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Efficacy and Safety of Angiotensin-Based Pharmacotherapy versus Conventional Therapy for the Management of Isolated Systolic Hypertension: A Meta-Analysis of Randomized Controlled Trials

Research Article

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Abstract

The angiotensin (AT) system is highly implicated in the pathophysiology of isolated systolic hypertension (ISH). Consequently, this meta-analysis was designed to quantitatively review the efficacy and safety of angiotensin (AT)-based regimens in comparison with conventional thiazide diuretics or calcium channel blockers (CCBs) for the management of ISH. MEDLINE and CENTRAL were searched for relevant randomized controlled trials (RCTs). The outcomes assessed were blood pressure (BP) reduction, mortality, myocardial infarction (MI), stroke, and adverse events (AEs). Statistical analysis was carried out as recommended by the Cochrane Collaboration using data weighted mean difference (WMD) and relative risk (RR). Fourteen studies involving 6296 patients met the selection criteria for inclusion in this meta-analysis. There was no beneficial fall in systolic BP using AT inhibitors versus diuretics or CCBs (WMD = 0.09, 95% confidence interval (CI) -1.02 – 1.21, P = 0.87). In addition, AT inhibitors did not adversely lower the diastolic BP compared to diuretics or CCBs. There was also no significant reduction by the AT inhibitors in the primary efficacy outcomes including mortality, MI and stroke. Interestingly, AT inhibition demonstrated a significantly lower incidence of AEs better than conventional therapy (RR = 0.66, 95% CI 0.5 - 0.87, P = 0.003). Therefore, there is strong evidence to conclude the comparative effectiveness of AT inhibition versus thiazide-induced diuresis or calcium antagonism regarding efficacy outcomes. There is also sufficient evidence to recommend AT inhibition as initial choice with regard to its safety for the management of ISH in adults.

Keywords: Angiotensin Inhibitors; Isolated Systolic Hypertension; Meta-Analysis; Safety; Efficacy.

Introduction

Hypertension is the most common disease that leads to serious morbidities and death if not diagnosed early and managed properly according to the eighth Joint National Committee (JNC-8) guideline [1].

The prevalence of hypertension increases noticeably with age, such that approximately two thirds of those over 60 years of age have hypertension in a world population that is already aging. After the age of 50, as systolic pressure continues to escalate and diastolic pressure tends to drop, systolic hypertension prevails. Particularly, the systolic hypertension is more associated with clinical cardiovascular (CV) disease and mortality than the diastolic one [2-5]. Isolated systolic hypertension (ISH) has commonly been defined as a systolic blood pressure (sBP) above 160 mmHg, with a diastolic BP(dBP) below 90 mmHg [2, 6, 7]. ISH is a key risk factor for CV and renal diseases. Ample data are available to warrant rigorous efforts to manage systolic pressure [4, 8, 9].

The pathophysiology of ISH involves reduced elasticity and amenability of arteries resulting from age and from the atherosclerosis-linked accumulation of calcium and collagen and the degradation of elastin. Stiffened arteries increase the rate of returned

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arterial pressure waves from the periphery, in this manner raising the peak systolic pressure. This hypertension itself can stimulate further arterial stiffening and deteriorate endothelium-dependent vasodilatation [2].

The clinical presentation and diagnosis of hypertension should be based on BP assessments, measured on ≥2 separate office visits. At least 2 assessments should be measured once the patient is seated comfortably for at least 5 minutes with the back arm supported horizontally, and the cuff at heart level [4].

The general recommended BP goal in uncomplicated hypertension was <140/90 mm Hg. However, this target for elderly hypertensive patients was based on expert opinion rather than on randomized controlled trials (RCTs). It was also unclear whether targets BP should be the same in patients 65 - 79 years of age as in those >80 years of age. Nowadays, the sBP goal is recommended to be < 150 mmHg based on evidence derived from several guidelines produced by the European Society of Hypertension/European Society of Cardiology (ESH/ESC), the eighth Joint National Committee (JNC-8), the American Heart Association (AHA), the American Society of Hypertension/International Society of Hypertension (ASH/ISH), and the Canadian Hypertension Education Program (CHEP) [1, 10-12].

Three classes of drugs are considered first-line agents for the treatment of ISH in elderly patients: thiazide diuretics, calcium channel blockers (CCBs), and angiotensin (AT) inhibitors; either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) [1]. CCBs or diuretics were generally preferred for the treatment of elderly patients with ISH mainly because of increased efficacy in blood pressure lowering [2, 4, 7, 8, 10, 13-15]. On the other hand, others argue in support of the use of AT inhibitors based on their safer profile [2, 5, 8].

