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RESEARCH ARTICLE

EFFICACY AND SAFETY OF ZILEBESIRAN FOR HYPERTENSION: A SYETAMTIC REVIEW AND META- ANALYSIS

Dr Ramya Rachamanti[1]*, Ms. Supritha Sakhamuri[2], Ms. Narra Jyoothika[3], Mr Sakhamuri Kamalnatha Sai[4]

[1]Assistant professor, Dept. of Pharmacology, Guntur Medical College and Govt. General Hospital, Guntur1*
[2]Intern, Guntur Medical College and Govt. General Hospital, Guntur2
[3]MBBS Student, Guntur Medical College and Govt. General Hospital, Guntur3
[4]MBBS Student, Guntur Medical College and Govt. General Hospital,Guntur, Andhra Pradesh, India4

*Corresponding Author
Dr Ramya Rachamanti

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Abstract: ***Background:*** Hypertension is a majore global cardiovascular risk factor in spite of various available antihypertensive drug classes. Poor adherence and suboptimal blood pressure (BP) control prove the need for novel, durable therapeutic options. Zilebesiran, a subcutaneously administered RNA interference (RNAi) therapeutic targeting hepatic angiotensinogen synthesis, provides long-acting BP reduction through twice-yearly dosing. ***Objectives:*** To systematically evaluate the efficacy and safety of zilebesiran in adult patients with hypertension, synthesising data from early-phase clinical trials. ***Methods:*** A systematic review and meta-analysis were conducted including data from four trials—Desai et al. (Phase 1), KARDIA-1, KARDIA-2, and KARDIA-3 (Phase 2). Eligible studies enrolled adults (≥18 years) with primary hypertension treated with zilebesiran as monotherapy or add-on therapy. Primary efficacy outcomes were change in systolic and diastolic BP (office and ambulatory). Safety outcomes are adverse events (AEs), serious AEs (SAEs), and mortality. Pooled analyses were done using random-effects (DerSimonian–Laird) models, with heterogeneity assessed by I^2 statistics. ***Results:*** Among 821 zilebesiran-treated participants, pooled mean reduction in ambulatory systolic blood pressure(SBP) was −6.81 mm Hg and in office SBP −6.60 mm Hg. Ambulatory and office DBP reductions averaged −5.8 mm Hg and −6.6 mm Hg. Overall AE rate was 23.7%, SAEs 4.6%, and mortality 0.4%. Common AEs were injection-site reactions (≈10%) and mild headache or dizziness; hepatic, renal, or cardiac events were infrequent. ***Conclusion:*** Zilebesiran showed consistent, clinically meaningful BP reductions and an acceptable short-term safety profile across Phase 1–2 studies. Its 6 montly dosing provides promising strategy to improve adherence in hypertension management. Larger, long-term outcome trials are needed to confirm durability, cardiovascular benefits, and cost-effectiveness.

Keywords: Zilebesiran, Hypertension, RNA interference, Angiotensinogen, Blood pressure, Meta-analysis.

INTRODUCTION

Hypertension is one of the most prevalent global cardiovascular risk factors, affecting more than 1.3 billion adults worldwide.[1] It contributes significantly to morbidity and mortality from stroke, myocardial infarction, heart failure[2] and chronic kidney disease (CKD). In spite of availability of multiple classes of antihypertensive medications like ACE inhibitors, ARBs, calcium-channel blockers, diuretics, and β-blockers, many patients fail to achieve and maintain guideline-recommended blood-pressure (BP) target. This could be due to suboptimal adherence, pharmacologic escape phenomena, and residual risk from 24-hour BP variability. So, there is a need for novel therapies that can provide durable BP control with improved adherence and mechanism of action.

Zilebesiran is an investigational, subcutaneously administered RNA interference (RNAi) therapeutic agent which targets production of angiotensinogen (AGT). This is precursor of the renin-angiotensin-aldosterone system (RAAS). By inhibiting hepatic AGT synthesis, Zilebesiran helps to blunt the generation of angiotensin II and downstream vasoconstrictive and sodium-retaining effects, thus offering a novel mechanism of BP reduction. Its unique feature is the possibility of infrequent dosing (once every 3 to 6 months) through GalNAc-conjugate technology, improving adherence and providing sustained BP lowering over extended period.[3]

Clinical development of Zilebesiran for hypertension has progressed through Phase 1 and Phase 2 trials. In a first-in-human Phase 1 study, single subcutaneous doses of Zilebesiran provided dose-dependent reduction in serum angiotensinogen and ambulatory BP, with effects maintained for up to 24 weeks.[4] Later, KARDIA-1 Phase 2 dose- trial among adults with mild-to-moderate hypertension reported that Zilebesiran significantly decreased 24-hour mean ambulatory systolic BP compared with placebo.[5] Later it progressed through KARDIA-2 and KARDIA-3 trials.[6-7]

