Comparison of safety and efficacy of combinations of Azilsartan-medoxomil/Chlorthalidone and Olmesartan-medoxomil /Hydrochlorothiazide among hypertensive patients: A meta-analysis and systematic review

Satesh Kumar [1], Kamran Mahfooz[1], Asad Ali Siddiqui[1], Jordan Llerena-Velastegui[1], Akhil Raj Anumolu[1], Sowkhya Panakala[1], Rahat Ahmed Memon[1], Taha Nadeem[1], Fatima Tanveer[1], and Mahima Khatri Mahima Khatri[1]

[1]Affiliation not available

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Abstract

Aims: This study intends to compare AZI-M/CT's efficacy and side effect profile to the OLM/HCTZ in hypertensive patients.

Materials and methods: Online databases (PubMed, Google Scholar, and ClinicalTrials.gov) were searched until January 15, 2022, for original articles exploring the effects of AZI-M/CT on pertinent outcomes among hypertensive patients in contrast to OLM/HCTZ. Data on baseline characteristics and endpoints were extracted. Review Manager version 5.4.1 and STATA 16.0 were used for analyses. Risk ratios (RR) and the weighted mean differences (WMD) with corresponding 95% confidence intervals were calculated.

Results: Four studies were included having 3146 patients in total (AZI-M/CT: 1931 and OLM/HCTZ: 1215). The pooled analysis exhibited that compared to OLM-HCTZ, mean DBP was significantly lower in the AZI-M/CT group (WMD –2.64 [-2.78, -2.51]; p= <0.00001, I2= 1%), whereas no significant differences were noted in mean SBP (WMD –2.95 [-6.64,0.73]; p= 0.12, I2=100%) and achievement of target blood pressure (RR 0.95 [0.84,1.07]; p= 0.36, I2= 80%). Additionally, the risk of any TEAE (RR 1.11 [1.03, 1.20]; p= 0.007, I2= 51%) and serious adverse events RR 1.58 [1.20, 2.08]; p= 0.001, I2= 11%) was significantly higher in the AZI-M/CT group. However, no significant differences were observed in the risk of mortality between the two groups (RR 0.74 [0.14, 3.91; p = 0.72, I2= 0%).

Conclusions: Our pooled analysis indicates that AZI-M/CT is more efficient at lowering blood pressure in elderly hypertensive patients than OLM/HCTZ. However, given the limited number of studies, positive results should be discretely re-evaluated and require further research.

Keywords: Azilsartan-medoxomil; Meta-analysis; Chlorthalidone; AZI-M/CT; Olmesartan-medoxomil; OLM/HCTZ.

INTRODUCTION

By definition, hypertension is systolic blood pressure >140 mm Hg and diastolic blood pressure >90 mm Hg. It is highly associated with morbidity and mortality due to cardiovascular issues. In 2013, systolic hypertension caused close to 10.4 million deaths around the world[1]. Therefore, recent guidelines by the European Hypertension Society have suggested considering a lifestyle change with pharmacological therapy for managing hypertension[2]. In this respect, various medicinal therapies are considered, notably angiotensin receptor inhibitors (ARBs) and thiazide diuretics. ARBs and thiazides are first-line drugs used in hypertension, leading to a drop in blood pressure[3]. As a result, these medications have a protective role in reducing the number of life-threatening adverse events, such as heart failure and stroke[1,4].

Azilsartan medoxomil (AZI-M) is a recently accepted long-acting angiotensin receptor blocker. It is more potent and efficacious as compared to the remainder of ARBs[5]. Although thiazide diuretics are the first

line, the effects of Hydrochlorothiazide (HCTZ) compared with Chlorthalidone (CT) remain controversial by comparison[6]. Both drugs have preventative and favorable effects in lowering high blood pressure, the risk of cardiovascular events and can be used as monotherapy or combined therapy. Unfortunately, despite the beneficial effects, these drugs are not free from adverse effects[4]. These include electrolyte abnormalities, variations in blood glucose levels, kidney problems, and worsening of gout.

Several studies have been carried out to compare intragroup and intergroup drug categories. As a result, an extensive comparative profile of efficacy and safety has been elucidated[7]. Current studies document variable outcomes within a heterogeneous population, and the small sample size is not adequately resourced to study associations. Therefore, we meta-analyzed the recent results to find a complete overview of effects of AZI-M/CT versus Olmesartan (OLM) in combination with HCTZ on lowering blood pressure.

METHODS:

Methodology

This meta-analysis assimilates to the guidelines set by Preferred Reporting Items for Systemic Review and Meta-analysis (PRISMA)[8,9].

