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Decoding the efficacy and safety profiles of anti-hypertensive agents by targeting RAAS: A systematic review and meta-analysis of clinical trials

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ABSTRACT

Introduction: This study reviews the efficacy and safety of angiotensin receptor neprilysin inhibitor (ARNI), nonsteroidal mineralocorticoid receptor antagonists (NMRA), brain rennin-angiotensin system (RAS) therapy, and ribonucleic acid (RNA)-based therapy with evaluating systolic blood pressure and diastolic blood pressure control as well safety by counting adverse events.

Methods: Risk of Bias 2.0 were used for quality appraisal and RevMan 5.4 was applied for the meta-analysis.

Results: From five databases, 20 articles were selected for review. Six high-risk and fourteen low-risk studies. ARNI and RNA-based therapies improved BP regulation, while NMRA and brain RAS were less effective in managing high blood pressure. In terms of safety, NMRA and RNA-based therapies had fewer adverse events, whereas ARNI and brain RAS had more AEs compared to their control groups.

Conclusion: RNA-based therapy outperforms the four antihypertensive drugs studied in terms of efficacy and safety, underscoring its potential as the leading option and justifying further research.

Keywords: antihypertensive, angiotensin receptor neprilysin inhibitor, nonsteroidal mineralocorticoid receptor antagonist, brain renin-angiotensin system therapy, RNA-based therapy

INTRODUCTION

Hypertension is considered the most important risk factor of cardiovascular disease (CVD) and has remained a public health problem with high global mortality and morbidity. With about one billion adults already afflicted with the disease, its prevalence is predicted to rise 1.5 folds by 2025 [1]. The World Health Organization reports nearly 77% of non-communicable diseases are due to hypertension [2]. Furthermore, hypertension is a cause and also result of chronic kidney disease (CKD) that contributes to kidney structural damage in the form of end stage renal disease [3, 4]. Thus, optimal blood pressure (BP) control becomes paramount in limiting the kidneys contribution to BP elevation as both can result fluctuations that abet progession of CKD and may cause cardiovascular complications [5]. The current treatments use calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, diuretics and renin inhibitors [6-8]. Nevertheless, these drug categories have a different effectiveness in reducing BP among hypertensive subjects [6]. As a result, the shortcomings in therapy and difficulty in achieving BP goals illustrate that there is a need for an additional drug class.

The renin-angiotensin aldosterone system (RAAS) is responsible for regulating BP and maintaining body fluid balance. Hyperactivity of RAAS triggers a cascade leading to high BP, often complicated with hypertension and followed by cardiorenal fatal events [9]. Commonly prescribed antihypertensive drugs inhibit RAAS, including ACE inhibitors, ARBs, renin inhibitors, and mineralocorticoid receptor blockers. Despite significant advancements achieved by these agents in impeding the progression of established cardiorenal disease, ACE inhibitors and ARBs only yield a 20% reduction in the relative risk of CVD progression when compared to therapies not specifically targeting RAAS [10, 11]. These limitations highlight an ongoing requirement for improved and

more specific therapies, thus exploration of novel therapeutic strategies is vital. As a part of these novel RAAS blockade strategies, therapeutic agents such as angiotensin receptor neprilysin inhibitors (ARNIs), nonsteroidal mineralocorticoid receptor antagonists (NMRAs), brain renin-angiotensin system (RAS) therapies and ribonucleic acid (RNA)-based therapies have been suggested [12-15].

Previous studies have been shown to offer effective hypertension control in clinical trials [12-15]. However, an important research void still exists in comparing the safety and efficacy of these RAAS-targeted therapies. These strategies not only thus have the potential to correct dysregulation of RAAS, but they may also be better than existing treatments for overcoming some inherent efficacy limitations.

Thus, in this study we aimed to estimate the comparative efficacy and safety profiles of several antihypertensive treatments including ARNI, NMRA, brain RAS therapy as well as RNA-based treatment. We hope this thorough review of ARNI, NMRA, RAS therapy and RNA based-therapy provides beneficial information that will change the picture in our therapeutic armory for hypertension towards more impactful tailor-made treatments to cardiovascular Smith-Raines syndrome.

METHODS

This meta-analysis following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement guidelines was performed [16]. This study was registered in **PROSPERO** with registration number **CRD420244966981**.

Search Strategy

The literature search was performed in five various databases until December 2023 including PubMed, ScienceDirect, EBSCO, Cochrane, and ProQuest. Literature search was performed using the keywords with Boolean operators.