Safety profile in these early studies was favourable. There were mild injection-site reactions and low rates of renal, hepatic or electrolyte disturbances as per one systematic review and meta analysis done by Singh et al. Though there is a meta- analysis already done on this topic including 2 studies, the current meta- analysis

added complete results of KARDIA-1, 2 and 3 and Desai study.[4-7] KARDIA-3 trial-results, though not posted in clinicaltrials.gov, trial results are released through press release by European Society of Cardiology, which were used for the current meta-analysis.[8]

In the **KARDIA-1 trial**[5] zilebesiran monotherapy showed **sustained, dose-dependent reduction in systolic and diastolic blood pressure** after a single subcutaneous injection, **24-hour ambulatory BP monitoring confirmed consistent BP lowering throughout the dosing interval.**

KARDIA-2 trial evaluated zilebesiran as add-on therapy to single antihypertensive or placebo in patients with uncontrolled hypertension. Meaningful **reduction in blood pressure was seen.**[6]

KARDIA-3 explored the drug in patients with uncontrolled hypertension and high cardiovascular-risk on multiple antihypertensives. [7]

From a safety perspective, the available data indicated that Zilebesiran showed tolerable profile. Most adverse events are mild or moderate, non-serious and transient. Laboratory findings showed no meaningful changes in renal or hepatic function and minimal incidence of hypotension or hyperkalemia across the trials. The prospect of a twice-yearly dosing regimen may also reduce barriers of daily medication burden and non-adherence that reduce effective BP control in real-world practice.

But various knowledge gaps exist. The durability of BP reduction beyond six months, the effect on long-term cardiovascular outcomes, and the performance in diverse patient populations (like thoe with advanced CKD or varying racial/ethnic groups) still need formal demonstration. Though the mechanism is promising, real-world efficacy and cost-effectiveness in comparison with existing therapies should be evaluated.

Aim:
To systematically evaluate the **efficacy and safety of Zilebesiran in the treatment of hypertension**, synthesising evidence from the Phase 1 and Phase 2 trials, and to summarise its role in future hypertension management.

Objectives:
To know the mean reduction in systolic blood pressure(SBP), Diastolic Blood Pressure(DBP)
Adverse-event profile and tolerability of Zilebesiran.

MATERIAL AND METHODS

Study Design

A systematic review and meta analysis were conducted to evaluate the **efficacy and safety of zilebesiran** in adult patients with hypertension. The analysis included data from four main clinical trials that represent the full scope of zilebesiran's clinical development program to date:

Desai et al. (2023) – Phase 1 first-in-human dose-escalation study.4
KARDIA-1 (Bakris et al., 2024) – Phase 2 monotherapy dose-ranging trial.[5]
KARDIA-2 – Phase 2 add-on therapy trial in patients on background antihypertensives.[6]
KARDIA-3 (ESC 2025) – Phase 2 trial in high cardiovascular-risk hypertensive patients on multiple background agents.[7,8]
All four studies were evaluated for blood pressure efficacy outcomes and for safety endpoints, including incidence of adverse events (AEs), serious adverse events (SAEs), and mortality.
Efficacy was assessed in terms of reduction in office and ambulatory blood pressure monitoring(ABPM) SBP and DBP.

Eligibility Criteria:
Inclusion criteria were as follows:

Study design: Clinical trials
Observationsl studies
Single or multicentric studies
Population: Adults ≥ 18 years diagnosed with primary (essential) hypertension.
Intervention: Zilebesiran administered as subcutaneous monotherapy or in combination with standard antihypertensives.
Outcomes: Must report at least one efficacy measure (office or ambulatory systolic/diastolic blood pressure change) **and** one safety outcome (AEs, SAEs, or death).
Comparators: Placebo or background therapy.
Exclusion criteria included non-human studies, narrative reviews, pharmacokinetic-only reports, systematic review, meta-analysis and studies lacking extractable outcome data.