Generally, first-line antihypertensives have all been effective in lowering BP and reducing CV events when prescribed at pharmacologically comparable doses for treatment of hypertension in general and ISH in particular. However, there is still no convincing strong enough evidence that would indicate superiority of monotherapy with 1 class over the other. Also, most ISH elderly patients will require combination drug therapy besides the non-pharmacological (lifestyle modifications)management in all patients [1, 4, 7]. The thiazide diuretics and CCBs have been the best-studied drugs in older cohorts. However, there is growing body of evidence both of the essential role of renin–angiotensin–aldosterone system (RAAS) mechanisms in the cardiovascular pathogenesis and hypertension in the elderly and of the benefits of pharmacologically blocking this system. Furthermore, AT inhibitors may exhibit additional antimitotic or anti-atherosclerotic actions to BP lowering providing even more protective effects on the CV system [4, 8, 16, 17].

Several RCTs have previously investigated the comparative efficacy and safety between AT inhibitors and conventional first-line agents either on hypertension generally [18, 19] or ISH specifically [8, 20-32]. Moreover, the comparative effects of different antihypertensive regimens on major cardiovascular events were investigated by meta-analyses of randomized trials in patients with hypertension generally [15, 16, 19, 33, 34]. Nevertheless, no conclusive robust high level evidence by a meta-analysis tackled this important concern in cases of ISH till now.

Meta-analysis is the statistical analysis of a combination of results derived from a review of two or more separate studies. Most meta-analyses are differences on a weighted average of the effects from the different included trials [35]. Meta-analysis is a quantitative review that provides new data whose reliability depends on the quality of combined studies. In case the combined studies were RCTs, these represent the most reliable and frequently used design for clinical research [36]. Meta-analyses have several advantages including an increase in trials power and precision. In addition, meta-analysis has the ability to answer questions not previously asked by individual studies, and the opportunity to settle different controversies. Nonetheless, they also have the potential of misleading mainly due to biases and included studies designs, if not carefully considered [35, 36].

Therefore, our work aimed to quantify the efficacy and safety of angiotensin-based antihypertensive drugs with increased power and precision of a meta-analysis from a review of clinical RCTs treating ISH cases. Specifically, the research aimed to quantify the antihypertensive drug effect on BP reduction in people with ISH treated by AT inhibitors compared with the other conventional antihypertensive first-line agents (diuretics or CCBs). Also, the aim was to quantify antihypertensive drug effect on overall mortality, cardiovascular-specific morbidity and mortality, and the incidence of clinical adverse events in the two antihypertensive regimens against ISH based on AT inhibition compared with thiazide-induced diuresis or calcium antagonism.

Materials and Methods

Search Strategy

Electronic databases of PubMed/Medline and the Cochrane Central Register of Controlled Trials: Issue 7 of 12, July 2015 (CENTRAL) were searched up to August 2015.

Search strategy combined terms related to the keywords: "isolated systolic hypertension", therapy, and "randomized controlled trial" using Boolean operators and database-specific syntax.

This search led to 112 hits in MEDLINE and 21 hits in CENTRAL. Both title and abstract text of each record have been evaluated.

Selection Criteria

- RCTs of at least six weeks duration in ISH patients comparing antihypertensive drug therapy between active treatments (AT inhibitors vs diuretics or CCBs) and assessing efficacy (sBP lowering) and safety (side effects and dBP lowering) were included.
- RCTs on primary clinical endpoints of at least one year duration in ISH patients comparing antihypertensive drug therapy (AT inhibitors vs diuretics or CCBs) and assessing total mortality, as well as, CV morbidity and mortality were included.

Criteria of Inclusion and Exclusion

Inclusion criteria of this review include: all the trials be prospective RCTs published in English and of at least six weeks duration;

the participants were all adults (age > 18 years) with clear diagnosis of ISH and received first-line treatment for it according to the JNC8 [1]; outcomes including BP reduction, total mortality, CV mortality, stroke, MI, and clinical adverse events were clearly measured in the articles.

Exclusion criteria include: the patients were diagnosed as secondary hypertension; trials were duplicated publications on the same group of patients; the trial was on experimental animals; essential data was missing.

Types of Participants

Men and women with ISH defined as a systolic blood pressure (sBP) above 140 mmHg, with a diastolic blood pressure (dBP) below 95 mmHg.

Types of Interventions

Acceptable drug therapy included AT inhibitors, diuretics and CCBs.

Data Collection and Analysis

Outcomes assessed were BP reduction, total mortality, CV mortality, stroke, MI, and clinical adverse events. Measures assessed for blood reduction trials were means and SDs of decrease in sitting BP among first-line treatments and assessing the reported adverse events. Measures assessed for total mortality, CV mortality, stroke, MI, and clinical adverse events were occurrence of event dichotomous data summarized as risk ratio (RR).