Study Eligibility Criteria

We predefined the inclusion and exclusion criteria before searching for studies to ensure that the included studies were homogeneous. Inclusion criteria were

(1) studies provide or can be extracted data in English,

(2) clinical trial,

(3) studies with patients diagnosed by hypertension,

(4) studies with interventions such as ARNI, NMRA, brain RAS therapy, or RNA-based therapy being analyzed, and

(5) studies incorporating at least one parameter examined in this study, namely: systolic blood pressure (SBP) control, diastolic blood pressure (DBP) control, and adverse event rates.

In contrast, the exclusion criteria consisted of

(1) non-human samples studies and

(2) non-peer reviewed articles.

No restrictions were applied in this study for publication dates. The authors independently screened for eligibility, with discrepancies resolved by discussion.

Outcome Measures

The aim of the current study is to evaluate two efficacy parameters as well as one safety parameter in order to conclude on the effectiveness and safety aspect of RAAS-based antihypertensive therapies. Efficacy outcomes were defined as “control of SBP and DBP”, determined by the attainment rate of target BP levels according to American Heart Association or local hypertension practice guidelines in each included study [17-19].

On the other hand, safety evaluated by adverse events that were not present before treatment or pre-existing events worsened either in intensity and/or frequency after treatment, as defined by treatment-emergent adverse events (TEAEs) [19-21]. The quantitative analysis involved independent extraction of results from the included papers by each author, and any disparities were resolved through discussion.

Quality Assessment

The risk of bias (ROB) assessment for the included studies used the revised tool for risk of bias in randomized trials (RoB 2.0) [22]. After that, results were entered in Microsoft Excel 2021 Spreadsheet under “bias” of the assessment findings. The spreadsheet was then uploaded to the ROBVIS website https://mcguinlu.shinyapps.io/robvis/ (accessed on 13 December 2023) where results of the risk-of-bias assessments were depicted in a traffic light system side by side with ‘bars’ summarizing overall RoB judgements per bias domain [23]. These systematic steps led to a full and transparent representation of bias within the relevant studies.

Statistical Analysis

ROB in the included studies was assessed using the RoB 2.0 [22]. Subsequently, the assessment findings were documented in the “bias” section of a Microsoft Excel 2021 spreadsheet. Following this, the spreadsheet was uploaded to the ROBVIS website (https://mcguinlu.shinyapps.io/robvis/ [accessed on 13 December 2023]), where assessment results were visually presented using a traffic light system [23]. This systematic approach ensured a comprehensive and transparent representation of bias levels in the included studies. The meta-analysis was conducted by Review Manager 5.4.

RESULTS

Study Selection and Identification

After the removal of duplicates and abstract screening, 39 full-text studies were assessed by two independent reviewers. A total of 20 clinical trials were finally included in this meta-analysis, as indicated in **Figure 1**.

Seven studies were excluded due to unrelated data to the focus of this study, and seven others were excluded due to insufficient details for proper evaluation. Moreover, five studies were excluded because their outcomes were irrelevant to this study. The studies were assessed and different outcomes were extracted to determine the safety and efficacy of ARNI, NMRA, brain RAS therapy, and RNA-based therapy.

Demography and Clinical Characteristics of the Included Studies

The demography and clinical characteristics of each study were examined and listed.

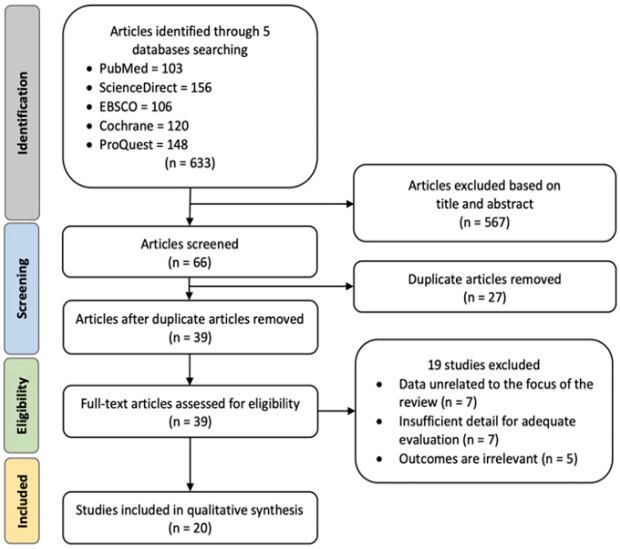

Figure 1. PRISMA flow chart showing study identification and selection (the initial database search identified 633 studies from five databases [PubMed, ScienceDirect, EBSCO, Cochrane, & ProQuest], a total of 567 articles were excluded as they met the exclusion criteria after title and abstract screening, while 66 full text papers underwent further checking for duplication, after duplicate screening, 27 articles were eliminated, 19 articles were excluded that did not contain appropriate data, examination or results, & the last step led to the inclusion of 20 clinical trials in the qualitative synthesis) [24-40]

