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# RNA Interference Therapeutics in Cardiology: Focus on Zilebesiran and Olpasiran

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## Abstract

Background: RNA interference (RNAi) therapeutics represent a novel approach in cardiovascular medicine, enabling durable and selective inhibition of disease-relevant proteins.

Objective: This systematic review aimed to evaluate the efficacy, safety, and clinical potential of two leading RNAi therapeutics-zilebesiran for hypertension and olpasiran for elevated lipoprotein(a).

Methods: We systematically searched PubMed, Embase, Cochrane Library, and Google Scholar for articles published between January 2018 and June 2025 using the keywords: "RNA interference", "siRNA", "zilebesiran", "olpasiran", "hypertension", and "lipoprotein(a)". Eligible studies included randomized controlled trials (RCTs), systematic reviews, meta-analyses, narrative reviews, and preclinical mechanistic studies in English. Two independent reviewers screened records and extracted data. A total of 20 studies were included: 6 RCTs (Phase 1–2), 5 systematic reviews/meta-analyses, 8 narrative reviews, and 1 preclinical/mechanistic study.

Results: Zilebesiran demonstrated sustained blood pressure reduction up to six months with an acceptable safety profile, while olpasiran produced profound and durable decreases in lipoprotein(a) levels, exceeding 90% in phase 2 trials. Safety considerations include long-term tolerability, off-target effects, and accessibility. Emerging reversal agents, such as REVERSIR, may enhance therapeutic safety.

Conclusions: RNAi therapeutics hold significant promise in cardiovascular medicine, with zilebesiran and olpasiran addressing major unmet needs. Ongoing large-scale outcome trials are essential to define their role in clinical practice.

**Keywords (EN):** RNA interference; siRNA; zilebesiran; olpasiran; hypertension; lipoprotein(a); cardiovascular disease.
**Słowa kluczowe (PL):** interferencja RNA; siRNA; zilebesiran; olpasiran; nadciśnienie tętnicze; lipoproteina(a); choroby sercowo-naczyniowe.

## Materials and Methods

### Study Design

This is a systematic review evaluating RNA interference (RNAi) therapeutics in cardiology, focusing on zilebesiran and olpasiran, including preclinical studies, clinical trials, systematic reviews, and meta-analyses.

### Literature Search

PubMed, Embase, Cochrane Library, and Google Scholar were searched for publications from January 2018 to June 2025 using keywords and MeSH terms: “RNA interference”, “siRNA”, “zilebesiran”, “olpasiran”, “hypertension”, “lipoprotein(a)”, and “cardiovascular disease”. Only English-language articles were included. Reference lists of relevant studies were also screened.

### Inclusion and Exclusion Criteria

**Inclusion**: RCTs (Phase 1–2), early-phase clinical trials, systematic reviews, meta-analyses, narrative reviews with mechanistic insights, and preclinical studies.

**Exclusion**: Non-English articles, case reports, conference abstracts, editorials, or studies lacking relevant outcomes.

### Study Selection

Two independent reviewers screened titles and abstracts, followed by full-text assessment. Disagreements were resolved by discussion and consensus.

**Selection Summary**
Out of 120 records identified, 95 were excluded during title/abstract screening. Full texts of 25 articles were assessed, 5 were excluded, leaving 20 studies included in the qualitative synthesis: 6 RCTs, 5 systematic reviews/meta-analyses, 8 narrative reviews, and 1 preclinical/mechanistic study.

### Data Extraction and Quality Assessment

Data on study design, population, intervention, comparator, outcomes, follow-up, and adverse events were extracted. RCTs were assessed for risk of bias; systematic reviews for comprehensiveness; preclinical studies for experimental rigor.

### Data Synthesis

Results were synthesized qualitatively by agent (zilebesiran vs olpasiran) and outcome type (efficacy, safety, mechanistic insights), with discussion of comparative perspectives and clinical implications.

## Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for substantial healthcare burden and premature death. Despite advances in pharmacotherapy for hypertension, dyslipidemia, and other modifiable risk factors, residual cardiovascular risk persists, highlighting the urgent need for innovative treatment strategies. Conventional therapies, including ACE inhibitors, beta-blockers, statins, and PCSK9 inhibitors, have improved outcomes, yet challenges such as suboptimal adherence, drug resistance, and incomplete risk factor control remain prevalent. RNA interference (RNAi) therapeutics represent a novel, gene-silencing approach that selectively degrades disease-relevant messenger RNA (mRNA), preventing translation of pathogenic proteins. By enabling long-lasting biological effects with infrequent dosing, RNAi has the potential to improve adherence, reduce polypharmacy, and address unmet therapeutic needs in cardiovascular medicine. Among RNAi agents, zilebesiran, targeting angiotensinogen for hypertension, and olpasiran, targeting apolipoprotein(a) to lower lipoprotein(a) levels, exemplify the promise of this approach. While early-phase clinical trials and preclinical studies indicate robust efficacy and acceptable safety profiles, a comprehensive systematic evaluation is lacking. Existing reviews are largely narrative or focused on single trials, providing limited guidance on clinical implementation, comparative effectiveness, and long-term outcomes. Furthermore, uncertainties remain regarding optimal patient selection, mechanistic effects, and integration into multimodal cardiovascular care.

## Research Question (PICO):

Population: Adults with hypertension or elevated lipoprotein(a)

Intervention: RNA interference therapeutics – zilebesiran (targeting angiotensinogen) or olpasiran (targeting apolipoprotein(a))

Comparison: Standard therapy or placebo

Outcome: Blood pressure reduction, lipoprotein(a) lowering, safety profile, cardiovascular risk reduction, adherence

Hypothesis: RNAi therapeutics (zilebesiran and olpasiran) are effective and safe interventions for controlling blood pressure and lipoprotein(a) in adults with cardiovascular disease.

Objective of the Review: The aim of this systematic review is to evaluate current evidence on the efficacy, safety, mechanistic rationale, and clinical potential of zilebesiran and olpasiran, providing a comprehensive synthesis to inform future research, clinical practice, and precision cardiovascular medicine strategies.

## RNA Interference in Cardiovascular Medicine

RNAi therapy capitalizes on the ability of siRNA molecules to engage the RNA-induced silencing complex (RISC), which guides degradation of complementary mRNA targets. The technology has already yielded approved drugs in rare diseases such as hereditary transthyretin amyloidosis, establishing proof of concept for clinical utility.

In cardiology, siRNA therapies offer an opportunity to address key unmet needs:

1. Long-term suppression of hypertensive mechanisms through targeting angiotensinogen.
2. Reduction of lipoprotein(a), a causal risk factor for atherosclerosis not modifiable by standard therapies.
3. Improved adherence due to infrequent dosing intervals ranging from every 3 months to annually.

Challenges include delivery efficiency, off-target effects, long-term safety and cost-effectiveness, but early cardiovascular trials provide encouraging results.

**Zilebesiran: Targeting Hypertension**

Hypertension remains the leading modifiable risk factor for CVD worldwide. Despite the availability of multiple drug classes, nearly half of patients fail to achieve optimal blood pressure control. Adherence issues and the complexity of polypharmacy are major contributors. Zilebesiran provides an innovative solution by targeting angiotensinogen, the substrate for renin, thereby inhibiting the renin-angiotensin-aldosterone system (RAAS) at its origin. A landmark first-in-human trial demonstrated that a single subcutaneous injection produced dose-dependent reductions in systolic blood pressure lasting up to six months [1]. The KARDIA-1 trial confirmed robust blood pressure reduction in patients with mild-to-moderate hypertension [2]. The subsequent KARDIA-2 trial evaluated zilebesiran as add-on therapy in patients with uncontrolled hypertension despite background medications, again showing significant improvements [3]. Beyond efficacy, safety has been a central consideration. Systematic reviews have reported generally favorable tolerability, though questions remain regarding long-term effects and rare adverse events [4];[5];[6]. Importantly, novel REVERSIR technology has been described as capable of reversing zilebesiran's effects, offering a potential safety valve in cases of severe hypotension or overdose [10]. Narrative reviews emphasize the paradigm-shifting nature of zilebesiran, highlighting its potential role in both primary therapy and resistant hypertension management [7];[8];[9]. Overall, the evidence suggests zilebesiran could redefine hypertension control strategies.

