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Original Article

A Pairwise and Network Meta-Analysis Comparing the Efficacy and Safety of Ribonucleic Acid Interference Therapeutics in the Management of Hypertension

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ABSTRACT

Background: Small interfering RNA (siRNA) and antisense agents targeting angiotensinogen are emerging antihypertensives. We synthesized their efficacy and safety.
Methods: We searched PubMed, Web of Science, Scopus, and CENTRAL through 25 Nov 2024. Eligible studies were randomized controlled trials in adults with hypertension comparing RNA-interference therapeutics with placebo. Primary outcomes were the change in ambulatory and office systolic/diastolic blood pressure. We conducted random-effects pairwise meta-analyses and a network meta-analysis with SUCRA ranking, and appraised certainty with GRADE.
Results: Four trials (n=486) met criteria. Versus placebo, RNA-interference therapy reduced ambulatory SBP (mean difference [MD] 15.46 mmHg; 95% CI 18.79 to 12.12) and DBP (MD 8.45 mmHg; 10.67 to 6.23), and lowered office SBP (MD 8.07 mmHg; 11.58 to 4.56) and DBP (MD 5.18 mmHg; 7.73 to 2.63). Injection-site reactions increased (risk ratio 5.26; 1.01–27.44); other adverse events, potassium, and eGFR were similar. In network analyses, zilebesiran 300 mg ranked highest for blood-pressure lowering; for AGT reduction, 800 mg ranked highest. GRADE certainty was high for blood-pressure outcomes and moderate for AGT, potassium, and eGFR. Few, short-term trials and sparse networks limit precision and generalizability; publication bias was not assessable.
Conclusion: siRNAs effectively reduced BP in hypertensive adults with an acceptable safety profile. Despite the indistinguishable efficacy or safety between the doses or types of siRNAs, Zilebesiran 300 mg best reduced BP compared to placebo.

1. Background

Hypertension (HTN) is considered the primary cause of heart disease, affecting more than one billion individuals globally [1, 2]. Around 31.1% of adults were diagnosed with HTN in 2010, which reflects the significant burden of the disease [3]. Recent studies indicate an increase in the prevalence of HTN, especially in low- and middle-income countries. Despite the wide availability and usage of antihypertensive drugs, many people still struggle to control their blood pressure (BP) [4]. This highlights the critical need for developing novel pharmacological interventions, particularly in response to the growing global burden of HTN.

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RNA interference (RNAi), small interfering ribonucleic acid (siRNA), has demonstrated promise as a therapy for HTN. They work by targeting molecules to prevent or reduce their gene expression. This technology enables targeted inhibition of specific genes implicated in the pathophysiology of HTN [5]. Angiotensinogen (AGT), a precursor to angiotensin peptides, including angiotensin II, is one of the main targets for RNA interference in HTN. Interfering with the expression of AGT can disrupt the renin-angiotensin-aldosterone system (RAAS), the central regulator of BP homeostasis [6]. Two potential RNAi-based therapeutics, Zilebesiran and IONIS-AGT-LRx, have been developed to manage HTN by targeting AGT. Zilebesiran is designed with a small interfering RNA (siRNA) linked to an N-acetylgalactosamine (GalNAc) specifically aimed at reducing hepatic AGT synthesis [7]. IONIS-AGT-LRx is an antisense oligonucleotide (ASO) inhibiting AGT expression in the liver [6]. Recent trials in phases 1 and 2 have revealed promising results for using RNAi-based therapeutics for HTN [8, 6]. Zilebesiran has demonstrated sustained drops in systolic and diastolic blood pressure for up to 24 weeks following a single subcutaneous injection of 200 mg or more, as well as dose-dependent reductions in serum AGT levels. IONIS-AGT-LRx has also exhibited significant reductions in circulating AGT levels without major safety concerns [8, 6]. Despite the optimistic evidence about siRNAs in HTN management, there are no direct comparisons of different

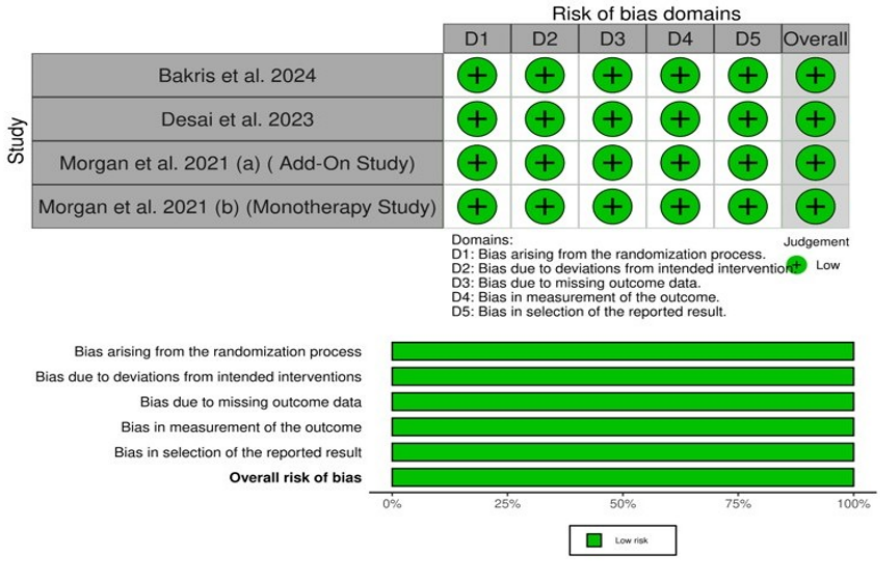

Figure 1: Risk of Bias assessment for included studies using the ROB2 tool

siRNAs, such as Zilebesiran and IONIS-AGT-LRx. Besides, there is a lack of a comprehensive pooled analysis evaluating the role of siRNAs in HTN management.

This study provides preliminary evidence on the efficacy and safety of siRNAs in the management of adult hypertension. Besides, the study compares the efficacy and safety of different doses of the investigated siRNAs, Zilebesiran, and IONIS-AGT-LRx with and without add-on therapy. Following an assessment of the efficacy of this novel family of antihypertensive agents, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) framework to evaluate the quality of the evidence.

2. Methods

This systematic review, pairwise meta-analysis, and network meta-analysis adhered to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions [9]. The study protocol has been registered in PROSPERO (CRD42024584595).

2.1. Eligibility Criteria

We included studies and patients meeting all the following criteria in our meta-analysis: 1) randomized controlled trials (RCTs); 2) the intervention was any drug that belongs to RNA interference therapeutic agents used in hypertension management; 3) the comparator was placebo; 4) English studies only; 5) patients were adults $\geq$ 18 years old; 6) they were untreated or treated with up to two antihypertensive medications; and 7) Patients had a minimum mean systolic blood pressure of 130 mmHg. Besides, we excluded studies meeting any of the following criteria: 1) observational studies, case reports, and conference abstracts; 2) uncontrolled studies; 3) studies with duplicated or overlapping populations; and 4) studies not written in English.