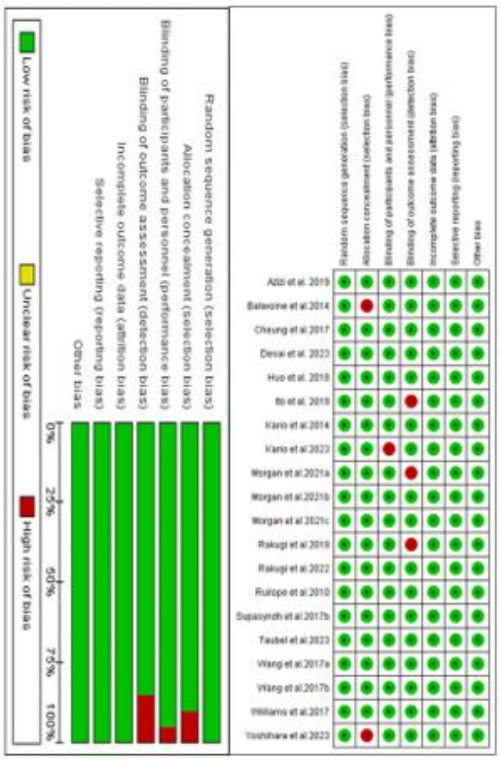

Figure 2. ROB summary for RCT studies using Cochrane Risk of Bias 2.0 tool (colored regions: green, low ROB; yellow, unclear ROB; & red, high ROB) [41]

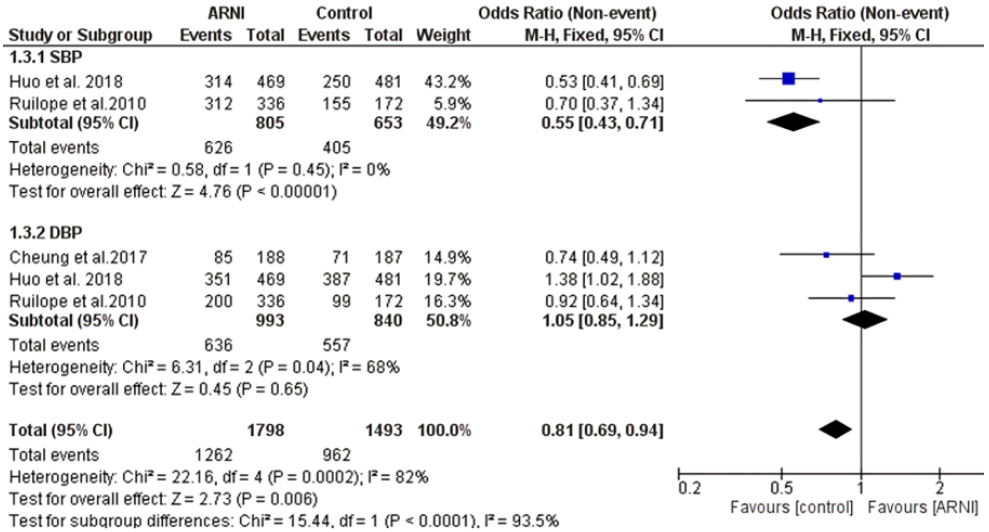

Figure 3. Forest plot showing the OR of BP control in angiotensin receptor neprilysin inhibitor, compared with the control group (the risk ratio was presented as a blue square, with 95% CIs shown to either side by the solid lines, each study has a fixed weight, and its size square shows how much it tends to dominate, & black rhombus indicates pooled estimate with 95% CI) [24, 25, 34]

Quality Appraisal

The final clinical trial studies that were included in the analysis underwent a thorough quality assessment using the Cochrane RoB 2.0 tool.

The assessment identified all the 20 studies independently across each domain, and output categorized a total of 14 studies that were graded as low risk and six moderate to high risk on every one scale (**Figure 2**).

Efficacy and Safety Analysis of Angiotensin Receptor Neprilysin Inhibitor

The efficacy analysis was conducted with 1,290 patients throughout three eligible studies for SBP and DBP control (**Figure 3**).

SBP analysis revealed a higher rate of control in the ARNI group compared to control (odds ratio [OR] = 0.55; 95% confidence interval [CI] = 0.43, 0.71; $p < 0.00001$; $I^2 = 0\%$). However, DBP analysis showed a higher rate of control in the control group (OR = 1.05; 95% CI = 0.85, 1.29; $p = 0.65$; $I^2 = 68\%$).