**Olpasiran: Targeting Lipoprotein(a)**

Elevated lipoprotein(a) [Lp(a)] has been identified as a causal, genetically determined, and independent risk factor for atherosclerotic cardiovascular disease (ASCVD). Traditional lipid-lowering therapies, including statins and PCSK9 inhibitors, have little to no impact on Lp(a) levels, leaving a significant residual risk unaddressed. Olpasiran, a GalNAc-conjugated siRNA, selectively silences hepatic apolipoprotein(a) mRNA, reducing Lp(a) synthesis. Preclinical development and early-phase clinical trials reported profound Lp(a) reductions exceeding 90% [12];[14]. The phase 2 OCEAN(a)-DOSE trial demonstrated sustained reductions up to 95% with quarterly or biannual dosing, with an acceptable safety profile [13]. Systematic reviews and meta-analyses confirm that siRNA-based therapies produce greater and more durable reductions in Lp(a) than antisense oligonucleotides or other approaches [15];[16]. Additional analyses discuss the implications of olpasiran as a precision medicine tool, particularly for individuals with genetically elevated Lp(a) [19]. Health economic evaluations emphasize the potential cost-effectiveness of widespread Lp(a)-lowering interventions, although large-scale outcome data are essential [20]. Reviews stress that while surrogate endpoint data are compelling, clinical outcome trials will be critical in defining the ultimate role of olpasiran in secondary prevention [17];[18].

## Comparative Insights and Future Perspectives

Taken together, zilebesiran and olpasiran demonstrate the breadth of RNAi's applicability in cardiovascular medicine. Zilebesiran targets hypertension-arguably the most prevalent modifiable risk factor for CVD-while olpasiran addresses residual risk through Lp(a) lowering, an area of increasing recognition. Both therapies offer infrequent dosing schedules, potentially transforming adherence and long-term risk reduction.However, challenges remain. Long-term safety data are limited, and the risk of off-target effects or immune responses is not fully understood. Moreover, the cost of RNAi therapies is likely to be substantial, raising questions of accessibility and equity. Health technology assessments underscore the importance of economic evaluation early in development [20].

Future perspectives include:

1. Completion of phase 3 outcome trials to determine whether biomarker reductions translate into lower rates of myocardial infarction, stroke, and cardiovascular death.
2. Exploration of combination strategies integrating RNAi therapies with established agents such as statins, ACE inhibitors, and SGLT2 inhibitors.
3. Development of reversal agents to enhance safety.
4. Real-world implementation studies assessing adherence, safety, and cost-effectiveness outside clinical trials.

If efficacy in outcome trials is confirmed, zilebesiran and olpasiran could inaugurate a new era of precision, long-acting cardiovascular therapeutics.

## Advanced Mechanistic Insights and Emerging RNAi Strategies

Recent mechanistic studies have begun to elucidate how siRNA therapeutics can produce sustained cardiovascular benefits. Zilebesiran's inhibition of angiotensinogen leads to a marked reduction in angiotensin II levels, which not only lowers blood pressure but may also confer additional end-organ protection, including renal and vascular benefits. Preclinical studies indicate that chronic suppression of angiotensinogen may attenuate vascular remodeling and reduce cardiac hypertrophy in hypertensive models [10]. Similarly, olpasiran-mediated suppression of apolipoprotein(a) mRNA reduces Lp(a) levels dramatically, which is expected to decrease pro-inflammatory oxidized phospholipid burden in atherosclerotic plaques. Emerging evidence suggests that Lp(a) reduction may stabilize vulnerable plaques and improve endothelial function, although long-term outcome studies are needed to confirm these effects.

## Integration into Multi-Modal Cardiovascular Therapy

RNAi therapies are unlikely to be stand-alone treatments for most patients. Zilebesiran and olpasiran are envisioned as part of multimodal therapeutic strategies:

- Zilebesiran may complement existing antihypertensives, potentially reducing the number of daily medications required.
- Olpasiran could be combined with statins, PCSK9 inhibitors, and lifestyle interventions to target residual cardiovascular risk in high-risk populations.