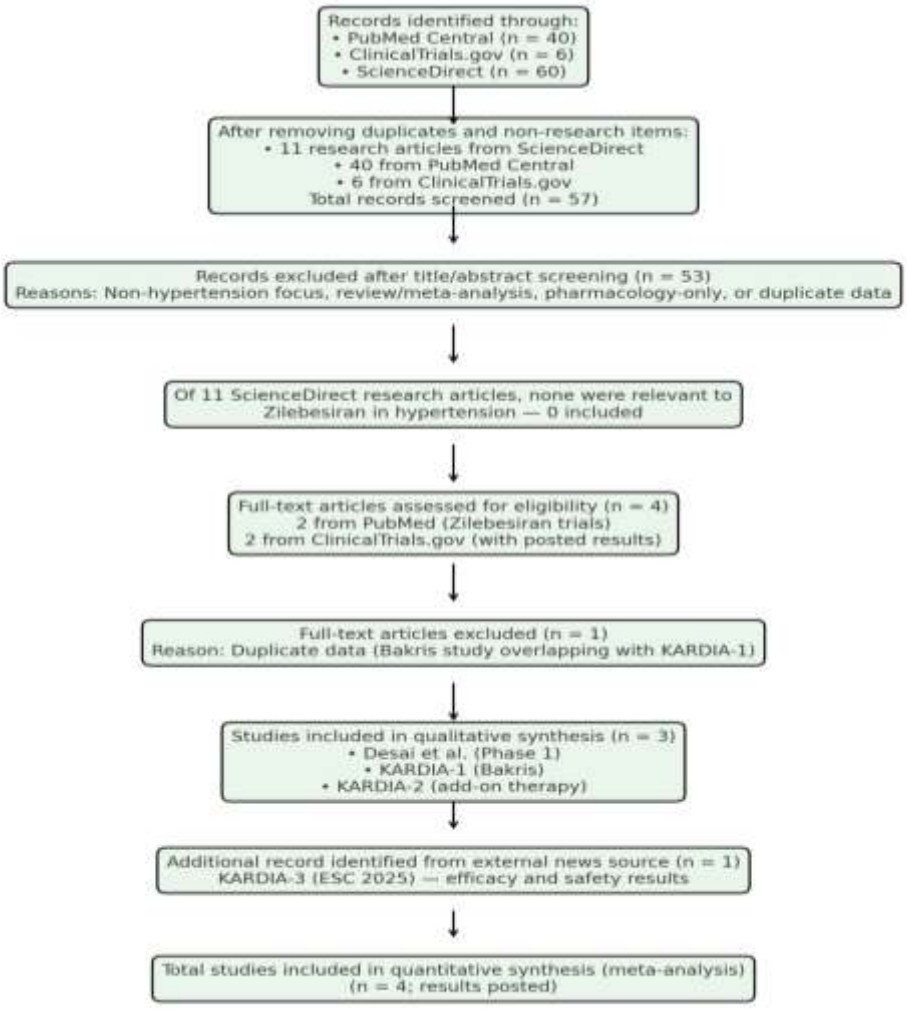
Data Sources and Search Strategy:
A comprehensive search of **PubMed Central (PMC)** and **ClinicalTrials.gov, sciencedirect** was done to identify all published and registered studies assessing zilebesiran in hypertension. Searches were done from database inception through **October 2025.** The following keywords and Boolean operators were used:

("Zilebesiran" OR "ALN-AGT01") AND ("hypertension)

Grey search was done for KARDIA-3 results and found press release from European Society of Cardiology 2025. Eligible study records from **ClinicalTrials.gov** were verified using their unique identifiers (NCT04606326, NCT04936035, NCT05103332, NCT05418119). Data were cross-referenced with published manuscripts to avoid duplication. 60 results were identified from sciencedirect after searcing for Zilebesiran and 11 results came for only research articles. None of those 11 were relevant to this meta-analysis. So none were included from sciencedirect.

RESULTS AND OBSERVATIONS:

Study Flow Chart:



Data Extraction:

Two independent reviewers extracted data using a standardized form. The following parameters were collected:

Study characteristics: author, trial last updated information, design, sample size, study phase, and intervention arms.

Patient demographics: age, sex distribution, baseline blood pressure, and background therapy.

Efficacy outcomes: change in mean office systolic BP (SBP), diastolic BP (DBP), and 24-hour ambulatory BP from baseline to follow-up.

Safety outcomes: Total AEs, SAEs, mortality, and other events like hepatic events, hyperkalaemia, hypotension, renal dysfunction, injection-site reactions, and infection-related events.

Any differences between reviewers were resolved by consensus or third-party adjudication. Where numerical values were not provided, proportions were calculated from event counts and denominators.

Data Synthesis and Statistical Analysis

For each study, proportions of patients experiencing adverse events were expressed as percentages. Mean changes in BP were extracted as continuous outcomes. A **random-effects meta-analysis** using the **DerSimonian-Laird method** was applied to estimate pooled effect sizes.
For adverse events, proportions were logit-transformed and pooled to estimate the overall event rate for:

All (non-serious) AEs
Serious AEs (SAEs)
All-cause mortality

Between-study heterogeneity was assessed using the **Cochran Q statistic** and **I^2**. Thresholds for interpretation were: *I^2 < 30% = low, 30–60% = moderate, >60% = high heterogeneity*. Forest plot is obtained using R studio.
When standard deviations (SDs) were not directly reported, they were obtained from available confidence intervals (CIs) or standard errors (SEs) using established statistical formulas. All subsequent analyses were done using these calculated SD values to ensure meaningful and consistent comparisons across studies.

Ethical Considerations:

All included studies were done according to the principles of the **Declaration of Helsinki** and approved by appropriate institutional review boards. The current meta-analysis used aggregated, publicly available data and therefore required no separate ethical approval.