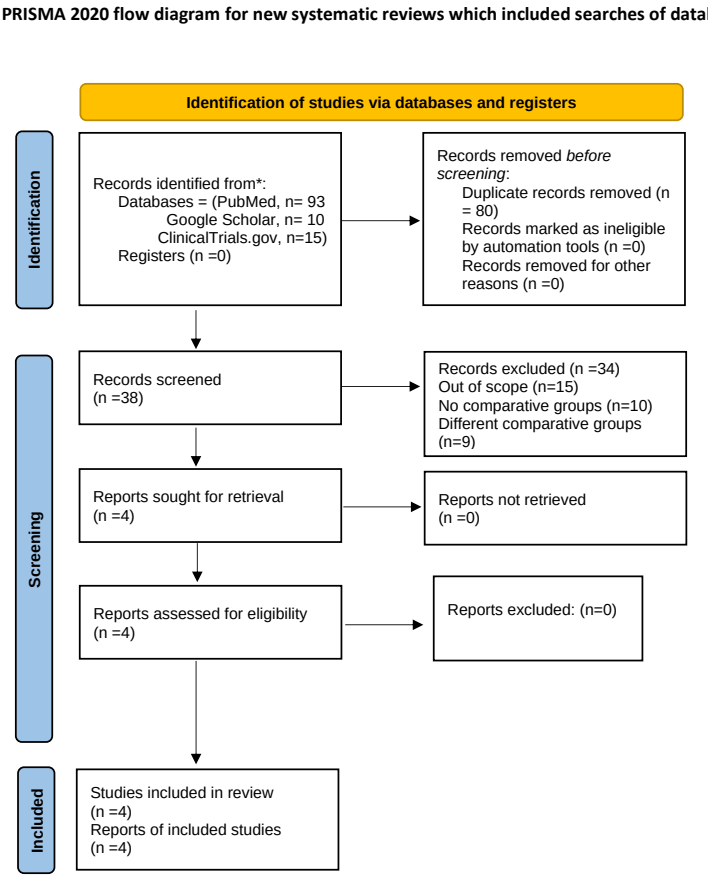

Figure 1: PRISMA FLOW CHART

Search Strategy and Selection

A systematic literature search was conducted up till January 15, 2022, on PubMed, Google Scholar, and ClinicalTrials.gov databases with the following subject keywords and their MeSH terms: (efficacy OR tolerability OR safety) AND (azilsartan OR ARB OR Angiotensin receptor blocker OR medoxomil AND (Chlorthalidone OR thiazides) AND (Olmesartan) AND (hydrochlorothiazide) AND (chronic kidney disease) OR (chronic renal disease). Two reviewers, (SK and MK) independently filtered the search results. A third reviewer (xx) was consulted in case of disparities. Studies were initially shortlisted based on title and abstract, after which the full text was assessed for eligibility. The references of the selected studies were also reviewed thoroughly.

Study Inclusion and Exclusion criteria

Studies were eligible with consideration of the following inclusion criteria: (1) Published full text in the English Language, (2) consisted of patients diagnosed with hypertension (3) Assessment of the effects of AZI-M/C) on relevant outcomes among hypertensive patients and compared it to the effects of OLM/HCTZ. In addition, studies were carefully assessed if they had provided the required data of efficacy and side effect profile of the two drug groups separately. Reviews, editorials, protocols, case reports, and studies without comparison and outcomes were excluded.

Data Extraction

Data extraction of the pertinent studies included the first author, year of publication, type and phase of the trial, study follow-up time, dosages of drugs administered, total number of patients included in the study, and number of patients in individual groups (AZI-M/CT and OLM/HCTZ). Baseline characteristics and additional anti-hypertensive drugs required were also extracted. Primary outcomes of mortality, treatment-emergent adverse events (TEAE), serious adverse events, the severity of adverse events, number of patients titrated to higher dose, mean blood pressure, number of patients who achieved target blood pressure, the system associated adverse events, and change in laboratory parameters were also extracted.

Assessment of Risk of Bias

Quality assessment of all the randomized controlled trials (RCTs) was done by using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials[8]. (Supplemental Table 1)

Data Analysis

The Statistical analysis was done using Review Manager version 5.4.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Denmark, Stata 16.0 (Stata Corporation LP, College Station, TX) and Comprehensive Meta-analysis version 3 (Biostat, Englewood, NJ 2013). Relative risks (RR) for dichotomous data and weighted mean difference (WMDs) for continuous data with 95% confidence intervals (CIs) were calculated using raw study data. They were pooled using a random-effects model. The results of pooled analyses were displayed through forest plots. Beggs's test and funnel plots for efficacy outcomes and treatment emergent and serious adverse events were visualized to assess publication bias. A leave-one-out sensitivity analysis was performed by iteratively removing 1 study at a time to confirm that our findings were not driven by any single study. Heterogeneity was evaluated using Higgin's I^2 tests, which corresponded to low ($< 25\%$), moderate (25–75%), and high ($> 75\%$) heterogeneity[10]. A p-value of <0.05 was considered significant for all analyses.

RESULTS

A total of 118 articles were identified from the initial literature search. After excluding duplicated articles and based on title and abstract, a total of 4 RCTs[5,11-13] was included in this meta-analysis. A detailed search is illustrated in the PRISMA flow-chart. (Fig. 1)

Characteristics of participants

A total of 3146 participants were analysed in the included studies. Out of which, 1931(61.3%) were given AZI-M/CT, and 1215 (38.6%) were in the OLM/HCTZ group.

An overview of patients' characteristics by interventions is presented in Table 1. The mean age of patients was 59.7 +/- 10.02 and the majority of patients were male (n = 1742; 55.37%) and Caucasian (n = 2263; 72%). The mean BMI of patients was 31.28 +/- 6.2 in the AZI-M/CT group and 31.75 +/- 6.3 in the OLM/HCTZ group. 325 (16.8%) patients in the AZI-M/CT group and 227 (18.6%) patients in the OLM/HCTZ group had diabetes at baseline. At the time of admission, the mean SBP was found to be 158.59 +/- 10.7 in the AZI-M/CT group and 157.62 +/-10.2 in the OLM/HCTZ group, whereas DBP was found to be 91 +/- 10.2 in the AZI-M/CT group and 90.9 +/- 10.18 in the OLM/HCTZ group. Additionally, it was seen that at the time of admission majority of patients had an eGFR >/= 60 to < 90ml/min/1.73 m2, 943 (48.8%) in the AZI-M/CT group and 518 (42.16%) in the OLM/HCTZ group, respectively.