Assessment of Risk of Bias

The risk of publication bias across studies was assessed visually by funnel plots. The effect measures were plotted against their standard errors (on a reversed scale) for precision of the estimated intervention effect that increases as the size of the trial increases, with the spread narrowing among larger studies.

Assessment of Heterogeneity

Random effects model was used to combine the data if significant heterogeneity existed (Chi^2 $P \leq 0.05$).

Statistics

Statistical analyses were carried out using specialized Meta-Analysis soft-wares such as Excel data collection sheets, and Review manager as recommended by the Cochrane Collaboration [35]. Weighted mean difference (WMD) with a 95% confidence interval (CI) were used for the calculation of continuous data, and relative risk (RR) with a 95% CI were used for dichotomous data.

When the mean BP reductions and standard deviations (SD) from the baseline to the end of the treatment were reported, they were retrieved directly. When standard errors (SE) were reported instead, SD was calculated using the formula: $SD = SE(n)^{0.5}$. When confidence intervals (CI) were reported instead, SD was calculated using the formula: $SD = \sqrt{n} \times (CI \text{ upper limit} - CI \text{ lower limit})/3.92$.

Results

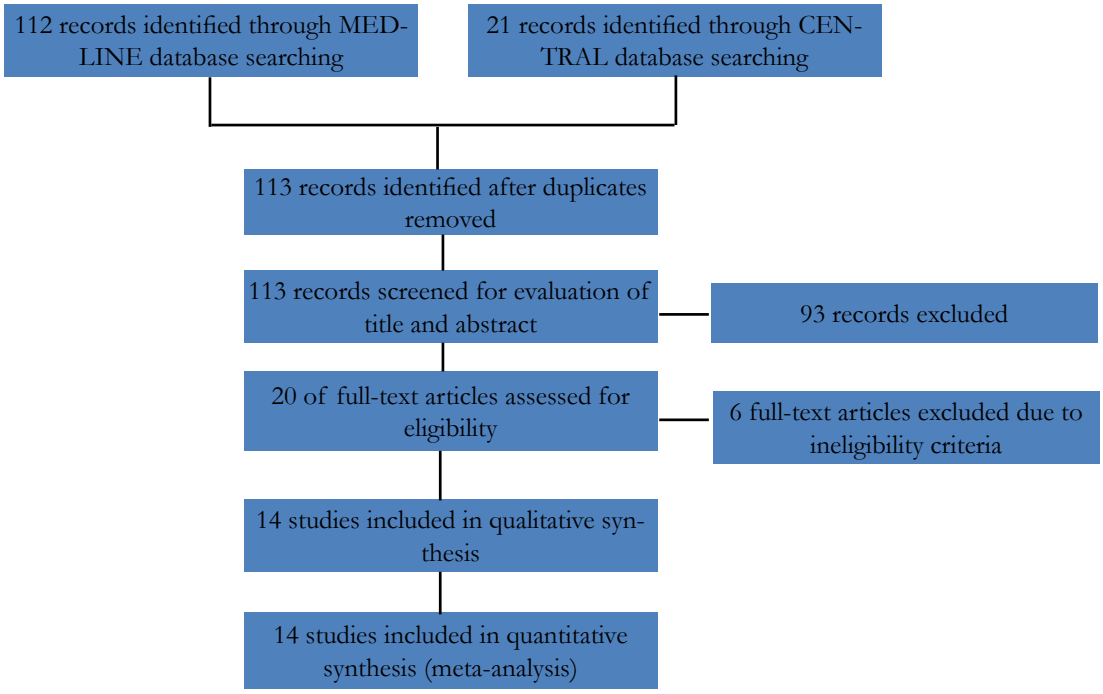
The study flow diagram was depicted in Figure 1 according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

The Characteristics of the included trials were tabulated in Appendix 1.

Effects of Interventions

Outcome: 1.1 sBP change: Twelve studies (Bendersky 2002

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Study Flow Diagram.



[20]; Heesen 1998 [22]; Leonetti 1997 [23]; Mackenzie 2009 [24]; Malacco 2003 [8]; Mallion 2007 [25]; Manolis 2004 [26]; Palatini 2004 [27]; Pavlovic 2004 [29]; Vogt 2005 [30]; Volpe 2003 [31]; Wing 2003 [32]) involving 3258 patients compared angiotensin (AT) inhibition with conventional first-line therapy using thiazide-induced diuresis or calcium antagonism on sBP reduction. There was no change (further reduction) in SBP from base-line in the (AT inhibitor) group compared with the (Diuretic or CCB) group [weighted mean difference (WMD): 0.09, 95% confidence interval (CI) -1.02 – 1.21] (Figure 2). No statistically greater response was reported after combining the P-values (combined P-value=0.87). There was significant degree of heterogeneity in the analysis for SBP using random effects model (P= 0.05, I^2 = 43%).