RESULTS:
Demography:

Overall Zilebesiran sample ≈ 821.
Overall placebo ≈ 568 (28 + 75 + 330 + 135).
Among the four trials (Desai Part A, KARDIA-1, KARDIA-2, KARDIA-3) **821 participants** received zilebesiran. **56.5 % were male** and **43.5 % female**.
Mean Age = 58.9 years

Study / Source	Design / Phase	Masking	Phase	Sample Size	Zilebesiran n	Placebo n	Overall Mean Age (yrs)	Overall Male (%)
NCT04936035 (KARDIA-1, 150 mg Q6M)	Interventional / Phase 2	Quadruple	2	394	65 (ABPM 62)	75	56.8 ± 10.6	55.7
NCT05103332 (KARDIA-2 – Amlodipine)	Interventional / Phase 2	Quadruple	2	658	103	102	58.4 ± 10.3	58.3
NCT06272487 (KARDIA-3)	Interventional / Phase 2 (ongoing)	Quadruple	2	270	180	90	67	55
Desai et al. (2023, 10 mg)	Phase 1 Part A	Double-blind	1	12 (8 / 4)	56	28	53	62

Table 1: Baseline characteristics of included studies

Pooled results (random-effects, DerSimonian–Laird)
ABPM SBP pooled MD (zile − placebo): −6.81 mm Hg (95% CI **−10.05 to −3.57**)
Q = 20.29, tau^2 = 10.75, **I^2 = 80.3%**
Office SBP pooled MD (zile − placebo): −6.60 mm Hg (95% CI **−10.30 to −2.90**)
Q = 24.14, tau^2 = 14.50, **I^2 = 83.4%**
Both pooled ABPM and office estimates showed meaningful reduction in SBP with zilebesiran vs placebo (~6–7 mm Hg). The 95% CIs exclude 0, so pooled effects are statistically significant

.

Efficacy of Zilebesiran in reducing SBP and DBP:

Study / Source	Dose / Background	Measurement Type	SBP Change (Mean ± SD or LSM diff ± SE mm Hg)	DBP Change (Mean ± SD or LSM diff ± SE mm Hg)
KARDIA-1 (NCT04936035)	150 mg Q6M	ABPM	−4.8 ± 7.2	−4.8 ± 7.2
		Office	−4.1 ± 9.1	−4.1 ± 9.1
	300 mg Q6M	ABPM	−6.1 ± 7.3	−6.1 ± 7.3
		Office	−6.8 ± 9.2	−6.8 ± 9.2
	300 mg Q3M	ABPM	−6.3 ± 7.2	−6.3 ± 7.2
		Office	−8.2 ± 9.1	−8.2 ± 9.1
	600 mg Q6M	ABPM	−6.3 ± 7.2	−6.3 ± 7.2
		Office	−5.0 ± 9.1	−5.0 ± 9.1
KARDIA-2 (NCT05103332)	Amlodipine add-on to Zilebesiran	ABPM	−9.0 ± 12.8	−5.7 ± 6.9
		Office	−12.6 ± 11.9	−6.7 ± 7.9
	Olmesartan add-on to Zilebesiran	ABPM	−8.3 ± 13.9	−4.3 ± 8.2
		Office	−12.4 ± 15.5	−7.1 ± 8.8
	Indapamide add-on to Zilebesiran	ABPM	−16.1 ± 12.7	−8.0 ± 8.1
		Office	−15.5 ± 14.0	−7.8 ± 8.8
KARDIA-3 (NCT06272487)	300 mg Q6M	ABPM	−5.5 (95 % CI −9.4 to −1.5) → (SE ≈ 2.0	NR
		Office	−3.9 (95 % CI −8.5 to 0.7) → SE ≈ 2.35	NR
	600 mg Q6M	ABPM	−7.4 (95 % CI −11.3 to −3.4) → SE ≈ 2.0	NR
		Office	−3.6 (95 % CI −8.2 to 1.0) → SE ≈ 2.35	NR
Desai et al. (2023, NEJM Phase 1)	Placebo	Office	−5.7	−5.7
	200 mg	Office	−12.5	−5.4
	400 mg	Office	−9.3	−5.4
	800 mg	Office	−22.5	−10.8
	Mean (200–800 mg)	Office	−14.8 ± 6.9	NR

NR: Not reported
6M: 6 months, 3M; 3 months
Table 2: SBP and DBP changes seen at varying doses of Zilebesiran at 3 months and 6 months