Table 1a: Baseline demographics of patients

Study and year	Study design	Phase of trial	Total number of participants	Duration of study	Patients in AZIM/CT	Patients in OLM/HCTZ	Dose of drug (mg/d)		Age, mean (SD)		Male gender, N (%)		Prior antihypertensive use N (%)	
							AZIM/CT	OLM/HCTZ	AZIM/CT	OLM/HCTZ	AZIM/CT	OLM/HCTZ	AZIM/CT	OLM/HCTZ
Cushmann (2012) [5]	RCT	3	1071	12 weeks	707 (66%)	364 (33.9%)	40/25, 40/25	40/25	56.4 (10.5)	56.7(10.1)	424 (59%)	205 (56%)	554(78.3 35%)	277 (76.1%)
Neutel (2017) [11]	RCT	3	837	52 weeks	418 (49.9%)	419 (50%)	40/12.5, 80/12.5, 80/25	20/12.5, 20/12.5, 40/12.5, 40/25	58.5 (10.8)	57.6 (10.8)	226 (54%)	247 (59%)	-	-
Cushmann (2018) [12]	RCT	3	1085	8 weeks	729 (67.1%)	356 (32.8%)	40/25, 40/12.5, 80/25	20/12.5, 5 40/25	56.1 (10.6)	55.7(9.8)	380 (52.1%)	183(51.4%)	-	-
Bakris (2018) [13]	RCT	3	153	52 weeks	77 (50.3%)	76 (49.6%)	20/12.5, 40/12.5, 40/25	20/12.5, 5, 40/12.5, 40/25	67.9 (8.24)	68.9(9.1)	31 (41%)	45 (59%)	-	-

AZIM/CT: Azilsartan-medoxomil/chlorthalidone, OLM/HCTZ: Olmesartan-medoxomil/hydrochlorothiazide

N= represents the

Quality assessment and Publication bias

The quality assessment of studies using the Cochrane's risk of bias tool showed low risk of bias in all the included studies (Supplemental Table 1). The Begg's test (Table 2) and funnel plots showed no publication bias (Supplemental Figure 1).

Table 2: Begg's test of Efficacy outcomes and Adverse events

Outcomes	Begg's test
Any TEAE	0.7341
Serious adverse event	1.9106
Mean SBP	1.2659
Mean DBP	0.3082
Achievement of Target Blood pressure	1.9633

Outcomes

An overview of patients' outcomes by interventions is presented in (Supplemental, Table 2).

Efficacy (Fig. 2)

The main outcome of interest was the difference in the mean blood pressure after the follow-up period. All four (Cushmann 2012[5], Neutel 2017[11], Cushmann 2018[12] and Bakris 2018[13]) studies reported the mean systolic and diastolic blood pressure. The analyses showed that the patients in the AZI-M/CT group had a lower SBP than those in the OLM/HCTZ group (WMD –2.95 [-6.64,0.73]; p= 0.12, I^2=100%). Similarly, the DBP was also found to be lower in the AZI-M/CT group (WMD –2.64 [-2.78, -2.51]; p= <0.00001, I^2= 1%). Additionally, the number of patients who achieved target blood pressure was reported by three out of four studies (Cushmann 2012[5], Cushmann 2018[12] and Bakris 2018[13]). Our study showed that there was no significant difference between the two groups in terms of achievement of target blood pressure (RR 0.95 [0.84,1.07]; p= 0.36, I^2= 80%).

Adverse events (Fig.3)

All four studies (Cushmann 2012[5], Neutel 2017[11], Cushmann 2018[12] and Bakris 2018[13]) reported adverse events. The pooled analysis showed that the patients in the AZI-M/CT group had a significantly higher risk of any TEAE than the patients in the OLM/HCTZ group (RR 1.11 [1.03,1.20]; p= 0.007, I^2= 51%). Moreover, our study showed that the risk of serious adverse events was significantly higher in the AZI-M/CT group (RR 1.58 [1.20,2.08]; p= 0.001, I^2= 11%). Of all the signs and symptoms reported only dizziness was found to be significantly higher in the AZI-M/CT group (RR 1.40 [1.12, 1.74; p = 0.003, I^2= 43%), whereas no significant association was found between headache (RR 0.76 [0.51,1.14; p = 0.19, I^2= 43%), fatigue (RR 1.41 [0.97,2.04; p = 0.07, I^2= 0%). and the two groups.

Only two studies (Cushmann 2018[12] and Bakris 2018[13]) reported the data on diarrhoea and hypotension. No significant association was found between diarrhoea ((RR 0.99 [0.10,9.79; p = 1.00, I^2= 74%), hypotension (RR 1.80 [0.54,5.97; p = 0.34, I^2= 0%) and the two groups.

Mortality (Fig. 4)

Only two out of four studies (Neutel 2017[11] and Bakris 2018[13]) documented the data for mortality. However, the pooled analysis showed that the risk of death was lower in the patients treated with AZI-M/CT than

the patients treated with OLM/HCTZ (RR 0.74 [0.14,3.91; p = 0.72, I^2= 0%).

Laboratory parameters (Fig. 5)

All four studies (Cushmann 2012[5], Neutel 2017[11], Cushmann 2018[12] and Bakris 2018[13]) reported hyperuricemia, hypokalaemia, and increased Creatinine. Of these outcomes, the risk of Hyperuricemia (RR 01.90 [1.43,2.53; p = < 0.0001, I^2= 36%), and rise in the Creatinine values (RR 1.79 [1.26,2.54; p = 0.001, I^2= 70%) was found to be significantly higher in the AZI-M/CT group, whereas no significant association was found between Hypokalaemia (RR 1.43 [0.78,2.62; p = 0.24, I^2= 0%) and either of the two groups.