2.2. Search Strategy

We conducted a rigorous and thorough search strategy from inception to November 25, 2024, across five databases, including PubMed, Web of Science (WOS), Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy utilized in all databases comprised keywords and MeSH terms like [Zilebesiran OR Ionis AGT-LRx OR Ionis-AGT-LRx OR "Ionis AGT" OR "RNA interference therapeutic" OR "RNA interference drug") AND (Hypertension OR "High Blood Pressure"). A detailed search strategy for each database is provided in Online Resource 1.

2.3. Study Selection and Data Extraction

Two independent reviewers conducted separate searches across five electronic databases and reviewed the reference lists of relevant studies, adhering to the established inclusion and exclusion criteria. Duplicate studies were removed using EndNote 20.4 [10]. To filter out ineligible studies, we initially screened titles and abstracts with the Rayyan online software [11] And finally screened the full-text articles. A third reviewer's opinion was involved in case any conflicts arose between the two authors in the inclusion decision. Two authors independently extracted the data on an online Excel sheet for easier access—the online spreadsheet comprised sections for study characteristics, baseline characteristics of the population, and outcome data. The study characteristics included the study name, year of publication, sample size, study design, treatment duration, population specifics, and main results. The baseline population characteristics included sample size, age, body mass index (BMI) (kg/m^2), race, ethnicity, and baseline blood pressure measurements.

2.4. Outcome Measures

Our primary outcomes included changes from baseline in ambulatory and office systolic blood pressure (SBP) at the end of follow-up, changes from baseline in ambulatory and office diastolic blood pressure (DBP) after three months, and percent changes from baseline in angiotensinogen (AGT) after three and six months. Our secondary outcomes included changes in estimated Glomerular Filtration Rate (eGFR), changes from baseline in serum potassium,

Table 1: Characteristics of Studies Evaluating Antihypertensive Therapies

Study name	Bakris et al. 2024	Desai et al. 2023	Morgan et al. 2021 (a) (Phase 2, Add-On Study)	Morgan et al. 2021 (b) (Phase 2, Monotherapy Study)
Sample size	377 in the final analysis	84 (Only Part A)	26	25
Design	Phase 2, randomized, placebo-controlled, double-blind, dose-ranging study	Phase 1, randomized, placebo-controlled, double-blind study of a single ascending dose (Part A)	Phase 2, randomized, placebo-controlled, parallel, double-blind study	Phase 2, randomized, placebo-controlled, double-blind study
Study setting and duration of treatment	The study took place in 78 sites across 4 countries (Canada, Ukraine, the UK, and the US). 394 patients were randomized to one of four treatment groups with zilebesiran or a placebo group: 79 to zilebesiran 150 mg, once every 6 mo; 78 to zilebesiran 300 mg, every 6 mo; 79 to zilebesiran 300 mg, every 3 mo; 79 to zilebesiran 600 mg, every 6 mo; and 79 to placebo. A total of 347 patients completed a 6-month treatment period.	The study was carried out at four different sites in the United Kingdom. The 12 participants enrolled in part A were distributed randomly to receive either a single subcutaneous dose of zilebesiran (10, 25, 50, 100, 200, 400, or 800 mg) or a placebo in a 2:1 ratio for 12 weeks.	The study was conducted at nine different sites in the USA. A total of 26 patients were randomly assigned in a 2:1 ratio to receive subcutaneous IONIS-AGT-LRx 80 mg once weekly or a placebo for 8 weeks.	The study took place at six different sites in the USA. A total of 25 patients were randomly assigned to receive either a once-weekly subcutaneous IONIS-AGT-LRx or placebo for 6 weeks, along with an additional loading dose on day 3.
Population	Adults aged 18 to 75 years with mild to moderate essential hypertension (daytime mean ambulatory systolic blood pressure between 135 mmHg and 160 mmHg after washout of antihypertensive medications if they are being taken).	Adults aged 18 to 65 years with mild-to-moderate hypertension, defined as a mean sitting systolic blood pressure > 130 and ≤ 165 mmHg without medication and a mean systolic blood pressure of 130 mmHg or more as assessed by 24-hour monitoring after a two-week washout period from anti-hypertensive medications.	Adults aged 18 to 75 with uncontrolled essential hypertension who are receiving 2 to 3 antihypertensive medications, including ACEi or ARB.	Adults aged between 18 and 72 years who had their blood pressure controlled on 2 antihypertensive medications (an ACEi or an ARB and a beta-blocker, calcium channel blocker, or diuretic). After 14 days from stoppage (washout) of antihypertensive medications, patients with systolic blood pressure (SBP) $140 < BP \leq 165$ mmHg were included.
Main results	There was a statistically significant reduction in 24-hour mean ambulatory SBP among all four groups of zilebesiran compared to placebo. Serum AGT levels exhibited a more than 90% reduction from baseline, which persisted to month 6 after a single 300-mg or 600-mg dose of zilebesiran. Most of the drug-related adverse events were mild to moderate in severity, with injection site reactions and hyperkalemia reported in more than 5% of patients in the zilebesiran groups.	In part A, patients who received zilebesiran (at all doses) showed greater reductions from baseline in SBP and DBP measurements compared to placebo. In addition, reductions in serum AGT levels from baseline in the zilebesiran group were greater than those of the placebo group. Most of the drug-related adverse events were mild to moderate in severity, with headache, injection-site reaction, and upper respiratory tract infection reported in more than 5% of patients who received zilebesiran.	There was a statistically significant absolute reduction in mean AGT levels in the IONIS-AGT-LRx group compared to the placebo after 8 weeks. However, there was a non-statistically significant larger reduction in SBP and DBP among the IONIS-AGT-LRx group compared to the placebo. The drug was well tolerated and did not cause any serious adverse events, hypotensive events, or renal abnormalities.	Patients who received IONIS AGT-LRx showed a nonsignificantly larger reduction in mean SBP or DBP compared with placebo. In addition, there was a considerable reduction in AGT levels in the IONIS-AGT-LRx group compared with the placebo group (11.2 ± 6.0 mg/ml vs. 2.0 ± 4.6; $p<0.001$). The drug was well tolerated and did not cause any serious adverse events, hypotensive events, or renal abnormalities.

AGT, Angiotensinogen; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blocker

and safety outcomes. Regarding safety, the following adverse effects were considered in our analysis: hyperkalemia, hypotension, injection site reaction, serious adverse effects, headache, and hepatic adverse effects.