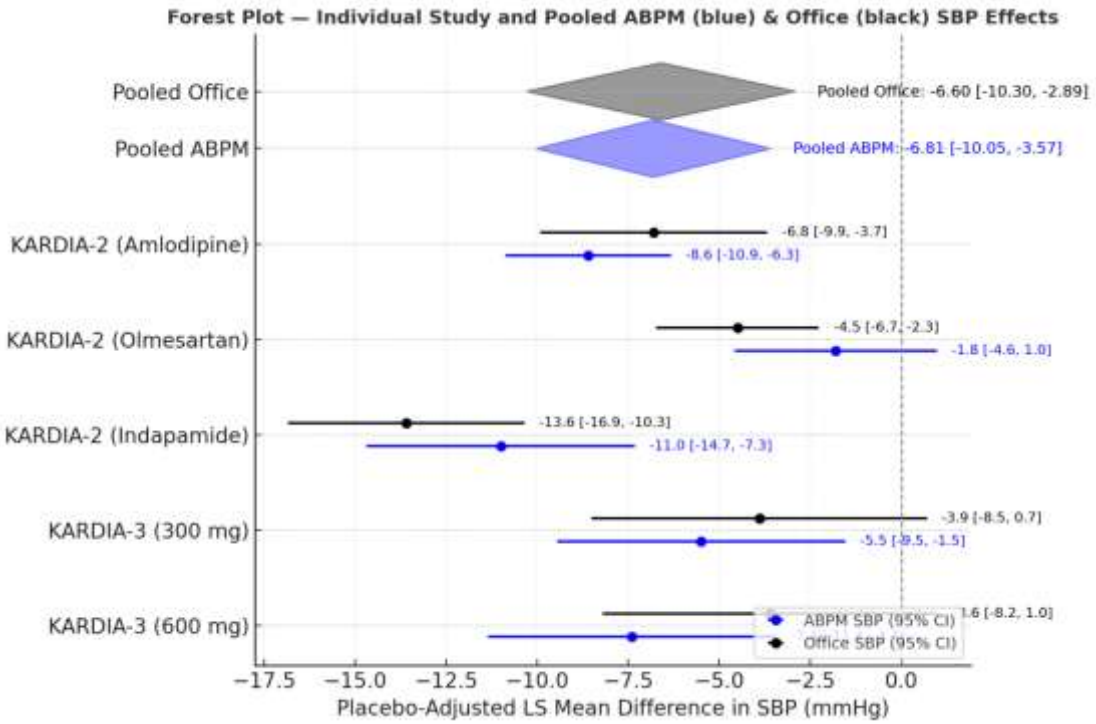


Image 1: Forest plot of Mean change in SBP among all studies at varying doses and varying medication combinations. (Both office and ABPM)

Heterogeneity is high ($I^2 \approx 80–83\%$). Magnitude of effect varies substantially across cohort, which could be due to differences in:
Background antihypertensive therapy (amlodipine/olmesartan/indapamide cohorts),
Dose regimen (KARDIA-1 doses vs KARDIA-3 doses),
Endpoint definitions and censoring (MMRM vs censored analyses),
Patient baseline characteristics (e.g., KARDIA-3 older, higher comorbidity).

CHANGE IN DBP: Kardia-3 is excluded.
Desai- results excluded as only mean is available.
Pooled Effects (Random-Effects Model)

Measurement	Pooled ΔDBP (mm Hg)	95 % CI	I^2 (Heterogeneity)
ABPM (24 h)	−5.80	[−6.61 , −4.98]	≈ 38 %
Office	−6.57	[−7.54 , −5.59]	≈ 41 %

plot showing pooled office and ABPM DBP
Ambulatory DBP (24-hour):
The pooled random-effects mean change was **−5.8 mm Hg (95 % CI −6.6 to −5.0)**, with moderate heterogeneity (**$I^2 \approx 38$ %**).
This indicates consistent reduction in DBP measured by 24-hour ABPM across varying doses and backgrounds.
Office DBP:
The pooled random-effects mean change was **−6.6 mm Hg (95 % CI −7.5 to −5.6)**, also with modest heterogeneity (**$I^2 \approx 41$ %**).
Office BP readings showed slightly greater average reduction than ABPM.

In **KARDIA-1**, DBP lowering showed maximal effect near the 300 mg and 600 mg regimens.
In **KARDIA-2**, when added to standard agents (amlodipine, olmesartan, indapamide), zilebesiran further reduced DBP by around **4–8 mm Hg**.