Three out of four studies (Cushmann 2012[5], Neutel 2017[11], Cushmann 2018[12]) reported the data on the following outcomes: the risk of change in the levels of sodium from normal to low was found to be significantly higher in the AZI-M/CT group (RR 2.23 [1.24,4.04; p = 0.008.72, I^2= 0%), whereas no significant association was found between fasting glucose shift from <7.0 to [?]7.0 mmol/L (RR 1.00 [0.76,1.30; p = 0.98, I^2= 0%), 2 consecutive elevations (1.5 baseline and >ULN) of Creatinine (RR 1.44 [0.49,4.26; p = 0.51, I^2= 73%) and the two groups.

Only two studies (Cushmann 2012[5] and Neutel 2017[11]) reported the data on the shift of fasting glucose Shift from [?]7.0 to <7.0 mmol/L, and the results showed no significant association between the shift in fasting glucose from [?]7.0 to <7.0 mmol/L and the two groups (RR 1.43 [0.72, 2.88; p = 0.31, I^2= 55%).

Leave one out sensitivity analysis (Fig 6)

Due to high heterogeneities in the pooled analysis of mean systolic blood pressure and the number of patients who achieved target blood pressure, a leave one out analysis was performed. According to the results, exclusion of Cushmann 2018[5] and Bakris 2018[13] individually substantially affected the mean systolic blood pressure, whereas exclusion of Bakris 2018[13] substantially influenced the results of achievement of target blood pressure.

DISCUSSION

This comprehensive systematic review and meta-analysis of 4 studies comprising of 3146 patients compared outcomes with AZI-M/CT to OLM/HCTZ in hypertensive patients. Both drugs were able to achieve the target BP, which is less than 140/90 mmHg, or <130/80 mm Hg for those with diabetes or chronic kidney disease[14]. In fact, AZI-M/CT generally showed a higher efficacy at the same doses compared to OLM/HCTZ, causing generally greater decreases in BP, especially significant decreases in DBP across the studies. Even though the decreases in SBP were found to be insignificant, minor reductions can still lead to various cardiovascular benefits. For instance, in middle aged adults, an SBP reduction of 2 mmHg can lead to a 10% lower stroke mortality and around a 7% decreased risk of mortality from ischemic heart disease[15]. Both treatments were mostly tolerated, though AZI-M/CT was found to have higher treatment-emergent adverse events (TEAEs), especially dizziness. However, majority of these were mild or moderate effects that were more commonly found in the higher dosage formulations. Similarly, higher doses of AZI-M/CT were also associated with higher rates of serious AEs and discontinuations. It should be noted that many of these discontinuations were likely because of patients being withdrawn from treatment, as advised by protocol guidance, due to high serum creatinine.

Creatinine levels were significantly higher in patients belonging to the AZI-M/CT group. Nevertheless, these increases were reversible on cessation of therapy, and reflected more of a physiological effect owing to the mechanism of the drugs rather than an adverse effect. In fact, in patients with renal disease who are prescribed ARBs, it is common for serum creatinine to rise to 35% above baseline as blood pressure decreases[16]. Indeed, higher reductions in blood pressure would be associated with greater increases in creatinine, thereby reflecting drug efficacy. ARBs inhibit the renin-angiotensin-aldosterone axis[17]. The decrease in angiotensin-II allows for vasodilation of the efferent arterioles in the glomeruli, increasing renal

blood flow whilst reducing glomerular filtration rate, leading to an increase in various blood metabolites such as urea and creatinine[17]. This effect can be exacerbated in patients with chronic hypertension who are less able to autoregulate renal blood flow due to endothelial dysfunction[18]. When potent diuretics, such as CLD are concomitantly used, volume contraction of blood may occur that can further exaggerate creatinine elevation[17].

This greater efficacy of AZI-M/CT is likely due to the individual benefits of both the component drugs. White et al[19] compared the effects of AZI-M against Olmesartan medoxomil (OLM) and valsartan (VAL). The study found that 80 mg of AZI-M caused a significantly lower reduction in 24 hours mean SBP compared to maximum clinically approved dosages of OLM (40 mg) and VAL (320 mg), while not being associated with any significant increase in AEs[19]. This higher efficacy maybe explained in part by its greater binding affinity to the angiotensin receptor, compared to other ARBs[20]. AZI-M has also been found to be more effective than other diuretics, specifically angiotensin-converting enzyme inhibitors (ACE-I) at reducing BP, while also having the same or fewer side effects, most notably dry cough. These benefits would effectively lead to better treatment compliance[20]. CT has a longer half-life, thus retaining its hypertensive efficacy for longer (47 – 72 hours) compared to HCTZ (16 – 24 hours)[21]. This allows for CT to have comparable reductions to HCTZ in office SBP, superior reductions in 24-hr ambulatory BP, and lower night-time BP[21]. However, a recent observational study found no significant differences between CT and HCTZ in cardiovascular outcomes, namely acute myocardial infarction, hospitalized heart failure, or stroke[4]. Additionally, CT use is associated with a high risk of hypokalemia, and other electrolyte abnormalities, making HCTZ the preferred drug. However, when lower doses of CT are used in combination with an ARB, notably AZI-M, the incidence of hypokalemia and other electrolyte abnormalities decreases and becomes comparable to those of OLM/HCTZ[5,13].