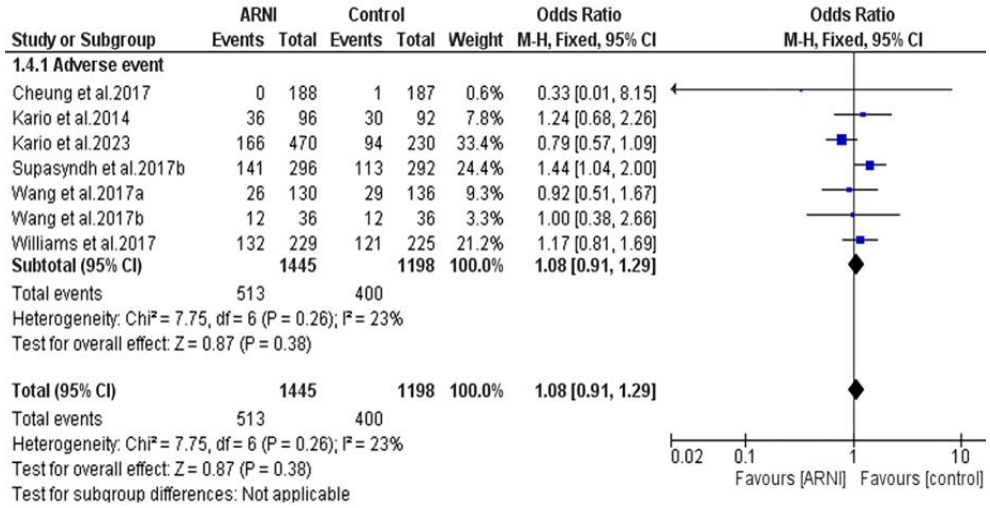

Figure 4. Forest plot of OR for adverse events rate in angiotensin receptor neprilysin inhibitor versus control group (blue square and solid lines display odds ratio with 95% CI, the squares represent the size or weight of each study, & the black rhombus denotes the pooled estimate, and horizontal lines represent 95% CI) [24, 25, 34]

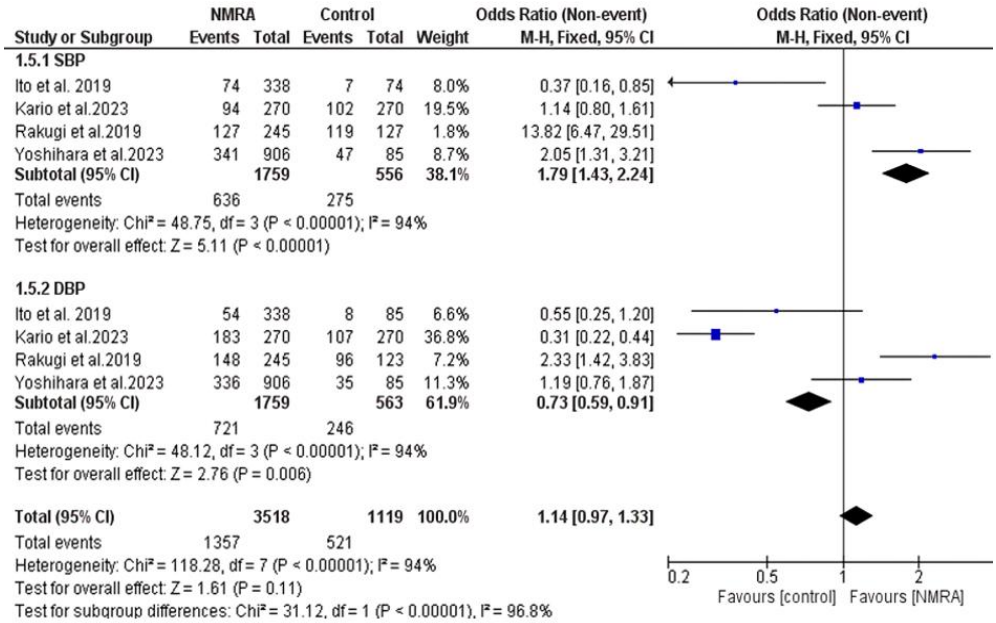

Figure 5. Forest plot of the OR of BP control in nonsteroidal mineralocorticoid receptor antagonist compared to the control group (the middle line is the OR plotted with 95% CI, blue square and solid lines, the weight of each study is shown by the size of the squares, & a black rhombus represents the pooled estimate with 95% CI) [25-28, 35-37]

Pooled efficacy analysis for ARNI revealed a higher rate of BP control in the ARNI group compared to control (OR = 0.81; 95% CI = 0.69, 0.94; p = 0.006; I^2 = 82%). The safety analysis was conducted with 2,643 patients throughout seven eligible studies for adverse events rate (**Figure 4**).

Pooled safety analysis for ARNI revealed a lower rate of adverse events seen in the control group compared to the ARNI group (OR = 1.08; 95% CI = 0.91, 1.29; p = 0.38; I^2 = 23%). These results suggest that ARNI displayed better efficacy but lower safety in comparison to the control group.