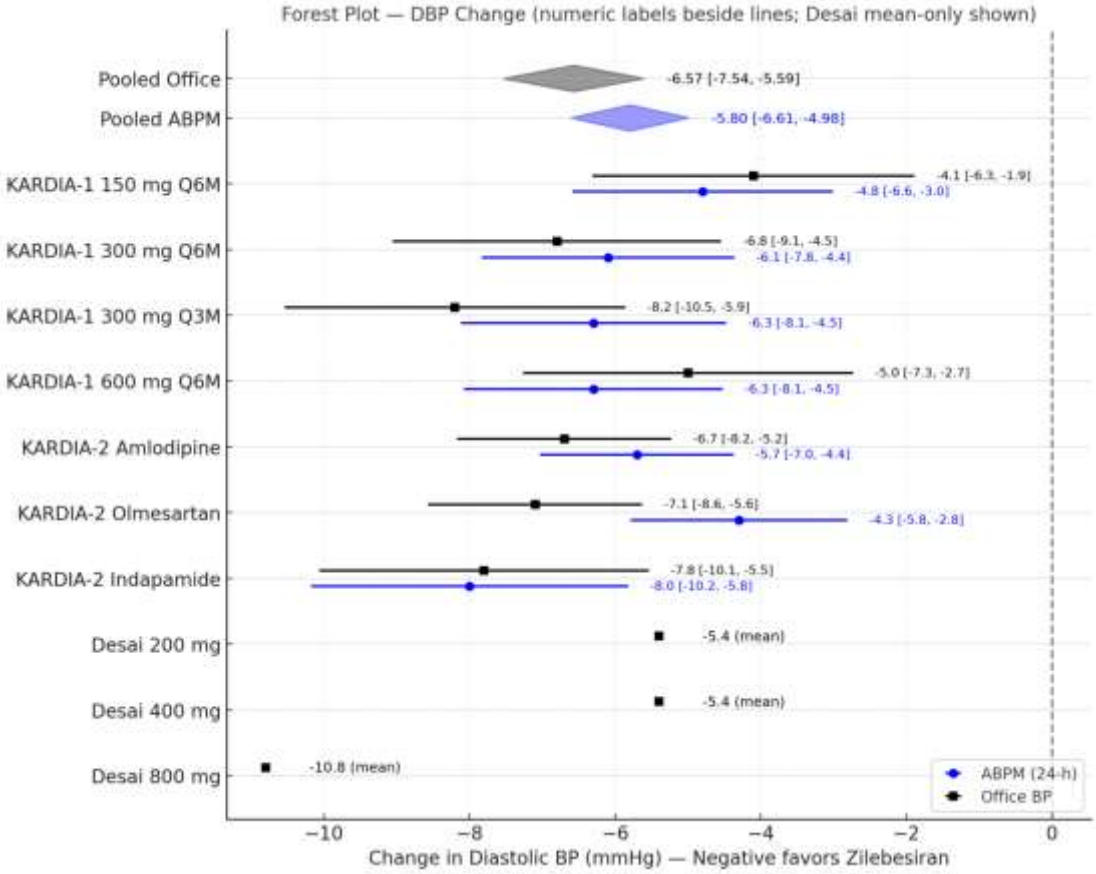
Desai et al. (phase 1) confirmed dose-related office DBP lowering up to −10.8 mm Hg at 800 mg.
A pooled DBP reduction of around **6 mm Hg** is clinically meaningful.

Image 4: Forest plot showing pooled office and ABPM DBP

Ambulatory DBP (24-hour):

The pooled random-effects mean change was **−5.8 mm Hg (95 % CI −6.6 to −5.0)**, with moderate heterogeneity (**$I^2 \approx 38$ %**).

This indicates consistent reduction in DBP me



asured by 24-

Adverse events: They are divided as overall non serious adverse events, serious adverse events and mortality.

Study	Hepatic Event	SAE (%)	Death (%)	Headache (%)	Injection Site (%)	URTI / COVID-19 (%)	Hypotension (%)	Hyperkalaemia (%)	Renal (AKI etc.) (%)	Cardiac Events (%)
Desai (Part A, single-dose)	2	2	0	18	9	7	0	0	0	0
KARDIA-1	0	7.9	1.3	5.5	10.7	5.5%/8 %	1.3 (orthostatic)	6.7	0	1.3
KARDIA-2	2.1 (ALT/AST ↑)	4.7	0.47	9.5 (max cohort)	4.7	7.6 %	0.68	6.8	1.6	0.68
KARDIA-3	Not reported	3.8	Not reported	Not reported	Not reported	Not reported	< 5 (mild / transient)	< 5 (mild / transient)	< 5 (mild / transient)	Not reported

Table 3: Adverse events reported in included studies
Most common AEs among zilebesiran program were:

Injection-site reactions (≈ 5–11 %)

Headache / dizziness (≈ 5–10 %)
COVID-19 or URTI (≈ 6–8 %)
Hyperkalaemia (≈ 5–7 %)
Serious adverse events (SAE) ranged from **2–8 %**, highest in **KARDIA-1 600 mg Q6M**.
Hepatic enzyme elevations were uncommon (≤ 2 %).
Renal and cardiac AEs were rare (≤ 2 %).
Deaths: only one reported case (1.3 %, KARDIA-1 300 mg Q3M).
In KARDIA-3, **hypotension, hyperkalaemia, and kidney dysfunction** were mostly **mild, non-serious, and transient**.
Overall (non-serious) AEs → *Pooled rate = 23.7 % (I^2 = 68 %)*