2.5. Quality Assessment

To evaluate the quality of the included RCTs, we used the Revised Cochrane Risk of Bias (ROB 2) tool. This tool focuses on five key areas of potential bias:

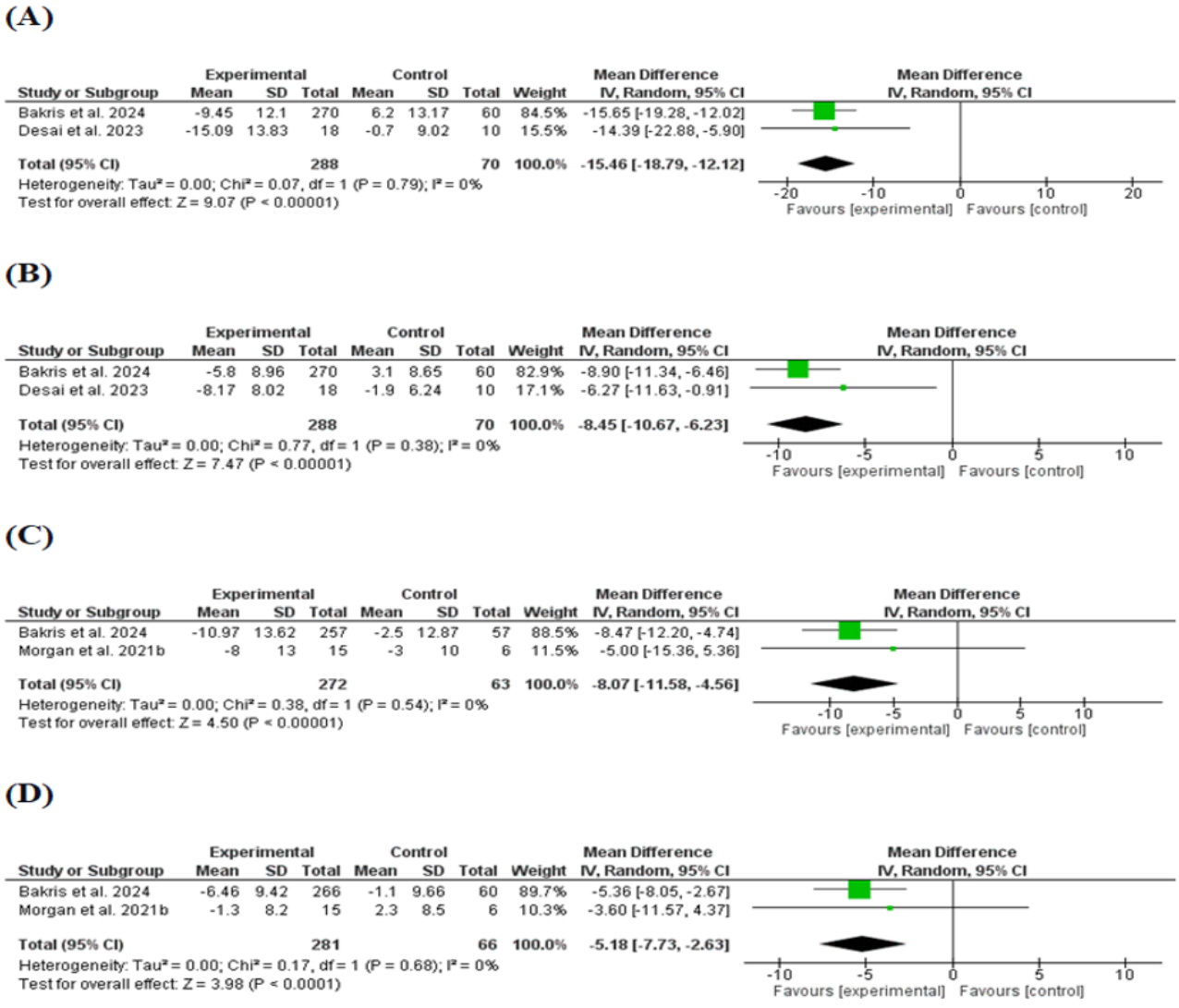

Figure 2: Ambulatory SBP, Ambulatory DBP, Office SBP, and Office DBP: (A) Mean change in ambulatory systolic blood pressure (SBP) at the end of follow-up (B) Mean change in ambulatory diastolic blood pressure (DBP) at the end of follow-up (C) Mean change in office SBP at the end of follow-up (D) Mean change in office DBP at the end of follow-up.

2.5.1. Bias in the Randomization Process

This examines how randomization was carried out, including the methods for generating sequences and concealing allocation.

2.5.2. Bias from Deviations in Intended Interventions

This evaluates whether the assigned interventions were adhered to and assesses how any deviations might have influenced the study outcomes.

2.5.3. Bias Due to Missing Outcome Data

This considers the presence of missing data and its potential impact on the reliability of the study findings.

2.5.4. Bias in Outcome Measurement

This assesses the accuracy of how outcomes were measured, with particular attention to whether assessors were blinded to group assignments.

2.5.5. Bias in Reporting Outcomes

This examines whether there was selective reporting of outcomes, specifically when multiple outcomes were assessed.

Two reviewers independently evaluated each study. Disagreements were resolved through discussion or, if necessary, by consulting a third reviewer. Based on the ROB 2 framework, studies were categorized as having a low risk of bias, some concerns, or a high risk of bias [12].

2.6. Statistical Analysis

Statistical analyses for the indirect comparisons were carried out using Review Manager 5.4 software (RevMan) [13]. We adopted a random-effects model for all outcomes assessed. Mean differences (MD) for continuous outcomes and risk ratio (RR) along with 95% confidence intervals (CIs) were calculated. A finding was considered statistically significant if the P-value was less than 0.05. We used the Higgins I^2 statistic to estimate heterogeneity between