Efficacy and Safety Analysis of Nonsteroidal Mineralocorticoid Receptor Antagonist

The efficacy analysis was conducted with 2,322 patients throughout four eligible studies for SBP and DBP control (**Figure 5**).

SBP analysis revealed a higher rate of control in the control group compared to the NMRA group (OR = 1.79; 95% CI = 1.43, 2.24; p < 0.00001; I^2 = 94%). Conversely, DBP analysis showed a higher rate of control in the NMRA group (OR = 0.73; 95% CI = 0.59, 0.91; p = 0.006; I^2 = 94%). Pooled efficacy analysis for NMRA revealed a higher rate of BP control in the control group compared to the NMRA group (OR = 1.14; 95% CI = 0.97, 1.33; p = 0.11; I^2 = 94%). The safety analysis was conducted with 1,253 patients throughout three eligible studies for adverse events rate (**Figure 6**).

Pooled safety analysis for NMRA revealed a lower rate of adverse events compared to the control group (OR = 0.78; 95% CI = 0.59, 1.05; p = 0.10; I^2 = 81%). These results suggest that NMRA displayed better safety but lower efficacy in comparison to the control group.

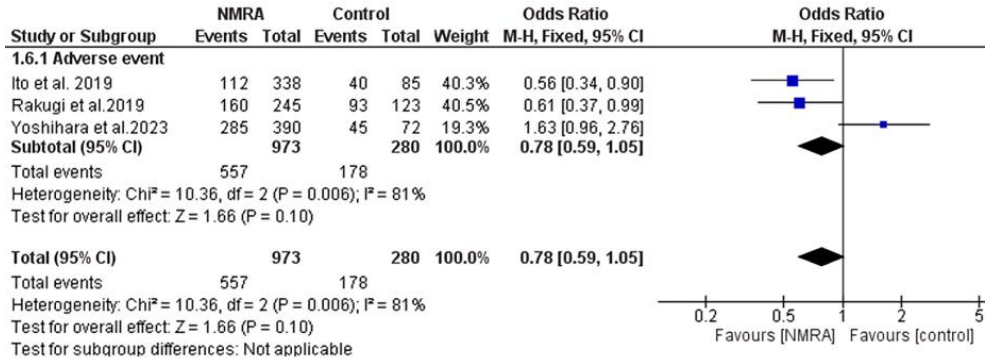

Figure 6. Forest plot of the OR of adverse events rate in nonsteroidal mineralocorticoid receptor antagonists compared to the control group (the blue square and solid lines represent the OR with 95% CI, the size of the squares indicates the weight of each study, & the black rhombus indicates pooled estimate, and 95% CI) [25-28, 35-37]

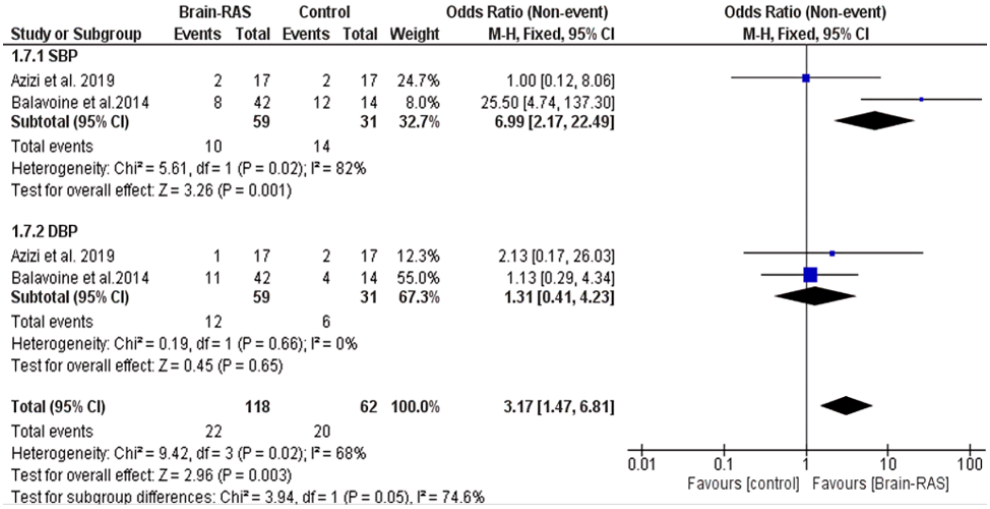

Figure 7. Forest plot of the OR of BP control in brain renin-angiotensin system therapy compared to the control group (the blue square and solid lines are the ORo with 95 % CI, each square represents a study, weighed by the size, & the black rhombus denotes the pooled estimate with 95 % CI) [26, 29, 38, 39]