Outcome: 1.2 dBP change: Twelve studies (Bendersky 2002 [20]; Heesen 1998 [22]; Leonetti 1997 [23]; Mackenzie 2009 [24]; Malacco 2003 [8]; Mallion 2007 [25]; Manolis 2004 [26]; Palatini 2004 [27]; Pavlovic 2004 [29]; Vogt 2005 [30]; Volpe 2003 [31]; Wing 2003 [32]) involving 3258 patients compared angiotensin (AT) inhibition with conventional first-line therapy using thiazide-induced diuresis or calcium antagonism on dBP reduction. There was no adverse change (further reduction) in dBP from base-line in the (AT inhibitor) group compared with the (Diuretic or CCB) group [weighted mean difference (WMD): -0.11, 95% CI -0.76 – 0.55] (Figure 3). No statistically greater toxicity was reported after combining the P-values (combined P-value=0.75). There was significant degree of heterogeneity in the analysis for dBP using random effects model (P= 0.005, I^2 = 59%).

Outcome: 2.1 Total mortality: Two studies (Ekbom 2004 [21], Papademetriou 2004 [28]) involving 3038 patients compared angiotensin (AT) inhibition with conventional first-line therapy using thiazide-induced diuresis or calcium antagonism on total mortality. There was no benefit or change (further reduction) in total mortality in the (AT inhibitor) group compared to the (Diuretic or CCB) group (RR =1.02, 95% CI 0.85 – 1.22) (Figure 4A). No statistically fewer outcome was reported after combining the P-values (combined P-value=0.87). There was also no heterogeneity in the analysis for total mortalityusing fixed effects model (P= 0.38, I^2 = 0%).

Outcome: 2.2 CV mortality: The combined results of the 2 trials (Ekbom 2004 [21], Papademetriou 2004 [28]) reporting cardiovascular mortality data indicated no significant reduction or CV mortality benefit in the (AT inhibitor) group compared with the (Diuretic or CCB) group (RR =1.05, 95% CI 0.82 – 1.36) (Figure 4B). No statistically lower outcome was reported after combining the P-values (combined P-value=0.68). There was also no heterogeneity in the analysis for cardiovascular mortality using fixed effects model (P= 0.69, I^2 = 0%).

Outcome: 2.3 MI: Analysis of the results of the 2 trials (Ekbom 2004 [21], Papademetriou 2004 [28]) reporting MI as an outcome indicated no significant reduction or benefit in the (AT

Figure 2. Forest Plot of Comparison: Outcome: 1.1 Systolic Blood Pressure Reduction.

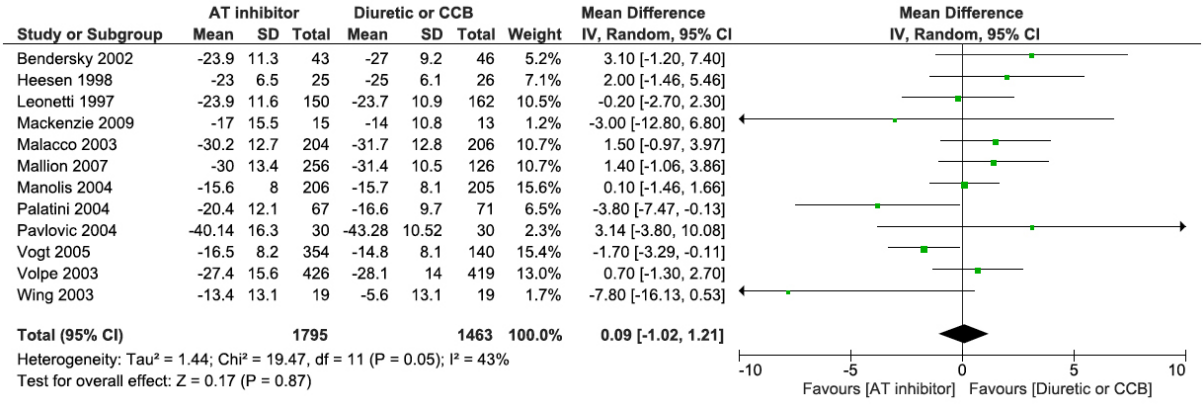


Figure 3. Forest Plot of Comparison: Outcome: 1.2 Diastolic Blood Pressure Reduction.