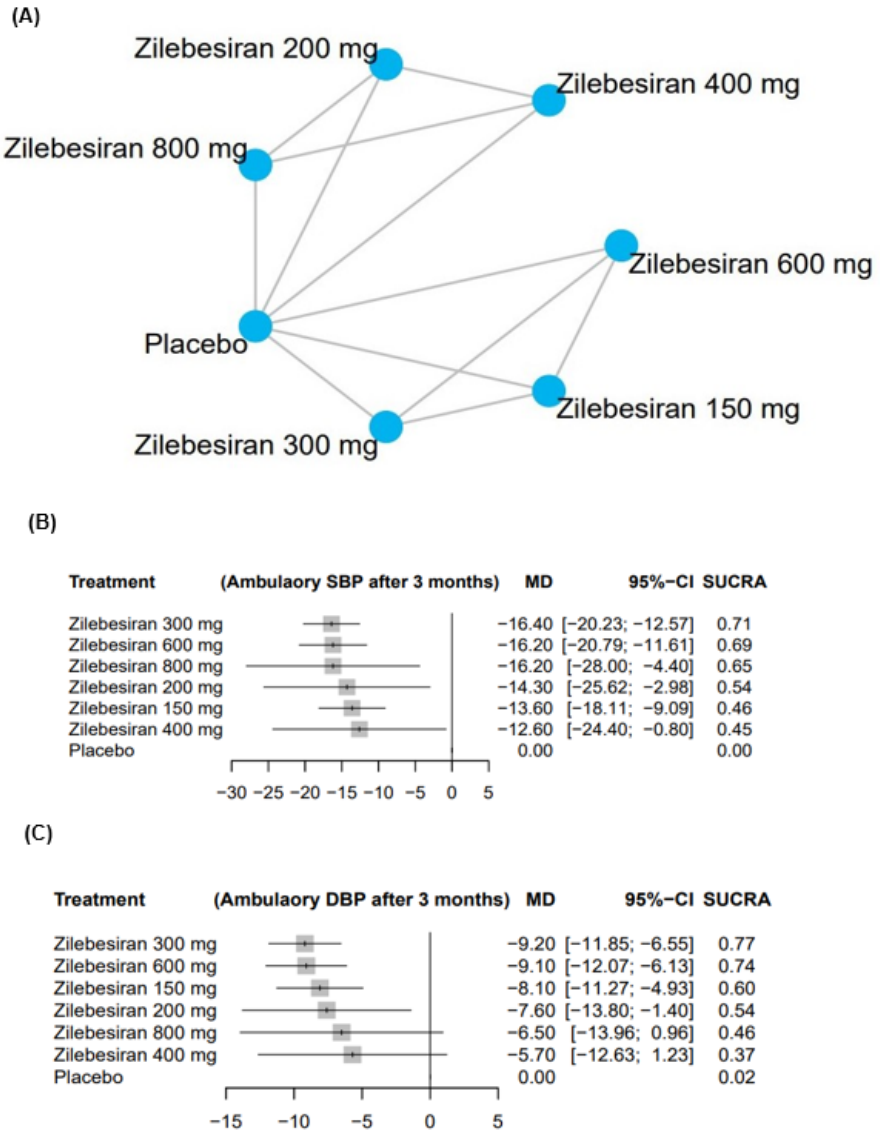

Figure 3: Network Plots and Forest Plots: (A) Network plot comparing ambulatory systolic blood pressure and ambulatory diastolic blood pressure across studies (B) Network forest plot showing the mean change in ambulatory systolic blood pressure after 3 months (C) Network forest plot showing the mean change in ambulatory diastolic blood pressure after 3 months.

studies. An I^2 statistic of 50% or more represents substantial heterogeneity. Heterogeneity was calculated using the chi-square test, with a P-value less than 0.1 considered to represent significant variations between the studies. We also conducted a formal power analysis for primary outcomes (both ambulatory and office SBP and DBP) using the metapower package in R [14, 15]. In executing the network meta-analysis, we utilized RStudio with a frequentist approach that involved a random-effects model employing the "netmeta" package [16]. This approach allowed for the comparison of multiple treatments by combining direct evidence with indirect evidence obtained from studies that included a common comparator. For outcomes measured continuously, effect sizes were represented as MD, and for dichotomous outcomes, RR was employed, accompanied by 95% CI. The relative effectiveness of the interventions was estimated using the Surface Under the Cumulative Ranking Curve (SUCRA). High SUCRA values indicate that an intervention is more effective, showing its probability of being ranked as the best option compared to others. We also constructed network diagrams to display the links between the interventions and used forest plots to show the effect sizes for each treatment comparison. To facilitate comparison of the treatments, we have used league tables to present the rankings of the treatments.

2.7. Quality of evidence

The level of confidence of the evidence provided was rated using the Grading of Recommendations, Assessment, Development, and Evaluation criteria (GRADE) by the GRADEpro Guideline Development Tool (GDT) online tool [17, 18, 19]. Based on the GRADE tool, the evidence is designated as one of four levels of confidence—very low, low, moderate, or high—based on several factors, including the risk of bias, inconsistency, indirectness, imprecision, publication bias, and additional factors such as dose-response gradients and potential confounding variables.

(A)

Zilebesiran 300 mg	-0.20 (-3.88; 3.48)	.	.	.	-2.80 (-6.37; 0.77)	-16.40 (-20.23;-12.57)
-0.20 (-3.88; 3.48)	Zilebesiran 600 mg	.	.	.	-2.60 (-6.98; 1.78)	-16.20 (-20.79;-11.61)
-0.20 (-12.61; 12.21)	0.00 (-12.66; 12.66)	Zilebesiran 800 mg	-1.90 (-16.21; 12.41)	-3.60 (-18.30; 11.10)	.	-16.20 (-28.00; -4.40)
-2.10 (-14.05; 9.85)	-1.90 (-14.11; 10.31)	-1.90 (-16.21; 12.41)	Zilebesiran 200 mg	-1.70 (-16.01; 12.61)	.	-14.30 (-25.62; -2.98)
-3.80 (-16.21; 8.61)	-3.60 (-16.26; 9.06)	-3.60 (-18.30; 11.10)	-1.70 (-16.01; 12.61)	Zilebesiran 400 mg	.	-12.60 (-24.40; -0.80)
-2.80 (-6.37; 0.77)	-2.60 (-6.98; 1.78)	-2.60 (-15.23; 10.03)	-0.70 (-12.88; 11.48)	1.00 (-11.63; 13.63)	Zilebesiran 150 mg	-13.60 (-18.11; -9.09)
-16.40 (-20.23;-12.57)	**-16.20 (-20.79;-11.61)**	**-16.20 (-28.00; -4.40)**	**-14.30 (-25.62; -2.98)**	**-12.60 (-24.40; -0.80)**	**-13.60 (-18.11; -9.09)**	Placebo

(B)

Zilebesiran 300 mg	-0.10 (-2.61; 2.41)	-1.10 (-3.84; 1.64)	.	.	.	-9.20 (-11.85;-6.55)
-0.10 (-2.61; 2.41)	Zilebesiran 600 mg	-1.00 (-4.05; 2.05)	.	.	.	-9.10 (-12.07;-6.13)
-1.10 (-3.84; 1.64)	-1.00 (-4.05; 2.05)	Zilebesiran 150 mg	.	.	.	-8.10 (-11.27;-4.93)
-1.60 (-8.35; 5.15)	-1.50 (-8.38; 5.38)	-0.50 (-7.47; 6.47)	Zilebesiran 200 mg	-1.10 (-9.11; 6.91)	-1.90 (-9.42; 5.62)	-7.60 (-13.80;-1.40)
-2.70 (-10.61; 5.21)	-2.60 (-10.63; 5.43)	-1.60 (-9.70; 6.50)	-1.10 (-9.11; 6.91)	Zilebesiran 800 mg	-0.80 (-9.39; 7.79)	-6.50 (-13.96; 0.96)
-3.50 (-10.92; 3.92)	-3.40 (-10.94; 4.14)	-2.40 (-10.02; 5.22)	-1.90 (-9.42; 5.62)	-0.80 (-9.39; 7.79)	Zilebesiran 400 mg	-5.70 (-12.63; 1.23)
-9.20 (-11.85;-6.55)	**-9.10 (-12.07;-6.13)**	**-8.10 (-11.27;-4.93)**	**-7.60 (-13.80;-1.40)**	-6.50 (-13.96; 0.96)	-5.70 (-12.63; 1.23)	Placebo

Figure 4: League Tables for Blood Pressure Measurements: (A) League table comparing ambulatory systolic blood pressure across studies (B) League table comparing ambulatory diastolic blood pressure across studies

3. Results

3.1. Literature search

We identified 390 records after implementing our search strategy. After detecting 20 duplicate records, we were left with 370 unique records. The records underwent rigorous title/abstract screening, yielding 20 records for the full-text screening process. Eventually, four studies were included in our qualitative and quantitative analysis. The PRISMA flow diagram is shown in Online Resource 2.