Integration strategies will require careful patient selection, monitoring, and possibly biomarker-guided dosing to maximize efficacy and safety.

### Regulatory, Economic, and Ethical Considerations

As these novel therapies move closer to widespread use, several regulatory and health system issues must be addressed. RNAi therapies are costly to develop and manufacture, which may limit accessibility. Health technology assessments emphasize the need for cost-effectiveness modeling, particularly in secondary prevention populations [20]. Ethical considerations include equitable access and informed consent regarding long-term gene-silencing interventions.

## Results

### Study Characteristics

A total of 20 studies were included: 6 randomized controlled trials (Phase 1–2), 5 systematic reviews/meta-analyses, 8 narrative reviews, and 1 preclinical/mechanistic study. Studies focused on zilebesiran (targeting angiotensinogen for hypertension) and olpasiran (targeting apolipoprotein(a) to reduce lipoprotein(a)). Populations included adults with hypertension, elevated Lp(a), or high residual cardiovascular risk. Follow-up durations ranged from single-dose studies up to 12 months in early-phase trials.

### Efficacy of Zilebesiran

Zilebesiran demonstrated robust and sustained reductions in systolic and diastolic blood pressure across all included trials. Early-phase and pivotal trials reported dose-dependent effects, with reductions lasting up to six months following a single subcutaneous injection. Add-on therapy in patients with inadequately controlled hypertension showed additional improvements compared to background therapy alone. Mechanistic studies suggest that angiotensinogen inhibition not only lowers blood pressure but may also reduce vascular remodeling and cardiac hypertrophy.

### Efficacy of Olpasiran

Olpasiran effectively reduced Lp(a) levels by up to 95%, with sustained effects over 3–6 months dosing intervals. Clinical trials confirmed both single-dose and repeated-dose efficacy in diverse populations. Evidence from systematic reviews and meta-analyses indicated that RNAi therapeutics provide greater and more durable Lp(a) reductions compared to antisense oligonucleotides or conventional lipid-lowering therapies. Mechanistic insights suggest potential stabilization of atherosclerotic plaques and reduction of pro-inflammatory oxidized phospholipids, although long-term outcome data are not yet available.

### Safety and Tolerability

Both RNAi agents were generally well tolerated. Most adverse events were mild to moderate and included injection-site reactions or transient laboratory abnormalities. No serious safety signals were reported in the early-phase trials. Emerging reversal strategies, such as REVERSIR for zilebesiran, offer an additional safety measure in the event of hypotension or overdose.

### Comparative Insights

Zilebesiran and olpasiran target distinct cardiovascular risk pathways: hypertension and elevated Lp(a), respectively. Both offer infrequent dosing, which may improve adherence and reduce polypharmacy. However, long-term safety, off-target effects, and cost-effectiveness remain to be fully evaluated. The included studies highlight the potential of these RNAi therapeutics as complementary agents to standard care.

### Research Gaps

Current evidence is limited by small sample sizes, short follow-up periods, and the early phase of clinical development. Outcome trials assessing hard cardiovascular endpoints, such as myocardial infarction, stroke, and mortality, are ongoing. Additional studies are needed to evaluate combination therapies, patient selection, and long-term safety in real-world populations.

## Discussion

### Summary of Findings

This systematic review highlights the therapeutic potential of RNA interference (RNAi) agents, zilebesiran and olpasiran, in cardiovascular medicine. Zilebesiran consistently demonstrated sustained blood pressure reductions in adults with hypertension, while olpasiran markedly decreased lipoprotein(a) levels, a genetically determined risk factor not adequately addressed by conventional therapies. Both therapies offer infrequent dosing, potentially improving adherence and reducing pill burden. Mechanistic studies further suggest additional benefits, such as attenuation of vascular remodeling and stabilization of atherosclerotic plaques.

### Comparison with Existing Literature

The results of this review align with previous narrative reviews and early-phase studies emphasizing the promise of RNAi therapeutics in precision cardiology. While prior work primarily focused on single-agent efficacy, our synthesis integrates preclinical, early-phase, and systematic review evidence, providing a more comprehensive understanding of efficacy, safety, and mechanistic rationale. Notably, this review also highlights the role of reversal strategies, such as REVERSIR, which have been less emphasized in earlier literature but are critical for safety and therapeutic flexibility.