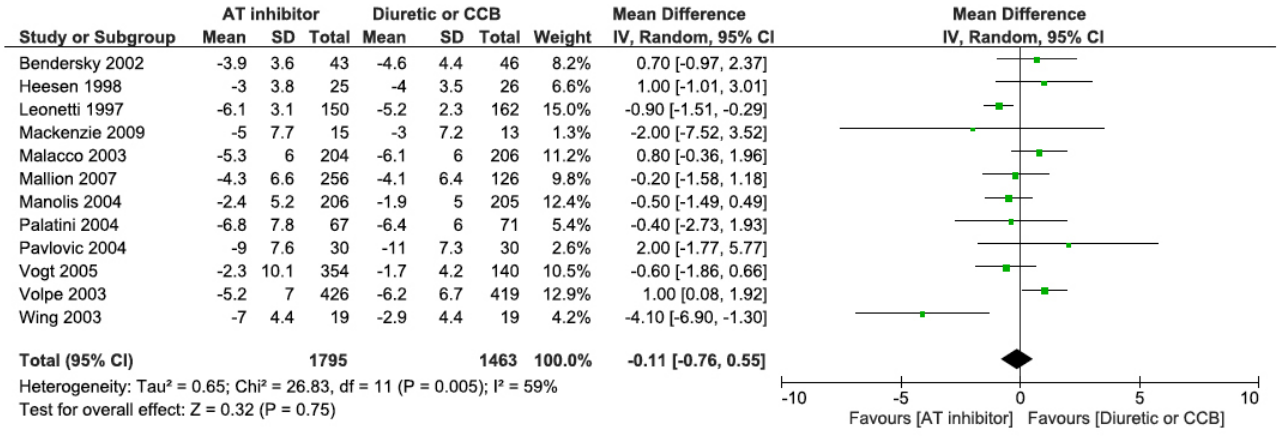


Figure 4. Forest Plot of Comparison: Outcomes:

Figure 4(A). 2.1 Total Mortality.

Figure 4(B). Cardiovascular Mortality.

Figure 4(C). 2.3 Myocardial Infarction.

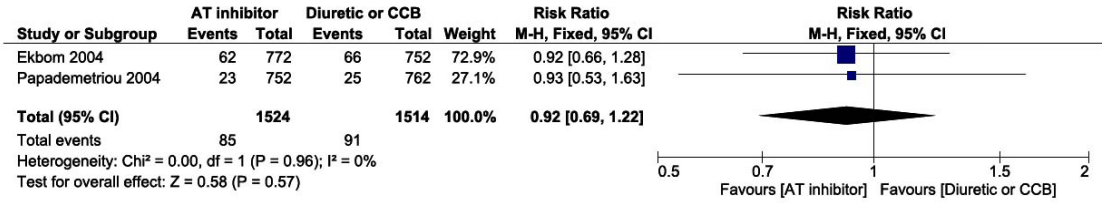
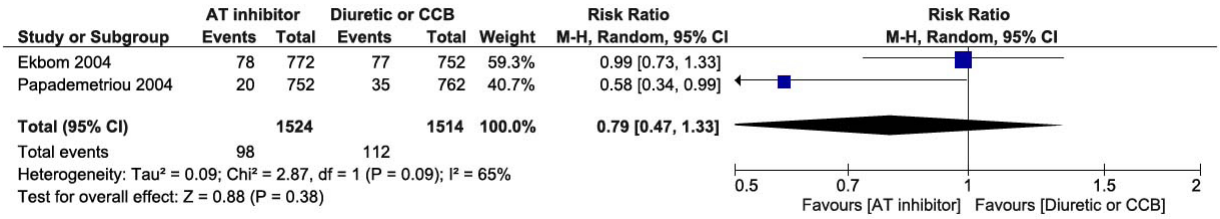


Figure 4(D). 2.4 Stroke.



inhibitor) group compared with the (Diuretic or CCB) group (RR =0.92, 95% CI 0.69 – 1.22) (Figure 4C). No statistically lower outcome was reported after combining the P-values (combined P-value=0.57). There was also no heterogeneity in the analysis for MI using fixed effects model (P= 0.96, I^2 = 0%).

Outcome: 2.4 Stroke: The combined results of the 2 trials (Ekbom 2004 [21], Papademetriou 2004 [28]) reporting stroke data indicated no significant difference or stroke benefit in the (AT inhibitor) group compared with the (Diuretic or CCB) group (RR =0.79, 95% CI 0.47 – 1.33) (Figure 4D). No statistically lower outcome was reported after combining the P-values (combined P-value=0.38). There was some heterogeneity (I^2> 50%), though non-significant, in the analysis for stroke using random effects model (P= 0.09, I^2 = 65%).