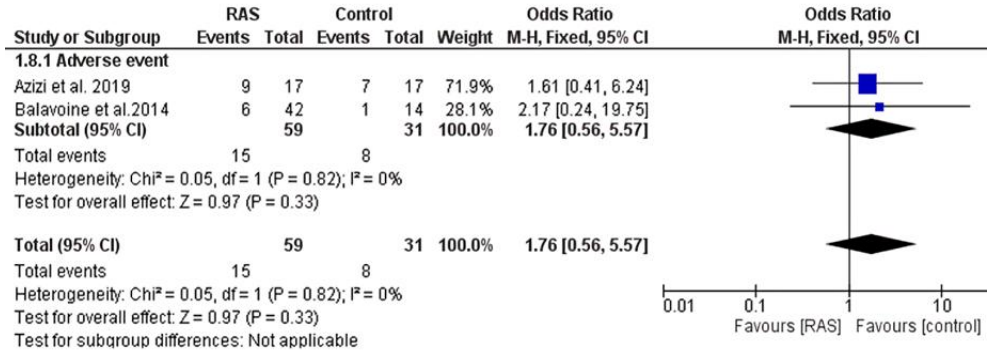

Figure 8. Forest plot of the OR of adverse events rate in brain renin-angiotensin system therapy compared to the control group (the blue square and solid lines are the odds ratio with 95 % CI, each square represents a study, weighed by the size, & the black rhombus denotes the pooled estimate with 95 % CI) [26, 29, 38, 39]

Efficacy and Safety Analysis of Brain Renin-angiotensin System Therapy

The efficacy analysis was conducted with 90 patients throughout two eligible studies for SBP and DBP control (**Figure 7**).

SBP analysis revealed a higher rate of control in the control group compared to the brain RAS therapy group (OR = 6.99; 95% CI = 2.17, 22.49; p = 0.001; I^2 = 82%). Furthermore, DBP analysis also showed a higher rate of control in the control group (OR = 1.31; 95% CI = 0.41, 4.23; p = 0.65; I^2 = 0%). Pooled efficacy analysis for brain RAS therapy revealed a higher rate of BP control in the control group compared to the brain RAS therapy group (OR = 3.17; 95% CI = 1.47, 6.81; p = 0.003; I^2 = 68%). The safety analysis was conducted with 90 patients throughout two eligible studies for adverse events rate (**Figure 8**).

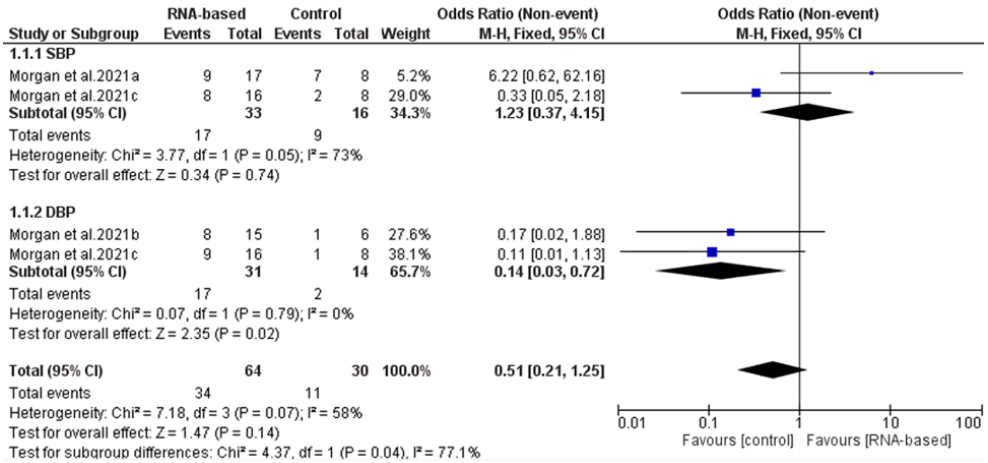

Figure 9. Forest plot of the OR of BP control in RNA-based therapy compared to the control group (the blue square and solid lines are the OR with 95 % CI, each square represents a study, weighed by the size, & the black rhombus denotes the pooled estimate with 95 % CI) [29, 38, 39]