LIMITATIONS

This meta-analysis has a few limitations that should be considered while interpreting the results. First, differences in study designs, interventions, and patient characteristics such as body weight, age, sample sizes and gender ratios present in the patient population, and differences in trial characteristics may have contributed to clinical heterogeneity. Second, the follow up ranges for most studies were variable, with some studies reporting longer follow up periods. Short term follow ups are more useful when evaluating disease prognosis. Conversely, long-term prognosis can overestimate progress by showing better recovery or can show worse decline in health. Third, some drugs/dose combination may have limited power compared to others.

CONCLUSION

Current systematic review and meta-analysis suggests that AZI-M/CT is the better treatment compared to OLM/HCTZ in lowering BP in elderly hypertensive patients. Larger clinical trials comparing efficacy and safety profiles of AZI-M/CT and OLM/HCTZ are warranted to affirm our results.

Declarations of interest

None

Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in the article.

Acknowledgements

None

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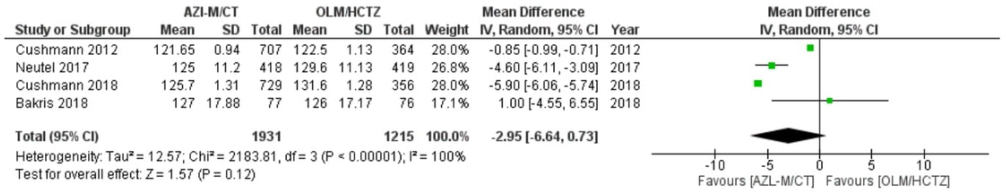

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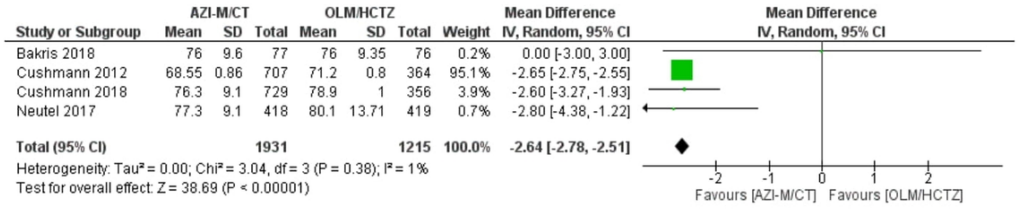

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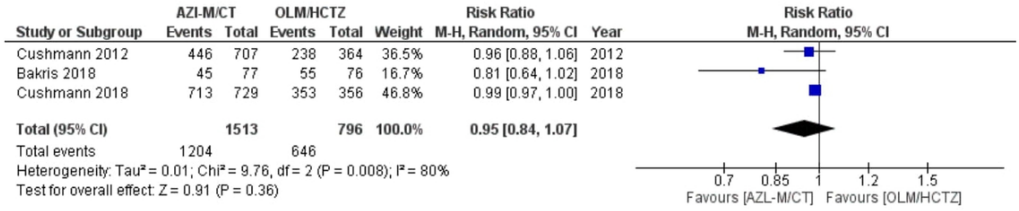

Figure 2: ***Efficacy Forest plot***

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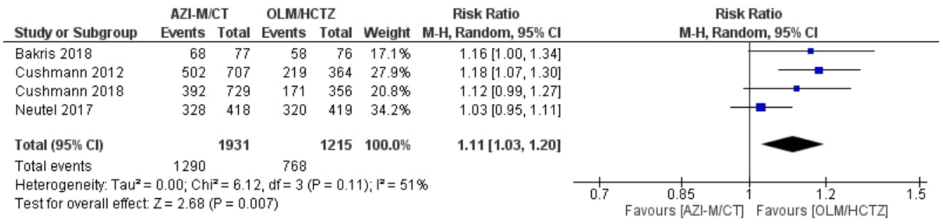

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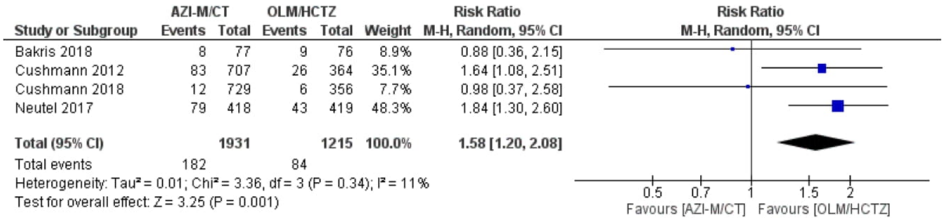

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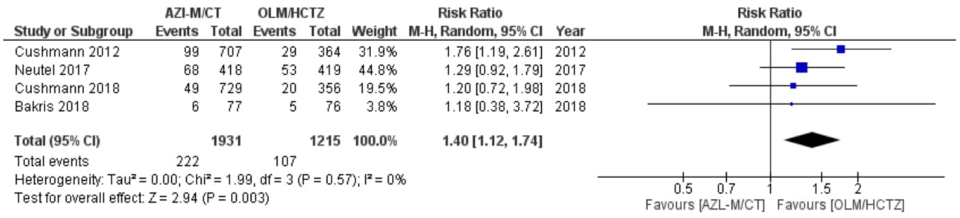