3.2. Study and population characteristics

Our study included four clinical trials assessing the efficacy of RNA interference therapeutics in patients with hypertension [8, 7, 6]. These trials, conducted in several countries including Canada, Ukraine, the UK, and the US, enrolled 486 participants. The trials involved hypertensive adults, with specific inclusion criteria, including elevated systolic blood pressure ranging from 130 mmHg to 160 mmHg. Sample sizes ranged from 25 to 377 patients, while treatment duration ranged from 6 weeks to 6 months. A summary of the characteristics of the included studies and the baseline population is presented in **(Table 1)** and **(Table 2)**, respectively.

3.3. Quality assessment

All studies appeared to have a low risk of bias across all domains, resulting in an overall low risk of bias, as illustrated in **(Figure 1)**.

3.3.1. Pairwise meta-analysis

Efficacy

Ambulatory blood pressure

The analysis comparing siRNAs and placebo involved two studies and revealed a significant difference favoring the intervention in terms of ambulatory SBP and DBP (MD: -15.46, 95% CI: [-18.79, -12.12], P < 0.00001, as shown in **Figure 2A**) and (MD: -8.45, 95% CI: [-10.67, -6.23], P < 0.00001, as shown in **Figure 2B**), respectively. No heterogeneity was detected in either outcome.

Office blood pressure

Two studies were involved in the analysis of office blood pressure. They showed a significant difference in favor of intervention in improving office SBP and DBP (MD: -8.07, 95% CI: [-11.58, -4.56], P < 0.00001, as shown in **Figure 2C**) and (MD: -5.18, 95% CI: [-7.73, -2.63], P < 0.0001, as shown in **Figure 2D**), respectively. No heterogeneity was observed in either outcome.

AGT, potassium, and eGFR

The mean percent change in AGT at the end of follow-up showed a significant difference between the intervention and placebo in favor of the intervention (MD: -87.58, 95% CI: [-102.76, -72.41], P < 0.00001, as shown in Online Resource 3A). However, there was significant heterogeneity (I2 = 88%, P-value = 0.0002). Similar significant reductions with statistical heterogeneity were observed when measuring AGT levels at the 3-month endpoint, as shown in Online Resource 3B. The potassium level change showed no statistically significant difference between the two groups (MD: -0.09, 95% CI: [-0.38, 0.19], P = 0.52, as shown in Online Resource 3C). Similarly, eGFR showed no statistically significant difference between the two groups (MD: -2.92, 95% CI: [-8.53, 2.68], P = 0.31, as shown in Online Resource 3D).

Safety

Side effects, including hypotension, hyperkalemia, headache, hepatic adverse effects, serious side effects, and death, showed statistically insignificant differences between the two groups, as shown in Online Resource 4 and Online Resources 5A and B. However, the only significant adverse event associated with siRNAs was injection site reactions (RR: 5.26, 95% CI: 1.01 to 27.44, P = 0.05), as shown in Online Resource 5C.

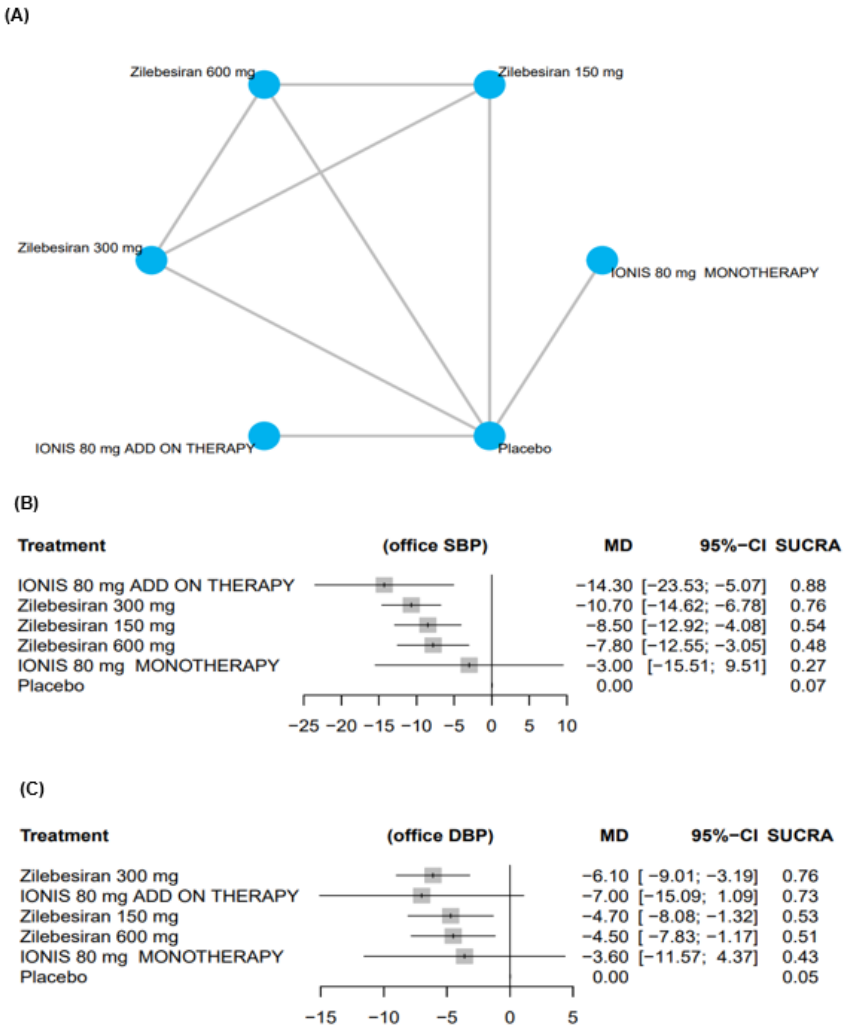

Figure 5: Office Blood Pressure Measurements: (A) Network plot comparing office systolic blood pressure and diastolic blood pressure across studies (B) Network forest plot for mean change in office systolic blood pressure (C) Network forest plot for mean change in office diastolic blood pressure.

3.3.2. Network meta-analysis

Efficacy

Ambulatory blood pressure

The NMA included two studies evaluating ambulatory SBP and DBP. The network plot for ambulatory blood pressure is presented in **Figure 3A**. Regarding SBP, all doses of zilebesiran showed significant MD compared to placebo, with zilebesiran 300 mg being the most effective in reducing SBP (MD: -16.40, 95% CI: [-20.23, -12.57], P < 0.0001, as shown in **Figure 3B**). According to surface under the cumulative ranking curve (SUCRA) rankings, zilebesiran 300 mg achieved the highest ranking (SUCRA = 71%), followed by zilebesiran 600 mg (69%), 800 mg (65%), 200 mg (54%), 150 mg (46%), and 400 mg (45%). Concerning DBP, all zilebesiran doses exhibited significant MD compared to placebo, except for 800 and 400 mg doses. Analogous to SBP, zilebesiran 300 mg was the most effective in reducing DBP (MD: -9.20, 95% CI: [-11.85, -6.55], P < 0.0001, as shown in **Figure 3C**), and it showed the highest ranking (SUCRA = 77%), followed by zilebesiran 600 mg (74%), 150 mg (60%), 200 mg (54%), 800 mg (46%), and 400 mg (37%). Although most doses were superior to the placebo in managing ambulatory blood pressure, there was no significant difference between the doses of Zilbesiran and each other, as shown in **(Figure 4)**.