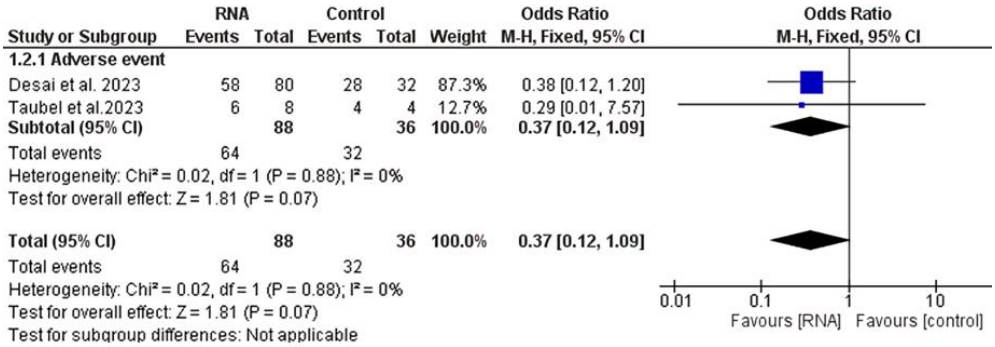

Figure 10. Forest plot of the OR of adverse events rate in RNA-based therapy compared to the control group (the blue square and solid lines are the OR with 95 % CI, each square represents a study, weighed by the size, & the black rhombus denotes the pooled estimate with 95 % CI) [29, 38, 39]

Pooled safety analysis revealed a higher rate of adverse events seen in the brain RAS therapy group compared to the control group (OR = 1.76; 95% CI = 0.56, 5.57; p = 0.33; I^2 = 0%). These results suggest that brain RAS therapy displayed both lower efficacy and safety in comparison to the control group.

Efficacy and Safety Analysis of RNA-Based Therapy

The efficacy analysis was conducted with 70 patients throughout three eligible studies for SBP and DBP control (**Figure 9**).

SBP analysis revealed a higher rate of control in the control group compared to the RNA-based therapy group (OR = 1.23; 95% CI = 0.37, 4.15; p = 0.74; I^2 = 73%). However, DBP analysis also showed a higher rate of control in the RNA-based therapy group (OR = 0.14; 95% CI = 0.03, 0.72; p = 0.02; I^2 = 0%). Pooled efficacy analysis revealed a higher rate of BP control in the RNA-based therapy group compared to the control group (OR = 0.51; 95% CI = 0.21, 1.25; p = 0.14; I^2 = 58%). The safety analysis was conducted with 124 patients throughout two eligible studies for adverse events rate (**Figure 10**).

Pooled safety analysis revealed a lower rate of adverse events seen in the RNA-based therapy group compared to the control group (OR = 0.37; 95% CI = 0.12, 1.09; p = 0.07; I^2 = 0%). These results suggest that RNA-based therapy displayed both better efficacy and safety in comparison to the control group.

DISCUSSION

From our findings, both NMRA and ribonucleic acid interference (RNAi) type of RAAS-based antihypertensive therapy indicate fewer adverse effects found in patients, while ARNI and brain RAS therapy favors control. Thus, this suggests RAAS-based antihypertensive therapy implementation, specifically in NMRA and RNAi types of RAAS-based antihypertensive therapy. This has been also supported by previous studies that overall RAAS can be used safely to treat hypertension [24]. Previous studies on COVID-19 patients in 2021 also found lower adverse effects, such as death, ARDS, shock, and ICU admission, in patients with RAAS-based antihypertensive therapies [25]. Major adverse events of therapy in RAAS inhibitors were found in correlation to the comorbidity in patients. Some comorbidities found in studies are organ damage, uncontrollable hypertension, older age, and heart dysfunction. These comorbidities caused the receptors of RAAS therapy. On the other hand, ARNI and Brain RAS therapy's higher adverse effect rates are mainly caused by a lack of studies that explore deeply its acute and chronic effects. The lack of data may be caused by recent innovations and progress of ARNI and Brain RAS therapy research. RAAS-based antihypertensive drugs are shown to have lower adverse effects because of their direct approach to block specific receptors in the RAAS. Thus, providing a more protective effect for the cardiovascular system. NMRA and RNAi provide a

specific yet systemic effect overall, while ARNI and brain RAS therapy have specific effects on RAAS production and hormone transformation. This caused specific adverse events that correlated to the RAA pathway. While having statistically more adverse events, RAAS-based therapies overall have a lower incidence of death and disease worsening. This suggests RAAS-based therapies for use in hypertension management while controlling the comorbidities of patients. On the other hand, all co-founders must also be controlled, such as traditional medicine given as control, large multicenter research, and long-term prospective studies must be seen.