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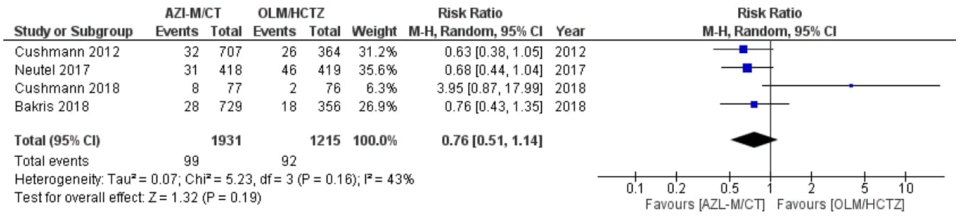

Figure 3: ***Adverse events Forest plot***

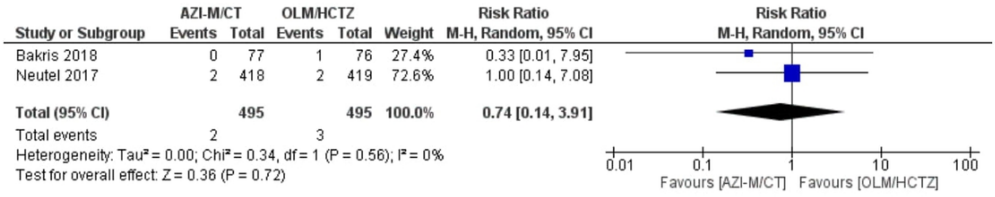

Figure 4: *Mortality Forest Plot*

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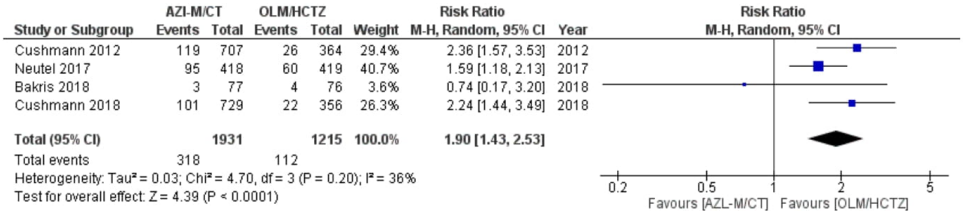

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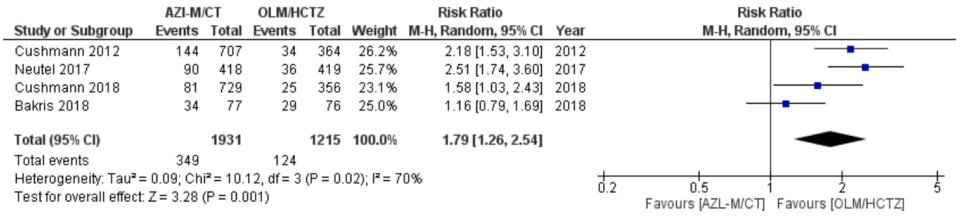

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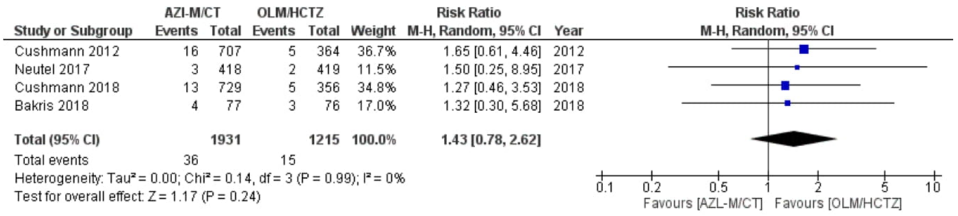

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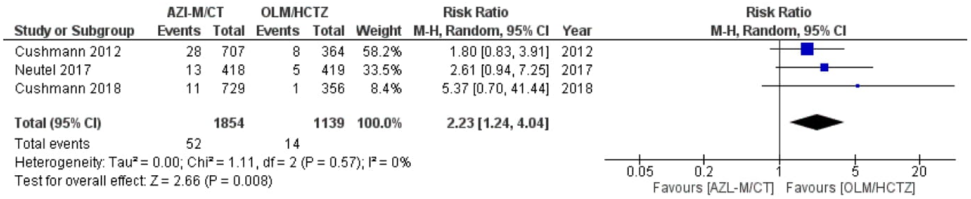

Figure 5: ***Laboratory parameters Forest Plot***

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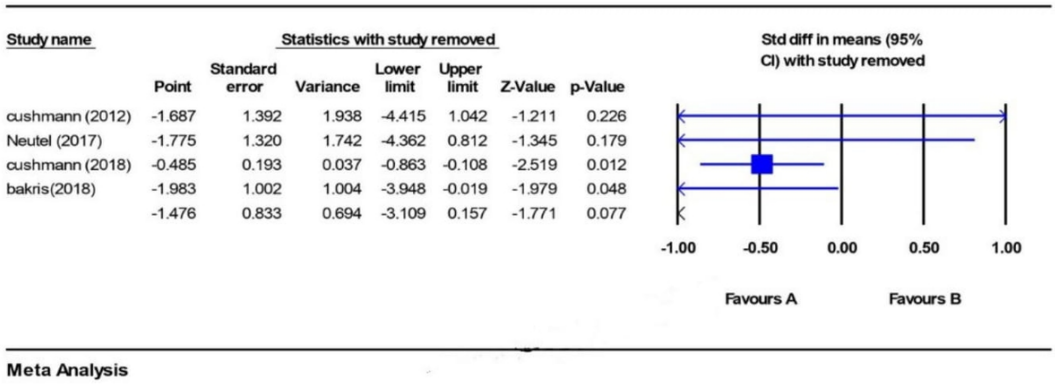