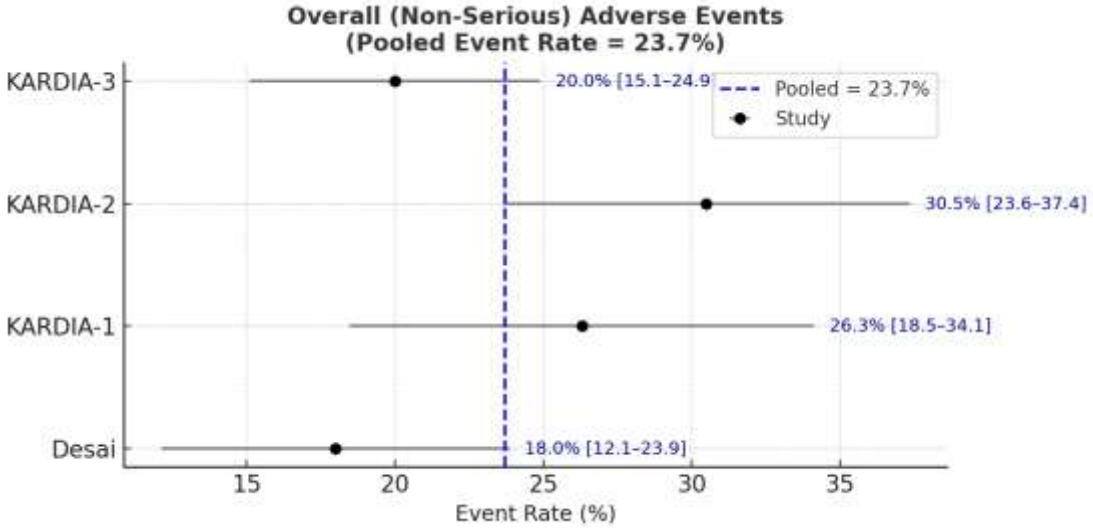


Image 5: Forest plot showing overall adverse events

Serious AEs (SAEs) → *Pooled rate = 4.6 % (I^2 = 73 %)*

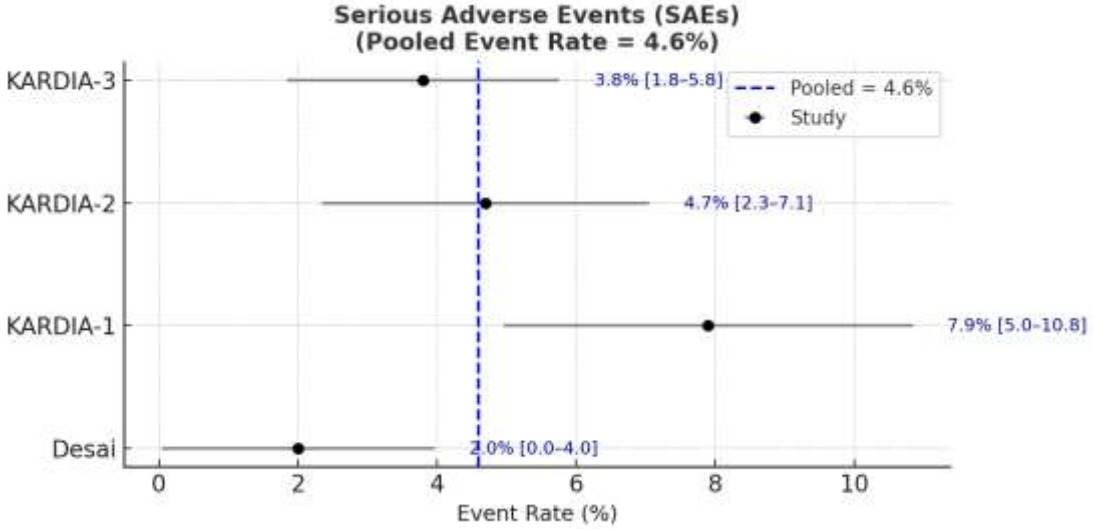


Image 6: Forest plot showing serious adverse events

All-cause mortality → *Pooled rate = 0.4 % (I^2 = 73 %)*

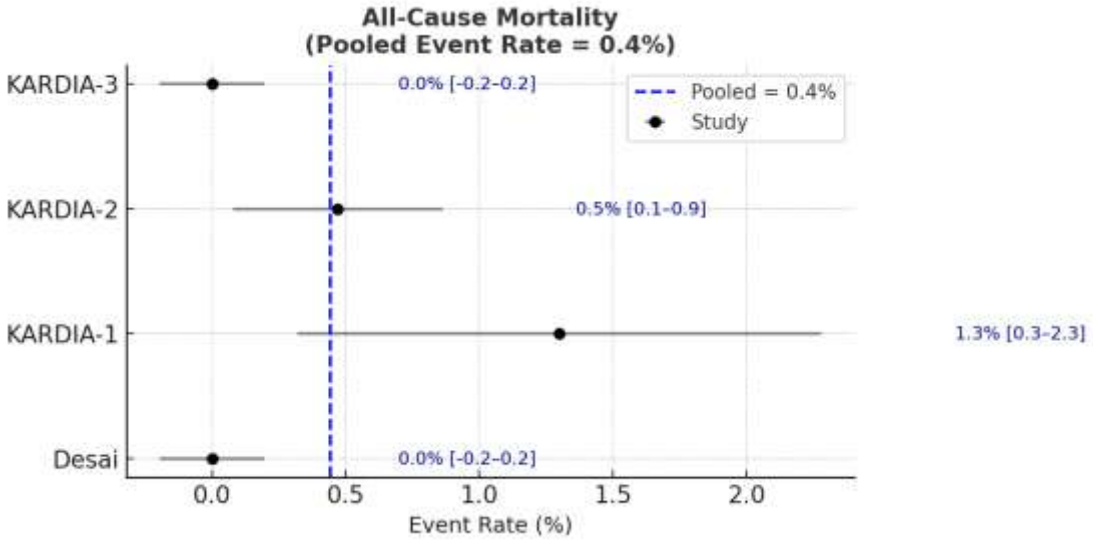


Image 7: Forest plot showing pooled mortality.

DISCUSSION

Our meta-analysis of four main trials investigating Zilebesiran for hypertension provided clarity into its dual profile of efficacy and safety in adult hypertensive populations. Overall (non-serious) adverse event (AE) rates pooled to around ~23.7 %, serious adverse event (SAE) rates were ~4.6 % and all-cause mortality extremely low at ~0.4 %. There was moderate to high heterogeneity ($I^2 \approx$ 68-73 %), these findings align with the trial-level individual results and support several key points.

In the Phase 1 trial,4 single doses of ≥ 200 mg led to decreases in 24-hour systolic BP of >10 mm Hg and diastolic BP of >5 mm Hg sustained up to 24 weeks or 6 months. In the Phase 2 monotherapy study (KARDIA-1)5 reduction in 24-hour mean ambulatory SBP ranged from −14.1 to −16.7 mm Hg at Month 3 and sustained to Month 6. In the add-on therapy study (KARDIA-2),6 a single dose caused placebo-adjusted −12.1 mm Hg reduction in 24-hour ambulatory SBP at Month 3 when added to a thiazide-like diuretic (indapamide), with similar smaller reduction when added to other agents. Zilebesiran may bridge the gap for patients whose hypertension is uncontrolled despite standard oral therapies.

Safety profile emerges as favourable in the limited follow-up window and sample size of available trials. Injection-site reactions, headache/dizziness and hyperkalaemia were among the more frequent AEs (≈5-10 % in some cohorts), and hepatic, renal or cardiac events remained uncommon (<2 % in most studies).
In Phase 1 trial no severe hypotension, hyperkalaemia requiring intervention or worsening renal function events were reported. In KARDIA-26, there were slightly more rates of hyperkalaemia (5.5 %), hypotension (4.3 %) and acute kidney injury (4.9 %) in the Zilebesiran arms compared with placebo. The low pooled mortality rate suggests no evident signal of excess risk in these studies.