In analyzing the efficacy of RAAS-based hypertensive therapies, ARNI displayed the best BP control, followed by RNA-based therapy, NMRA, and brain RAS therapy. However, it is important to note that NMRA and brain RAS therapy exhibited lower BP control compared to each control group. The efficacy of ARNI was supported by research indicating that treatment with sacubitril/valsartan at doses of 200 or 400 mg once daily was effective in yielding superior BP reduction in patients with mild-to-moderate hypertension. In comparison to the standard treatment using Olmesartan at an 8-week follow-up, sacubitril/valsartan exhibited a significant difference of -2.33 mmHg [18]. Another study reinforced these findings, reporting a notably greater reduction in mean sitting DBP across various doses of sacubitril/valsartan compared to placebo (mean reduction: -2.17 mmHg, 95% CI -3.28 to -1.06; $p < 0.0001$). In the case of RNA-based therapy, both phase one and two studies indicated a considerable reduction in SBP (-12 mmHg; 95% CI: -21 to -4 mmHg) and DBP (-6 mm Hg; 95% CI: -11 to -1 mmHg) with IONIS-AGT-LRx compared to placebo. Additionally, IONIS-AGT-LRx demonstrated significant efficacy in reducing mean angiotensin levels in comparison to the placebo group (-17.0 ± 4.1 mg/ml vs. -1.1 ± 4.5 mg/ml; $p < 0.001$) [15]. Although esaxerenone (NMRA) did not outperform standard therapy in BP control, it was observed that the combination of esaxerenone with a RAS inhibitor or calcium channel blocker effectively enhanced BP control [14]. In the context of brain RAS therapy, a phase 1 study on firibastat showed no significant changes in supine and standing BP across treatment groups compared to placebo [20]. However, a randomized-controlled trial in 2019 revealed that at 4 weeks, daytime ambulatory SBP decreased by 2.7 mmHg (95% CI -6.5 to 1.1 mmHg) with firibastat versus placebo. Furthermore, office SBP decreased by 4.7 mmHg (95% CI -11.1 to 1.8 mmHg) with firibastat compared to placebo [13].

Strength and Limitations

This study succeeded in developing a comprehensive understanding of antihypertensive therapies targeting the RAAS, encompassing the efficacy and safety of each therapy type. Nevertheless, to facilitate more homogenous and less biased systematic reviews and meta-analyses, several future clinical trials are deemed necessary. The overall quality of the evidence remains heterogeneous, and six of the included studies exhibit bias in at least one domain. It is undeniable that prospective, randomized trials, featuring stringent inclusion and exclusion criteria, along with standardized protocols, are imperative to conclusively determine the true efficacy of antihypertensive treatments.

CONCLUSION

RNA-based therapy is considered to have the superior efficacy and safety profile among the four antihypertensive therapies explored in this study. This study highlights the superiority of RNA-based therapy and underscores its promising potential for further exploration. Conversely, ARNI, NMRA, and brain RAS demonstrated notable efficacy in reducing BP in hypertensive patients with minimal TEAEs, suggesting their utilization as alternatives to conventional non-RAAS-targeted therapies.

LIST OF ABBREVIATIONS

ACE : Angiotensin-converting enzyme
AHA : American Heart Association
Ang I : Angiotensin I
Ang II : Angiotensin II
ARBs : Angiotensin receptor blockers
ARNI : Angiotensin receptor neprilysin inhibitor
AT1R : Angiotensin II type 1 receptor
AT2R : Angiotensin II type 2 receptor
BP : Blood pressure
CCB : Calcium channel blocker
CI : Confidence interval
CKD : Chronic kidney disease
CVD : Cardiovascular disease
DBP : Diastolic blood pressure
GalNAc : N-acetylgalactosamine
GFR : Glomerular filtration rate
HF : Heart failure
HFrEF : Heart failure with reduced ejection fraction
MRA : Mineralocorticoid receptor antagonist
MRs : Mineralocorticoid receptors
NEP-I : Neutral endopeptidase inhibitor
NMRA : Nonsteroidal mineralocorticoid receptor antagonist
NPs : Natriuretic peptides
OR : Odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAAS : Renin-angiotensin-aldosterone system
RAS : Renin-angiotensin system
RAS-Is : Renin-angiotensin system inhibitors
RISC : Ribonucleic acid-induced silencing complex
RNA : Ribonucleic acid
RNAi : Ribonucleic acid interference
ROB : Risk of Bias
SBP : Systolic blood pressure
siRNAs : Small interfering ribonucleic acids
TEAEs : Treatment-emergent adverse events
WHO : World Health Organization

Author contributions: DDCHR, RNR, SEW, JNJ, KCT, & LAKN: writing–original draft; **DDCHR, KCT, & SEW:** data analysis; **DDCHR, SEW, & JNJ:** conceptualization; **DDCHR & SEW:** data collection; **DDCHR, RNR, & JNJ:** data curation; & **RNR:** writing–review and editing & supervision. All authors have agreed with the results and conclusions.

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Ethical statement: The authors stated that the study does not require any ethical approval since it is a meta-analysis based on previously published data, without direct involvement of human participants or collection of identifiable personal information.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author. The reporting guidelines for this study are available through Mendeley Data. The PRISMA checklist and flowchart can be accessed in [26].

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