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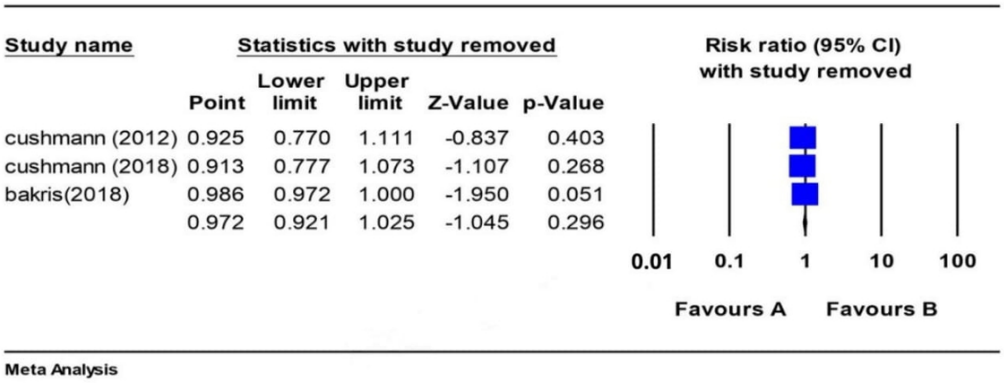

Figure 6: ***Leave one out sensitivity analysis***

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Summary: In this meta-analysis we compare the efficacy and safety profiles of AZI-M/CT with OLM/HCTZ. This supplementary file includes detailed search strategy, data extracted from the included studies for outcomes, quality assessment of the included studies and funnel plots for efficacy outcomes and adverse events.

Supplemental Table 1: Detailed search strategy

PubMed	(Efficacy OR tolerability OR safety) AND (azilsartan OR ARB OR Angiotensin receptor blocker OR medoxomil AND (Chlorthalidone OR thiazides) AND (Olmesartan) AND (hydrochlorothiazide) AND (chronic kidney disease) OR (chronic renal disease) No filters applied	93
Google Scholar	(Efficacy OR tolerability OR safety) AND (azilsartan OR ARB OR Angiotensin receptor blocker OR medoxomil AND (Chlorthalidone OR thiazides) AND (Olmesartan) AND (hydrochlorothiazide) AND (chronic kidney disease) OR (chronic renal disease) No filters applied	10
ClinicalTrials.gov	(Efficacy OR tolerability OR safety) AND (azilsartan OR ARB OR Angiotensin receptor blocker OR medoxomil AND (Chlorthalidone OR thiazides) AND (Olmesartan) AND (hydrochlorothiazide) AND (chronic kidney disease) OR (chronic renal disease) No filters applied	15

Supplemental Table 2: Quality assessment of Randomized controlled trials by Cochrane's risk of bias tool

Article	Selection Bias		Performance Bias	Detection bias	Attrition bias	Reporting Bias	Other bias	Our evaluation
	Random Sequence Generation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective Reporting**	**Anything else, ideally prespecified**	
Cushmann (2012) [5]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Neutel (2017) [11]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	Poor quality
Cushmann (2018) [12]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good quality
Bakris (2018) [13]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk	Poor quality

Supplemental Table 3a: Primary outcomes data extracted from included studies

Study and year	Total no of patients		Any TEAE (n)		Serious adverse events (n)		Death (n)		Mean SBP mm of hg (SD)		Mean DBP mm of hg (SD)		Achievement of target Blood pressure (n)		Patients who were titrated to higher dose (n)	
	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ
Cushmann (2012) [5]	707	364	502 (71%)	219 (60.1%)	83 (11.7 %)	26 (7.14%)	-	-	121.65 (0.94)	122.5 (1.13)	68.55 (0.86)	71.2 (0.8)	446 (63%)	238 (65.38 %)	-	-
Neutel (2017) [11]	418	419	328 (78.4%)	320 (76.37 %)	79 (18.89 %)	43 (10.26 %)	2 (0.48%)	2 (0.477%)	125 (11.2)	129.6 (11.13)	77.3 (9.1)	80.1 (13.71)	-	-	-	-
Cushmann (2018) [12]	729	356	392 (53.7%)	171	12 (1.64 %)	6 (1.68% (	-	-	125.7 (1.31)	131.6 (1.28)	76.3 (1)	78.9 (1)	713 (97.8%)	353 (99.1%)	266 (36.48%)	184 (51.7%)
Bakris (2018) [13]	77	76	68 (88.3%)	58	8 (10.38 %)	9 (11.84 %)	0	1 (1.31%)	127 (17.88)	126 (17.17)	76 (9.6)	76 (9.25)	45 (58.4)	55 (72.3%)	-	

Abbreviations: AZI-M/CT: Azilsartan-medoxomil/Chlorthalidone, OLM/HCTZ: Olmesartan medoxomil/Hydrochlorothiazide, TEAE: treatment emergent adverse events, SBP: Systolic blood pressure, DBP: Diastolic blood pressure
N= number of patients, SD: standard deviation

