adverse events administration of the drug. There was no hypotension, hyperkalemia or deterioration of kidney function. Zilebesiran reduced serum AGT concentrations by > 90%. A dose-dependent reduction in 24-hour BP was observed. A single dose of 800 mg of zilebesiran allowed for long-term BP control (in the 24th week of observation, the 24-hour systolic BP was reduced by 22.5 mm Hg and diastolic BP by 10,8 mm Hg) [54]. The results of this study indicate that zilebesiran had a good safety profile, and only one dose of this drug reduced systolic BP by more than 22 mm Hg and diastolic BP by more than 10 mmHg for 6 months. This indicates that using zilebesiran twice a year will allow BP control in some patients.

During the American Heart Association (AHA) congress in 2023, Bakris et al. published the preliminary results of the placebo-controlled, randomized, double-blind, dose-ranging phase 2 study KARDIA-1 (NCT04936035). The study included 377 patients with mild-to-moderate hypertension who were randomized to zilebesiran (n = 302) or placebo (n = 75). After antihypertensive washout, patients with a daytime mean SBP of 135–160 mm Hg, assessed by ambulatory BP monitoring, were randomized to a zilebesiran regimen [150, 300, or 600 mg subcutaneously once every 6 months (Q6M) or 300 mg subcutaneously once every 3 months (Q3M)] or to placebo subcutaneously Q3M. Reductions in 24-hour mean SBP were

shown to be significantly greater for all zilebesiran regimens than placebo at month 3 and month 6 (Fig. 4) with consistent reductions in daytime and nighttime SBP [55].

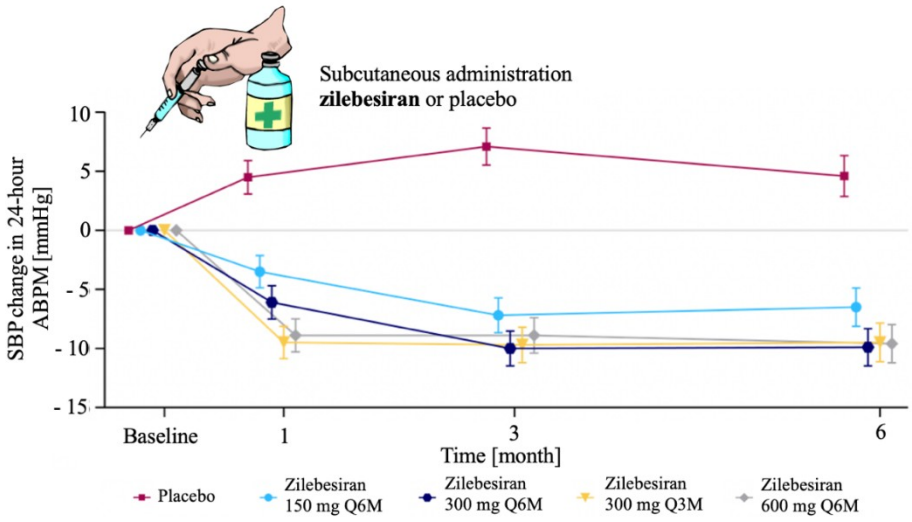


Figure 4. Antihypertensive effect of zilebesiran. Results of the KARDIA-1 study. Modified based on [55]. SBP — systolic blood pressure; ABPM — 24-hour automatic blood pressure measurement; Q6M — once every 6 months; Q3M — once every 3 months

The analysis of the safety profile allowed us to conclude that the most common side effects of zilebesiran included injection site reaction (6.3% zilebesiran, 0% placebo; all mild and transient) and hyperkalemia (5.3% zilebesiran, 1.3% placebo; most mild and transient). No renal or hepatic dysfunction was observed in patients taking zilebesiran. Thus, in this study, it was found that in patients with mild-to-moderate hypertension, a single dose of zilebesiran was characterized by a significant antihypertensive effect (24-hour SBP reduction by approximately 10 mm Hg) and an acceptable safety profile [55].

A problem related to the use of drugs based on siRNA technology is the formation of anti-drug antibodies (ADAs). In the zilebesiran study, transient, low-titer ADAs were observed in 2.5% of patients. As with all RAAS inhibitors, treatment escape is possible but was not observed over the extended follow-up period for zilebesiran [49].

Two randomized clinical trials phase II are currently underway: *A Study to Evaluate Efficacy and Safety of ALN-AGT01 in Patients With Mild To-Moderate Hypertension* (KARDIA-1; NCT04936035; expected completion of the study: 31 Dec 2024) and *Zilebesiran as Add-on Therapy in Patients With Hypertension Not Adequately Controlled by a Standard of Care Antihypertensive Medication* (KARDIA-2; NCT05103332; expected completion of the study: 31 Dec 2025).

The study by Bovijn et al. used genetic data from more than one million individuals to characterize the effects of AGT inhibition. It showed that a genetically determined lower AGT expression resulting in a 10 mm Hg reduction in systolic BP was associated with a 41% lower risk of major cardiovascular events, a composite of acute coronary syndrome, coronary revascularization and stroke (OR = 0.59; 95% CI: 0.47–0.74) and did not significantly increase adverse effects [56]. These results need to be confirmed in randomized, placebo-controlled clinical trials with zilebesiran with appropriately long follow-up periods.

In the context of the frequency of zilebesiran administration, it is worth mentioning that a study with spontaneously hypertensive rat (SHR) showed that deletion of the *AGT* gene by a CRISPR-Cas9 method resulted in a hypotensive effect lasting for a year of observation [57].

Thus, zilebesiran is an effective drug that safely lowers systolic BP by > 22 mm Hg and diastolic BP by > 10 mm Hg for 24 weeks after administration of a single dose (800 mg in subcutaneous injection). Further research is needed to confirm these very favorable results and indicate possible cardiovascular benefits.

Zilebesiran — perspective on hypertension treatment in the future

Despite the more than 100 medications approved to treat hypertension, as mentioned above, the effectiveness of antihypertensive treatment is unsatisfactory.

Zilebesiran may contribute to improving BP control (improving adherence and persistence) due to the possibility of administering it twice a year.

Although the safety profile of zilebesiran appears satisfactory, more extensive population-based studies in high-risk groups (chronic kidney disease, chronic kidney disease, type 2 diabetes, and heart failure) will reliably demonstrate adverse effects on kidney function, a significant concern in treatment with RAAS inhibitors. The most likely clinical safety issue is the potential need to reverse the long-acting effects of zilebesiran. Although evidence for emergency reversal agents with noradrenaline and Ang II is encouraging, these will require clinical testing. Use in women of reproductive age is likely to be an absolute

contraindication to drugs targeting AGT unless contraception can be assured, given the known teratogenic effects of RAS inhibition.

Further studies will determine the effect of zilebesiran on BP in patients with hypertension and disturbed BP circadian rhythm (non-dippers) and the effectiveness and safety of combining zilebesiran with other antihypertensive drugs.

In summary, according to the authors, zilebesiran is a new kid on the block and may change the face of hypertension treatment.

Author contributions

S.S. — idea, literature search, preparation of text and figures. S.O. — work revision and acceptance.

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