Outcome: 3.1 Safety (Adverse events): Nine studies (Bendersky 2002 [20]; Leonetti 1997 [23]; Malacco 2003 [8]; Mallion 2007 [25]; Manolis 2004 [26]; Pavlovic 2004 [29]; Vogt 2005 [30]; Volpe 2003 [31]; Wing 2003 [32]) involving 2932 patients were analyzed to compare the effects of angiotensin (AT) inhibition with conventional first-line therapy using thiazide-induced diuresis or calcium antagonism on the incidence of adverse events (AEs). It was found that there was an incidence of AEs in the (AT inhibitor) group significantly lower than those in the (Diuretic or CCB) group (RR =0.66, 95% CI 0.5 - 0.87, P= 0.003) (Figure 5). There was also significant heterogeneity in the analysis for AEs using random effects model (P= 0.0008, I^2 = 70%).

Assessment of Risk of Bias

The risk of publication bias across studies revealed symmetric funnel that was evident in the analysis plot of comparison on the BP reduction outcome (Figure 6A). In addition, no evident visual asymmetry could be noticed in the funnel plot of comparison on the safety outcomes (Figure 6B).

Discussion

ISH is a major risk factor for CV diseases and death, that's why extensive efforts are warranted to manage it [2, 7, 8]. There may be an essential role of the RAAS in the pathophysiologic mecha-

Figure 5. Forest Plot of Comparison: Outcome: 3.1 Safety (Adverse Events).

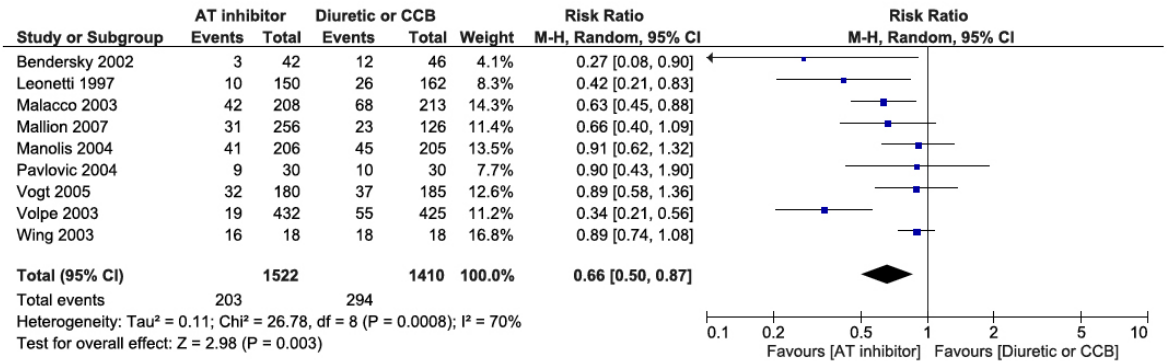


Figure 6. Funnel Plot of Comparison: Outcomes.

Figure 6(A). 1.1 Systolic Blood Pressure Reduction.

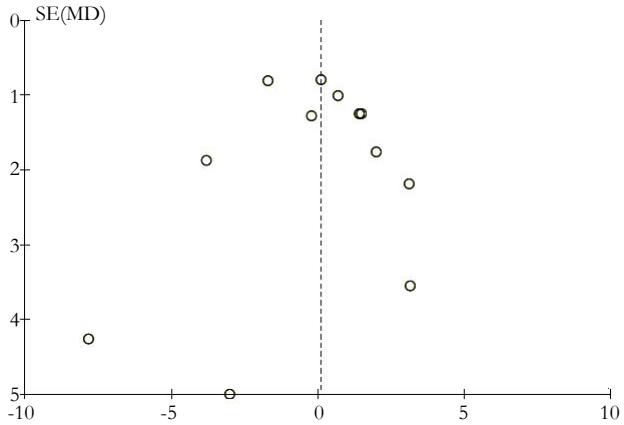
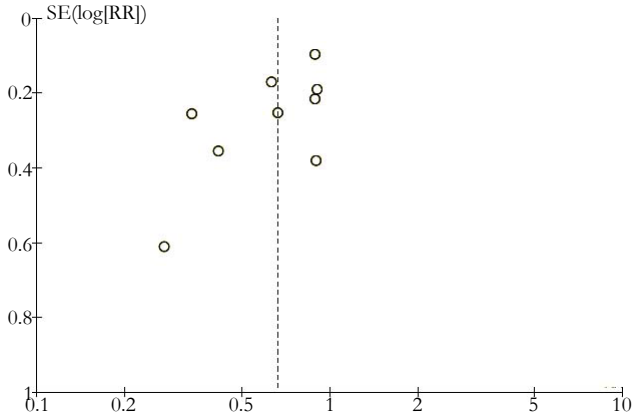