Office blood pressure

Concerning office blood pressure, the NMA included three studies evaluating SBP and DBP. The network plots are presented in **Figure 5A**. Regarding SBP, all interventions at all doses showed significant MD compared to placebo, except for IONIS 80 mg monotherapy. IONIS 80 mg add-on therapy displayed the highest effectiveness in reducing SBP (MD: -14.30, 95% CI: [-23.53, -5.07], P < 0.01, as shown in **Figure 5B**). According to SUCRA rankings, IONIS 80 mg add-on therapy showed the highest ranking (SUCRA = 88%), followed by zilebesiran 300 mg (76%), zilebesiran 150 mg (54%), zilebesiran 600 mg (48%), and IONIS 80 mg monotherapy (27%). Regarding DBP, all zilebesiran doses exhibited significant MD compared to placebo, while IONIS 80 mg add-on therapy and IONIS 80 mg monotherapy failed to show any significant difference from placebo. Zilebesiran 300 mg was the most effective in reducing DBP (MD: -6.10, 95% CI: [-9.01, -3.19], P < 0.0001, as shown in **Figure 5C**), and it showed the highest ranking (SUCRA = 76%), followed by IONIS 80 mg add on therapy (73%), zilebesiran 150 mg (53%), zilebesiran 600 mg (51%), and IONIS 80 mg monotherapy (43%). Although most

(A)

IONIS 80 mg ADD ON THERAPY	.	.	.	.	-14.30 (-23.53;-5.07)
-3.60 (-13.63; 6.43)	Zilebesiran 300 mg	-2.20 (-5.86; 1.46)	-2.90 (-6.95; 1.15)	.	-10.70 (-14.62;-6.78)
-5.80 (-16.04; 4.44)	-2.20 (-5.86; 1.46)	Zilebesiran 150 mg	-0.70 (-5.24; 3.84)	.	-8.50 (-12.92;-4.08)
-6.50 (-16.88; 3.88)	-2.90 (-6.95; 1.15)	-0.70 (-5.24; 3.84)	Zilebesiran 600 mg	.	-7.80 (-12.55;-3.05)
-11.30 (-26.85; 4.25)	-7.70 (-20.81; 5.41)	-5.50 (-18.77; 7.77)	-4.80 (-18.18; 8.58)	IONIS 80 mg MONOTHERAPY	-3.00 (-15.51; 9.51)
-14.30 (-23.53;-5.07)	**-10.70 (-14.62;-6.78)**	**-8.50 (-12.92;-4.08)**	**-7.80 (-12.55;-3.05)**	-3.00 (-15.51; 9.51)	Placebo

(B)

Zilebesiran 300 mg	.	-1.40 (-4.21; 1.41)	-1.60 (-4.36; 1.16)	.	-6.10 (-9.01;-3.19)
0.90 (-7.70; 9.50)	IONIS 80 mg ADD ON THERAPY	.	.	.	-7.00 (-15.09; 1.09)
-1.40 (-4.21; 1.41)	-2.30 (-11.07; 6.47)	Zilebesiran 150 mg	-0.20 (-3.45; 3.05)	.	-4.70 (-8.08;-1.32)
-1.60 (-4.36; 1.16)	-2.50 (-11.25; 6.25)	-0.20 (-3.45; 3.05)	Zilebesiran 600 mg	.	-4.50 (-7.83;-1.17)
-2.50 (-10.98; 5.98)	-3.40 (-14.76; 7.96)	-1.10 (-9.75; 7.55)	-0.90 (-9.54; 7.74)	IONIS 80 mg MONOTHERAPY	-3.60 (-11.57; 4.37)
-6.10 (-9.01;-3.19)	-7.00 (-15.09; 1.09)	**-4.70 (-8.08;-1.32)**	**-4.50 (-7.83;-1.17)**	-3.60 (-11.57; 4.37)	Placebo

Figure 6: League Tables for Office Blood Pressure Measurements: (A) League table for office systolic blood pressure (B) League table for office diastolic blood pressure.

interventions were superior to the placebo in managing office blood pressure, there was no significant difference between the interventions themselves, as shown in **(Figure 6)**.

AGT

Regarding the AGT percent change after approximately three months, the NMA included four studies, and the network plot is shown in Online Resource 6A. All interventions at all doses demonstrated significant MD compared to placebo, with zilebesiran 800 mg being the most effective in reducing AGT (MD: -111.90, 95% CI: [-120.45, -103.35], P < 0.0001, as shown in Online Resource 6B). Based on intervention rankings, zilebesiran 800 mg was the most effective intervention (SUCRA = 98%), while the IONIS 80 mg add-on had the lowest ranking (SUCRA = 9%). Additionally, zilebesiran 800 mg demonstrated significant reductions in AGT levels compared to most zilebesiran doses and IONIS 80 mg, with or without add-on therapy, as shown in Online Resource 8A.

Regarding the AGT percent change after six months, the NMA included two studies, and the network plot is shown in Online Resource 7A. Similar to the aforementioned AGT levels reductions, all interventions at all doses showed significant AGT reductions compared to placebo, with zilebesiran 800 mg being the most effective in reducing AGT (MD: -113.37, 95% CI: [-133.12, -93.62], P < 0.0001, as shown in Online Resource 7B). After ranking the interventions, zilebesiran 800 mg was the best intervention (SUCRA = 99%), while zilebesiran 50 mg showed the lowest ranking (SUCRA = 12%). As expected, zilebesiran 800 mg showed significant reductions in AGT levels compared to most zilebesiran doses and IONIS 80 mg with or without add-on therapy, as shown in Online Resource 8B.

Safety outcome

Three studies were included in the evaluation of hyperkalemia, with the network plot presented in Online Resource 9A. No significant differences were observed in the incidence of hyperkalemia between any intervention and the placebo. Based on the rankings, zilebesiran 800 mg was associated with the highest risk of hyperkalemia (RR: 3.50, 95% CI: [0.08, 162.90], $P = 0.52$, as shown in Online Resources 9B and C), while IONIS 80 mg add-on therapy was the safest (RR: 0.89, 95% CI: [0.03, 23.88], $P = 0.94$, as shown in Online Resources 9B and C) compared to placebo. Regarding hypotension, two studies were involved in the NMA, with the network plot presented in Online Resource 10A. There were no significant differences at any intervention compared to placebo, with zilebesiran 600 mg being the most associated with hypotension (RR: 3.95, 95% CI: [0.45, 34.50], $P = 0.21$, as shown in Online Resources 10B and C), whereas zilebesiran 150 mg was the safest (RR: 2.88, 95% CI: [0.31, 27.12], $P = 0.35$, as shown in Online Resources 10B and C). Four studies contributed to the NMA of injection site reactions; the network plot is shown in Online Resource 11A, with no difference observed between any of the interventions and the placebo, as shown in Online Resources 11B and C. The remaining side effects were insignificant and can be found in Online Resources (12–15).