The dosing schedule of Zilebesiran— once every 3 or 6 months—may provide paradigm shift in hypertension management. The durability of BP reduction after a single subcutaneous injection addresses the long-standing adherence problem to daily oral therapy. Durability along with acceptable tolerability shows its role as a foundational or adjunctive therapy especially in patients with suboptimal adherence or resistant hypertension.

Limitations:
Moderate-to-high heterogeneity suggests variation in study populations, background therapies, dosing regimens, and durations which temper generalizability.
Sample sizes and durations are relatively small—most data cover up to 6 months; So, long-term safety, durability of effect beyond six or twelve months, cardiovascular outcome benefits and performance in high-risk subpopulations (e.g., advanced CKD, severe hypertension, diverse ethnic groups) are to be established.

Longer-term effects of RNA-interference therapeutics in hypertensive populations are largely unknown.
Ccost-effectiveness, real-world implementation and comparison with established therapies must be addressed.

In summary, our meta-analysis affirms that Zilebesiran shows a strong antihypertensive effect with a safety profile comparable to many newer agents, and its infrequent dosing provides practical advantages for adherence. But it remains an investigational therapy and should be positioned accordingly in clinical algorithms

only after phase 3 outcome data are available. Zenith phase-3 clinical trial is an upcoming one assessing the efficacy and safety further, which will be conducted on around 11000 patients with hypertension.

CONCLUSION

Zilebesiran is a promising novel RNA-interference therapy for hypertension, providing meaningful blood-pressure reduction. It showed acceptable short-term safety profile and an innovative dosing regimen. More longer-term outcome trials helps in defining its role in routine clinical practice.

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