Figure 6(B). 3.1 Safety (Adverse Events).



nisms of ISH, and of the benefits of pharmacologically blocking this system [4, 8]. Several RCTs have investigated the comparative efficacy and safety between AT inhibitors and conventional first-line agents either on hypertension [18, 19] generally or ISH specifically [8, 20-32]. Moreover, the comparative effects of different antihypertensive regimens on major cardiovascular events were investigated by meta-analyses of randomized trials in patients with hypertension generally [15, 16, 19, 33, 34]. Nevertheless, no conclusive robust high level evidence by a meta-analysis tackled this important concern in cases of ISH until now. That's why, this meta-analysis was designed to focus on the efficacy and safety of AT-based regimens in comparison with other routine first-line antihypertensive regimens based on thiazide diuretics or calcium antagonists for the management of ISH. Overall, through pooling data from eligible RCTs, it was found that the evidence is sufficient to conclude the comparative effectiveness of AT inhibition versus thiazide-induced diuresis or calcium antagonism regarding efficacy outcomes. Interestingly, the results showed that the safety of AT inhibitors is better than conventional thiazide diuretics or CCBs concerning the incidence of adverse effects.

Achieving a desired target BP value is simply a surrogate goal of therapy for evaluating response and monitoring efficacy that does not guarantee prevention of hypertension-associated target-organ damage [37]. The therapeutic short-term outcome of sBP reduction was analyzed by combining twelve studies [8, 20-32] involving 3258 patients comparing AT inhibition with conventional first-line therapy using thiazide-induced diuresis or calcium an-

tagonism. There was no greater response i.e. beneficial reduction in sBP in the (AT inhibitor) group compared with the (Diuretic or CCB) group. The pooled results of the meta-analysis weighted mean difference are near to the zero value (WMD=0.09) (Figure 2). Only the two trials of Palatini et al., 2004 and Vogt et al., 2005 among the twelve included studies were in disagreement with these combined results. The reason why Palatini et al., 2004 obtained a different end of greater antihypertensive effect on sBP [mean difference (MD): -3.8, 95% CI -7.47 – -0.13] of valsartan compared to amlodipine may be due to the lower number (n=138 out of total 3258) and weight of only 6.5% of this study compared to the other eleven analyzed ones. Whereas, Vogt et al., 2005 might have demonstrated the greater antihypertensive effect on sBP [mean difference (MD): -1.7, 95% CI -3.29 – -0.11] of the lowest 20 mg dose of telmisartan versus hydrochlorothiazide 12.5 mg owing most probably to another reason of the shorter six weeks duration of this experiment and wider range of included participants' age (35–84 years). In addition, the sample size of the two compared groups is not the same (n=354 vs 140). This may have resulted in flawed statistical power to detect in between-treatment differences within these subgroups that may have led to difference in the pooled conclusions.

The primary goal of treating hypertension is to reduce hypertension-associated morbidity and mortality(e.g., MI, stroke)and the choice of pharmacotherapy should be determined by evidence proving such CV risk reduction [37]. Two studies [21, 28] involving 3038 patients compared the effects of the two regimens on efficacy primary outcomes of long-term goals including total mortality, CV mortality, MI and stroke (Figures 4A-D). There was no benefit by significant reduction in any of these primary outcomes using AT inhibitors versus diuretics or CCBs after combining the results. All these outcomes results were in accordance with those in the two included original trials analyzed [21, 28]. Nevertheless, the outcome of stroke prevention was shown to be significantly lower in case of AT inhibitor (candesartan) compared to the used diuretic (RR =0.58, 95% CI 0.34 – 0.99) in only one of these two studies [28]. This might have been due to the lower number of 1514 patients and weight (40.7%) of this study compared to the other one. In the same regard, the only two trials included in this meta-analysis represent a relatively small number, so we may further need more trials to get more convincing and flawless conclusions. Indeed, meta-analysis still provides a more comprehensive and precise method to review and analyze original studies, leading to higher level of evidence.

Concerning safety assessment, nine studies [8, 20-32] involving 2932 patients were analyzed to find that AT inhibition demonstrated significantly lower incidence of adverse events (AEs) than conventional thiazide-induced diuresis or calcium antagonism (RR =0.66) (Figure 5). This pooled result is in agreement with only four [8, 20, 23, 31] included trials that significantly favored the AT inhibitors safety profile, whereas, the remaining five [25, 26, 29, 30, 32] trials demonstrated an inclination to favoring AT inhibitors that was not enough to be significantly different from diuretics or CCBs. The reasons underlying the discrepancy of these five trials may show some diversity. The sample sizes of the two compared groups were dissimilar (n=256 vs 126) that may have resulted in low statistical power to detect in between-treatment differences and may have led to difference in the conclusions of Mallion et al., 2007. Also, the low number (60 and 36 out of total 2932) of the Pavlovic et al., 2004 and Wing et al., 2003 trials, respectively, compared to the other analyzed ones might have affected the results. In addition, the shorter six weeks duration of the Manolis et al., 2004 and Vogt et al., 2005 experiments and their wider range of included participants' age (35–84 years) might have flawed their conclusions compared to the pooled one.