Quality of evidence

The quality of evidence regarding the efficacy and safety of siRNAs in the most important and relevant outcomes versus placebo was assessed using the GRADE approach. A summary of the findings and a GRADE evaluation of the outcomes are represented in **(Table 3)**.

4. Discussion

The present meta-analysis provides preliminary evidence regarding the efficacy and safety of siRNAs in the management of hypertensive adults with mild to moderate hypertension. The pairwise analysis yielded statistically and clinically significant reductions in ambulatory blood pressure readings [20]. Targeting AGT to suppress the renin-angiotensin-aldosterone system reduced the ambulatory systolic blood pressure (ASBP) by 15 mmHg and the

Table 2: Baseline Characteristics and Intervention Details of Included Studies

Study names and groups		**Bakris et al. 2024**				**Desai et al. 2023**		**Morgan et al. 2021 (a)**		**Morgan et al. 2021 (b)**	
Interventions	**Zelibesiran**	**Zelibesiran**	**Zelibesiran**	**Zelibesiran**	**Placebo**	**Zelibesiran**	**Placebo**	**IONIS**	**Placebo**	**IONIS**	**Placebo**
	150 mg/6 m	300 mg/6 m	300 mg/3 m	600 mg/6 m							
Sample size	78	73	75	76	75	75	56	28	18	17	8
Age, Mean (SD)	55.5 (10.6)	56.4 (10.3)	57.7 (10.6)	57.4 (10.2)	56.8 (11.2)	56.8 (11.2)	53 (7.5)	52.9 (7)	60 (8)	60 (7)	57 (4)
BMI, Kg/m^2, Mean (SD)	NA	NA	NA	NA	NA	NA	28.6 (3)	29.3 (3.1)	28.1 (4.6)	NA	NA
Male, n (%)	39 (50)	44 (60)	45 (60)	45 (59)	37 (49)	37 (49)	35 (62)	16 (57)	4 (22)	10 (59)	2 (25)
Female, n (%)	39 (50)	29 (40)	30 (40)	31 (41)	38 (51)	38 (51)	21 (38)	12 (43)	14 (78)	7 (41)	6 (75)
Race, n (%)	White	53 (68)	54 (74)	48 (64)	52 (68)	52 (69)	35 (62)	21 (75)	15 (83)	10 (59)	5 (63)
	Asian	4 (5)	2 (3)	7 (9)	5 (7)	5 (7)	3 (5)	0	0	1 (6)	0
	Black or African American	20 (26)	17 (23)	19 (25)	19 (25)	18 (24)	16 (29)	6 (21)	3 (17)	5 (29)	2 (25)
	Other	1 (1)	0	1 (1)	0	0	2 (4)	1 (4)	0	1 (6)	1 (12.5)
Ethnicity, n (%)	Hispanic or Latino	19 (24)	16 (22)	10 (13)	20 (26)	18 (24)	18 (24)	NA	NA	8 (44)	2 (25)
	Not Hispanic or Latino	59 (76)	57 (78)	65 (87)	56 (74)	66 (88)	66 (88)	NA	NA	9 (53)	6 (75)
Office SBP, mmHg, Mean (SD)	142.0 (10.9)	143.0 (11.3)	140.0 (11.0)	140.8 (10.6)	143.1 (13.3)	143.1 (13.3)	139.2 (9.4)	140.6 (8.3)	154 (11)	146 (9)	149 (15)
Office DBP, mmHg, Mean (SD)	87.4 (9.6)	88.8 (8.8)	85.3 (9.1)	85.6 (8.8)	87.9 (10.5)	87.9 (10.5)	85.8 (6.8)	87.9 (7.9)	89 (9)	86 (7)	88 (10)
Serum angiotensinogen, ng/mL	22.1 (5.9)	23.2 (7.8)	20.8 (4.9)	21.7 (5.9)	23.9 (10.9)	23.9 (10.9)	NA	NA	25.1 (3.3)*	20.7 (4.7)	26.9 (19.1)

µg/mL, microgram per milliliter; NA, Not Available (these data were not reported in the studies.

Table 3: Summary of findings and quality of evidence

Certainty assessment							Summary of findings				
Outcomes / patients (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With inter-vention**		**Risk with Placebo**	**Risk difference with intervention**
Ambulatory SBP after 3 months											
358 (2 RCTs)	not serious	not serious	not serious	not serious	None	⊕⊕⊕⊕ High	70	288	–	–	MD 15.46 mmHg lower (18.79 to 12.12 lower)
Ambulatory DBP after 3 months											
358 (2 RCTs)	not serious	not serious	not serious	not serious	None	⊕⊕⊕⊕ High	70	288	–	–	MD 8.45 mmHg lower (10.67 to 6.23 lower)
Office SBP											
335 (2 RCTs)	not serious	not serious	not serious	not serious	None	⊕⊕⊕⊕ High	63	272	–	–	MD 8.07 mmHg lower (11.58 to 4.56 lower)
Office DBP											
347 (2 RCTs)	not serious	not serious	not serious	not serious	None	⊕⊕⊕⊕ High	281	66	–	–	MD 5.18 mmHg lower (7.73 to 2.63 lower)
AGT levels											
433 (3 RCTs)	not serious	serious[a]	not serious	not serious	None	⊕⊕⊕◦ Moderate	103	330	–	–	MD 87.58% lower (102.76 to 72.41 lower)
Hypotension											
461 (2 RCTs)	not serious	not serious	not serious	very serious[c]	None	⊕⊕ Low	2	13	RR 0.96 (0.06 to 16.63)	19 per 1000	1 fewer (from 18 fewer to 303 more)
Injection site reactions											
486 (3 RCTs)	not serious	not serious	not serious	very serious[c]	None	⊕⊕ Low	43	43	RR 5.26 (1.01 to 27.44)	9 per 1000	38 more (from 0 fewer to 238 more)
Serum potassium											
107 (2 RCTs)	not serious	not serious	not serious	serious[b]	None	⊕⊕⊕◦ Moderate	36	71	–	–	MD 0.09 mEq/L less (0.38 less to 0.19 more)
eGFR											
480 (3 RCTs)	not serious	not serious	not serious	serious[b]	None	⊕⊕⊕◦ Moderate	108	372	–	–	MD 2.92 mL/min/1.73m^2 less (8.53 less to 2.68 more)

a, Wide variance of point estimates across studies; b, Wide 95% confidence intervals which include clinically important differences; c, Very wide 95% confidence intervals which include clinically important differences and few number of events.

ambulatory diastolic blood pressure (ADBP) by 8. A reduction of 5–10 mm Hg in systolic blood pressure or 5 mm Hg in diastolic blood pressure is considered a minimal clinically significant difference in blood pressure [21], which would be associated with a significant reduction in major cardiovascular events by 20%, coronary heart disease by17%, heart failure28%, and stroke by 27% [22].