Supplemental Table 3b: Adverse events

Study and year	Hypotension (n)		Dizziness (n)		Headache (n)		Diarrhea (n)		Fatigue (n)		Myocardial infraction (n)		Cardiac arrest (n)		Pharyngitis (n)	
	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ
Cushmann (2012) [5]	-	--	99 (14%)	29 (7.96%)	32 (4.52 %)	26 (7.14%)	-	-	47 (6.64%)	16 (4.39%)	-	-	-	-	-	-
Neutel (2017) [11]	-	-	68 (16.26 %)	53 (12.6%)	31 (7.41 %)	46 (10.97 %)	-	-	21 (5%)	17 (4.05%)	0	1 (0.238 %)	1 (0.239 %)	0	-	-
Cushmann (2018) [12]	7 (0.96 %)	1 (0.28 %)	49 (6.74%)	20 (5.61%)	28 (3.856 %)	18 (5.05%)	27 (3.71%)	5 (1.40%)	21 (2.89%)	5 (1.4%)	-	-	-	-	-	-
Bakris (2018) [13]	4 (5.19 %)	3 (3.94 %)	6 (7.8%)	5 (6.6%)	8 (10.4 %)	2 (2.63%)	1 (1.3%)	4 (5.26%)	3 (3.9%)	4 (5.26%)	-	-	-	-	0	4 (5.26%)

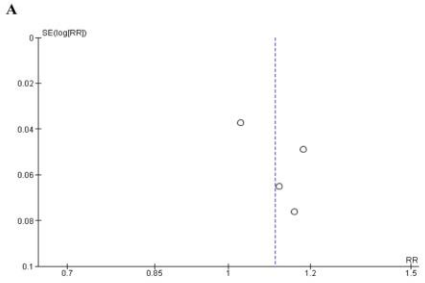
N= number of patients

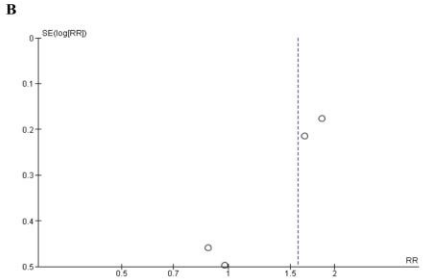
Supplemental table 3c: Laboratory parameters

Study and year	Creatinine: 2 consecutive elevations (1.5 baseline and >ULN) (n)		Cr increased (n)		Mean fasting glucose (SD)		fasting glucose Shift from <7.0 to ≥7.0 mmol/L, (n)		Shift from ≥7.0 to <7.0 mmol/L, (n)		Hyperkalemia (n)		Hypokalemia (n)		hyperuricemia (n)		Sodium from normal -low, (n)	
	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ	AZI-M/CT	OLM/HCTZ
Cushmann (2012) [5]	20 (2.82%)	10 (2.747%)	144 (20.4%)	34 (9.34%)	-	-	57 (8.06%)	26 (7.14%)	30 (4.24%)	15 (4.12%)	-	-	16 (2.26%)	5 (1.37%)	28 (4%)	8 (2.2%)	119 (16.8%)	26 (7.14%)
Neutel (2017) [11]	21 (5.02%)	5 (1.19%)	90 (21.53%)	36 (8.6%)	100.2 (1.19)	1000.24 (1.22)	29 (6.93%)	26 (6.2%)	23 (5.5%)	11 (2.6%)	7 (1.76%)	2 (0.47%)	3 (0.71%)	2 (0.477%)	13 (3.11%)	5 (1.19%)	95 (22.7%)	60 (14.3%)
Cushmann (2018) [12]	5 (0.68%)	4 (1.12%)	81 (11.14%)	25 (7.02%)	99.25 (13.65%)	99.8 (28.03%)	48 (6.79%)	29 (8.146%)	-	-	-	-	13 (1.79%)	5 (1.4%)	11 (1.51%)	1 (0.28%)	101 (14.28%)	22 (6.18%)
Bakris (2018) [13]	-	-	34 (44.15%)	29 (38.15%)	-	-	-	-	-	-	-	-	4 (5.2%)	3 (3.95%)	-	-	3 (3.9%)	4 (5.26%)

N= number of patients, SD= Standard Deviation

Supplemental Figure 1: Funnel plots of efficacy outcomes and adverse events





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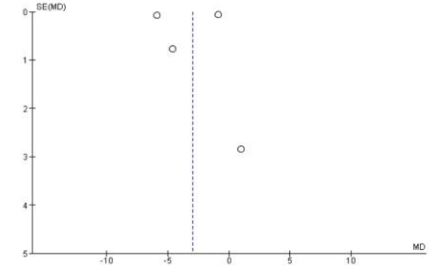

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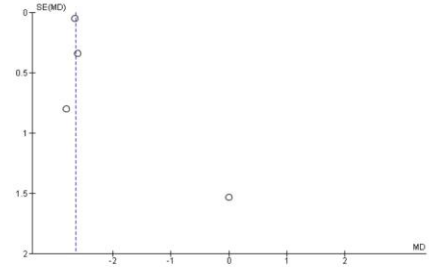

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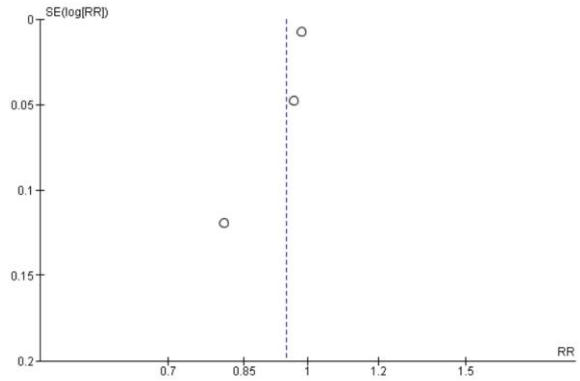

(A) Any TEAE, (B) Serious Adverse Event, (C) Mean SBP, (D) Mean DBP, (E) Achievement of target blood pressure