In cases of elderly with ISH, lower diastolic pressures are associated with increased CV risk. Adverse outcomes can be ascribed to excessive blood pressure lowering with antihypertensive drugs, particularly, if the diastolic pressure is reduced below the level needed to maintain perfusion to vital organs. A minimum post-treatment diastolic pressure of 60 mmHg is recommended [7]. We demonstrated that AT inhibitors did not adversely lower the dBP compared to diuretics or CCBs (WMD: -0.11, 95% CI -0.76 – 0.55, P=0.75) (Figure 3). This finding may represent an addition to the safety of AT inhibition.

Potential biases in the review process were assessed by estimating the risk of publication bias across studies visually by funnel plots. A symmetric funnel was evident in the analysis plot of comparison on the sBP reduction outcome (Figure 6A). Then, the unpublished small trials without statistically significant results would not have resulted in asymmetry and the meta-analysis would not overestimate the intervention effect. Moreover, the random effects model was used to combine the data if significant heterogeneity existed (Chi^2 $P \leq 0.05$) as between-study variance in intervention effects. Generally, the quality of evidence in this study was performed in compliance with the quality of reporting for meta-analyses [PRISMA] Statement [38].

The present meta-analysis safety pooled results are in agreement with the studies that argue in support of the use of AT inhibitors based on their safer profile [2, 5, 8]. Nevertheless, the collective results are in disagreement with the studies preferring CCBs or diuretics for the treatment of ISH patients mainly because of increased efficacy in blood pressure lowering [2, 4, 7, 8, 10, 13]. One [15] of the meta-analyses suggested that the initial use of a CCB might be superior to an ARB for prevention of stroke and MI in hypertensive patients. This discrepancy might be attributable to the different subtype of hypertension managed as they recruited patients with hypertension generally, whereas, we were focusing on ISH probably having some different pathophysiologic mechanisms and management. Moreover, pharmacogenetics may also influence these inter-individual variations in response to antihypertensive agents as narratively reviewed by our group [39].

In summary, through pooling data from eligible RCTs, it was found that the evidence is sufficient to conclude the comparative effectiveness of AT inhibition versus thiazide-induced diuresis or calcium antagonism regarding efficacy outcomes. The primary long-term outcomes of all-cause death, and CV mortality and morbidity did not differ between treated groups. Also, the therapeutic short-term outcome of sBP reduction demonstrated similar results, as did the dBP reduction. Interestingly, the results showed that the safety of AT inhibitors is better than conventional thiazide diuretics or CCBs concerning the incidence of adverse effects. Indeed, this meta-analysis provides a more comprehensive and precise method to review and analyze high level RCTs, leading to new conclusions with higher level of evidence. To our knowledge, this is the first meta-analysis focusing on the efficacy and safety of angiotensin-based pharmacotherapy for ISH. Our meta-analysis of RCTs provides a more comprehensive

and precise methodology to include, assess, and analyze original high level clinical trials, leading to higher level of evidence for a stronger clinical judgment.

Future research is warranted to conduct more studies on ISH treatment primary outcomes of mortality and morbidity. In addition, these future studies would better enroll higher number of patients with a wider range of age, and distributed equally between treatment arms. Moreover, there is a need to define more appropriate sBP inclusion criteria for the ISH patients, as well as dBP values and treatment BP goals.

Important implications for practice emerge from this analysis including the recommended initial use of AT inhibition with regard to safety for the management of ISH in adults. In case of combination required, thiazide-induced diuresis or calcium antagonism may be added with closer monitoring for adverse events. There is, however, insufficient evidence to determine if AT inhibitors provide a therapeutic advantage versus diuretics or CCBs in terms of reducing the sBP or the risk of mortality and cardiovascular morbidity in ISH patients. Furthermore, AT inhibitors are recommended in adults generally, and not only elderly ISH patients.

This study may, however, have some limitations including the need to define more appropriate sBP inclusion criteria for the ISH patients to either > 160 mm Hg or 140 mm Hg. In addition, there is still a potential to mislead due to some variation across studies and heterogeneity.

Finally, strategies based on non-physician health care providers such as clinical pharmacists should be planned, given the increasing needs of an expanding elderly population with ISH.

Acknowledgments

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