This novel approach to RAAS system suppression has several advantages, in addition to its aforementioned efficacy. In contrast to traditional RAAS antagonists, compensatory angiotensin reactivation and aldosterone escape mechanisms cannot reduce the effectiveness of siRNAs [23]. Moreover, our meta-analysis revealed no significant risks compared to the placebo regarding hyperkalemia

and reduced eGFR, which are typically associated with aggressive regimens of dual RAAS blockade [24, 25]. Besides, our network analysis revealed that zilebesiran 300 mg was ranked most effective in reducing ASBP and ADBP after three months: SUCRAs: 71% and 77%, respectively. These findings align with Bakris et al.'s findings, which revealed dose-related reductions in BP until 300 mg, after which increasing the dose to 800 mg had minimal effect on reducing BP. However, our analysis yielded pharmacologically intuitive results regarding AGT reduction, with zilebesiran 800 mg being the most effective in reducing AGT levels at both 3 and 6 months. The similar or arguably better management of hypertension by zilebesiran 300 mg supports the hypotheses presented in participating trials, which suggest that angiotensinogen reductions of greater than 90% would be sufficient for the most effective and longest-lasting decrease in blood pressure [8]. Therefore, managing BP might be accomplished using a relatively small dose of 300 mg with a potentially better safety profile.

Adverse events associated with novel pharmacotherapeutics represent an apprehension for physicians and patients alike. However, our meta-analysis revealed a generally acceptable short-term safety profile, as a duration of 6 weeks to 6 months is considered a relatively short period to assess the long-term safety of the drug, with injection site reactions being the only significant adverse effect. Fortunately, most patients reporting site reactions experienced mild symptoms and didn't require treatment withdrawal. Another theoretically feared adverse reaction to siRNAs is hypotension. Thankfully, most of the participating trials didn't display significant hypotensive events, and our analysis further confirms a statistically nonsignificant difference in hypotension incidence compared to the placebo ($P = 0.98$). Even if hypotension were to occur in selected patients, restoration of blood pressure was observed to be sufficient with standard interventions, such as a high-sodium diet [7]. Moreover, preclinical models displayed patency of residual RAAS system activation mechanisms, like sympathetic nervous system activation, which would supposedly allow compensatory BP regulation if a hypotensive crisis occurs [26]. However, it is crucial to note that the safety profile presented in this systematic review and meta-analysis reflects short-term safety in adults with mild to moderate hypertension and no comorbidities. The effect of long-term administration of siRNAs in a heterogeneous population of hypertensive patients with variable comorbidities is yet to be known.

Numerous studies have shown that cardiovascular disease and hypertension are related [27, 28]. The Kokubo et al. study found that, in comparison to optimal blood pressure, the cardiovascular risk ratio was 2.04 (95% CI 1.19 to 3.48) for normal blood pressure, 2.46 (1.46 to 4.14) for high normal blood pressure, 2.62 (1.59 to 4.32) for grade 1 hypertension, and 3.95 (2.37 to 6.58) for grade 2 hypertension [29].

Hypertension remains one of the most common diagnoses and reasons for physician office visits in the United States [30, 31]. With the hypertensive population experiencing challenges in terms of treatment compliance and adherence, siRNAs represent a revolution in this aspect [32]. First and foremost, siRNAs' pharmacodynamic properties allow for single-dose administration three or four times a year. In addition, siRNAs displayed a steady decline during three months, both during the day and at night, as shown in our analysis, and for six months in some participating trials [8]. Therefore, the administration of siRNAs may be a method to mitigate the residual risk associated with between-visit unpredictability, which represents a challenge to current oral antihypertensive management.

The current meta-analysis stands out in different points. It is the first comprehensive meta-analysis investigating RNA-interference therapeutics in hypertensive adults. Furthermore, the study examines the effects of various doses, providing practical and clinically valuable insights. In addition, the study provides a comprehensive assessment of the quality of evidence using the GRADE framework, offering a more rigorous and structured appraisal of the evidence. While the study provides valuable insights, it is not without its limitations. The analysis incorporated a relatively small number of trials and patients. With only 486 patients, this meta-analysis has insufficient statistical power to detect rare adverse events. Moreover, the small population and very wide confidence interval, especially in outcomes related to injection site reactions, necessitated the authors to downgrade the "imprecision" domain in the GRADE assessment [33]. Another limitation is that the application of any test for publication bias (Egger test or funnel plots) is unreliable, as the minimum number of studies required to perform such tests is 10, as recommended by Cochrane [34].

Also, Lin et al. suggest that a publication bias test can be done with 8 or 6 studies [35]. But it is still a limitation for us, as we have only four studies in our meta-analysis. Besides, the limited number of RCTs provided a simple spur network analysis. A network meta-analysis for only 2-4 studies per comparison deviates from standard assumptions and provides inaccurate indirect estimates. This further precluded investigating possible sources of heterogeneity, if found, such as hypertension severity and patient characteristics, and exploring potential relationships between baseline variables and expected reductions in blood pressure in both network and pairwise analyses. Moreover, it deterred us from identifying any inconsistency in the network analysis. Finally, the findings presented in this study are limited to the short term in patients with mild to moderate hypertension. This might not fairly reflect the outcomes in a larger group of unselected patients, such as those using aggressive antihypertensive medication, those with more severe blood pressure increases, or those with other comorbidities. However, these constraints are understandable, given the novelty of the interventions investigated.

Our future research recommendations are based on the limitations of this meta-analysis. Studies with larger sample sizes with broader populations, including elderly populations with severe hypertension and significant comorbidities, focusing on the long-term safety and efficacy of siRNAs, are recommended. Studies combining siRNAs with other commonly prescribed antihypertensives are highly recommended to yield more generalizable results. Furthermore, investigating siRNAs' efficacy in hypertensive patients with comorbidities like heart failure or Obstructive Sleep Apnea might show new insights into the effect of this novel family of drugs.

5. Conclusion

In conclusion, siRNAs are potentially drugs to manage BP in hypertensive adults with mild to moderate HTN. The safety profile in the short term was acceptable, with only injection site reactions being statistically significant. Despite the absence of significant differences in either efficacy or safety between the doses or types of siRNAs, Zilbesiran 300 mg best reduced BP compared to placebo. Further trials focusing on the long-term safety and efficacy of siRNAs in a more diverse hypertensive population are recommended.

Conflicts of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Authors Contribution

The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). MEH and ZB contributed equally to this work and were designated as co-first authors. MEH and ZB contributed to the conception and design of the study. MEH, ZB, GH, and MN performed studies, screening, and data extraction. HEM, ZB, MEH, and NSJ wrote the initial draft of the manuscript. ZB, MEH, HEM, GH, MN, NSJ, MKD, and HA revised and prepared the manuscript for submission. MKD, MEH, and ZB contributed to performing the reviewers' revisions and preparing the revised manuscript. All authors provided feedback on earlier drafts of the manuscript. All authors read and approved the final manuscript.

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary file.

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