### Clinical Implications

RNAi therapeutics have the potential to complement existing cardiovascular treatments by targeting previously unmodifiable risk factors. Zilebesiran may be particularly beneficial in patients with resistant or inadequately controlled hypertension, while olpasiran could address residual cardiovascular risk in individuals with elevated Lp(a). The infrequent dosing schedules may improve adherence, simplify polypharmacy, and enhance long-term cardiovascular outcomes. Integration into multimodal therapy, including statins, ACE inhibitors, and lifestyle interventions, may optimize patient benefit.

Limitations

Several limitations should be considered when interpreting these findings:

1. Study Size and Duration: Most included trials were early-phase studies with small sample sizes and relatively short follow-up periods.

2. Outcome Measures: Hard clinical endpoints such as myocardial infarction, stroke, and mortality are not yet available; most evidence is based on surrogate markers (blood pressure and Lp(a) reduction).

3. Heterogeneity: Variability in study populations, dosing regimens, and trial designs may limit direct comparability.

4. Long-term Safety: Limited long-term data exist regarding off-target effects, immunogenicity, and rare adverse events.

5. Cost and Access: High development and manufacturing costs may restrict widespread implementation, raising ethical and health equity considerations.

**Future Research Directions**

Key areas for future investigation include:

**Long-term cardiovascular outcomes:** Large, multicenter randomized trials are needed to determine the impact of zilebesiran and olpasiran on myocardial infarction, stroke, and mortality.
**Combination therapy optimization:** Studies evaluating RNAi agents alongside conventional cardiovascular therapies could clarify synergistic effects.
**Personalized medicine approaches:** Genetic and biomarker profiling may help identify patients most likely to benefit from RNAi therapies.
**Safety and reversibility:** Ongoing research on reversal agents (like REVERSIR for zilebesiran) will enhance safety and expand therapeutic flexibility.

These research directions underscore the potential for RNAi therapeutics to become a transformative element of precision cardiovascular medicine.

**Conclusion**

RNA interference therapeutics, exemplified by zilebesiran and olpasiran, represent a paradigm shift in cardiovascular medicine, offering highly specific, durable, and potentially transformative interventions for two of the most significant residual risk factors: hypertension and elevated lipoprotein(a). Clinical trials and systematic reviews have demonstrated that zilebesiran can achieve sustained reductions in blood pressure by targeting angiotensinogen, while olpasiran produces profound and durable decreases in Lp(a), a genetically determined atherogenic lipoprotein. These therapies offer the advantage of infrequent dosing, which may improve adherence, reduce pill burden, and ultimately enhance long-term cardiovascular outcomes. Beyond efficacy, these RNAi agents introduce novel considerations regarding safety, reversibility, and long-term organ protection. Mechanistic studies suggest that

zilebesiran may mitigate vascular remodeling and cardiac hypertrophy, while olpasiran has the potential to stabilize atherosclerotic plaques and reduce inflammatory burden, though large-scale outcome trials are still needed to confirm these benefits. The integration of RNAi therapies into standard cardiovascular care offers an unprecedented opportunity for precision medicine. Patients with resistant hypertension, elevated Lp(a), or high residual cardiovascular risk could particularly benefit from such approaches. However, challenges remain, including regulatory approval, cost-effectiveness, equitable access, and ethical considerations related to long-term gene-silencing therapies. Health system planning and real-world studies will be critical to ensure safe and effective implementation. Looking ahead, the next decade will likely be defined by outcome trials, combination therapy studies, and personalized approaches that identify patients most likely to benefit. Additionally, the development of reversal agents such as REVERSIR may enhance safety and therapeutic flexibility, paving the way for broader clinical adoption. In conclusion, zilebesiran and olpasiran exemplify the transformative potential of RNA interference in cardiology. By directly targeting the molecular drivers of disease, these therapies have the capacity to redefine the prevention and management of cardiovascular disease, offering hope for more durable, effective, and personalized interventions. Their continued development and rigorous evaluation will determine whether RNAi can transition from an innovative scientific breakthrough to a cornerstone of cardiovascular therapy in the years to come.

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