QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCE

THE EFFECT OF RENIN ANGIOTENSIN SYSTEM BLOCKERS VERSUS CALCIUM CHANNEL BLOCKERS ON PROGRESSION TOWARDS CKD IN HYPERTENSIVE PATIENTS: SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS (RCTS)

BY

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ABSTRACT

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Title: The effect of Renin angiotensin system blockers versus calcium channel blockers on progression towards hypertensive chronic kidney disease: A comprehensive systematic review based on Randomized controlled trials

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Background:

Decline in estimated Glomerular filtration rate (eGFR) is associated with further progression of chronic kidney disease. Evidence suggests that Renin Angiotensin System blockers (RAS), which can be angiotensin-receptor blockers (ARBs) or Angiotensin converting enzymes Inhibitors (ACEIs), have reno- protective effect, but results are variable. Similarly, effects of Calcium channel blockers (CCBs) are shown to have a role in protecting renal function but differ across studies. Hence, the relative effect of ARBs or ACEIs as well as CCBs, and their administration as monotherapy, remain uncertain.

Purpose:

To summarize and determine the pooled effect of RAS versus CCBs on progression towards hypertensive CKD amongst diabetic as well as non-diabetic patients with CKD of any stage from I-IV.

Data Sources:

All language studies in PubMed, the Cochrane Library Central, Clinical Registry of unpublished Trials, WHO, Embase, Scopus, ProQuest, reference lists, and expert contacts up to September 2019.

Study Selection:

This study included all the full text articles that studied diabetic and non-diabetic patients with eGFR ≥ 15 ml/min per 1.73m^3 or Urinary albumin excretion levels (UAE) ≤ 300mg/d during RAS based treatment an intervention in direct comparison with CCBs treatment based approach as comparator at baseline and at the end of follow-up. However, pooling of all the included studies using meta-analysis was not feasible due to substantial study heterogeneity and the small number of included studies that are meta-analyzable. So, studies were selected for systematic review, and out of which, all the meta-analyzable studies were quantitatively analyzed on the basis of main outcomes such as (i) Relative risk for CKD progression and (ii) Mean differences in SBP and DBP for both the arms. Doi plot and funnel plot were used for detection of publication bias.

Results:

Review with seven included trials, and meta-analysis using IVhet model was done on three studies for primary CKD outcome and four studies for secondary BP outcomes. RAS blockers and CCBs did not show any statistically significant differences in terms of its effects on further progression CKD with RR of 0.90 [95% CI 0.69, 1.16]. Moreover, there was no statistically significant difference in BP from baseline to final end points between CCBs and RAS inhibitors with WMD of -2.09 mmHg [95% CI -5.96, 1.79] for mean SBP change and -0.71 mmHg [95% CI -2.16, 0.73] for mean DBP change.

Conclusion:

Evidence asserts no difference between RAS and CCB concerning the risk of progression for CKD and in terms of mean BP differences. However, the study have its own set of limitations due to which more well designed and well conducted RCTs with robust findings are required to confirm the inferences based on this review.

.DEDICATION

"I dedicate my work to my beloved family. For my parents Rafeeque and Saleena for their continuous love and immense support, my husband Aahidh for his unyielding love, commendable level of patience and constant motivation, and sisters Fatma, Zainab, Maryam, Manal and Haya as well as my sister like best friend Diyana for being the best cheerleaders and lifelines. Without their love and care along with Mercy of Allah, I wouldn't have completed my thesis. Alhamdulillahi Alaa Kulli haal. "

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LIST OF ABBREVIATIONS

HTN – Hypertension

WHO – World Health Organization

CDC – Center for Disease Control

BP – Blood Pressure

RAS – Renin Angiotensin System

CCB – Calcium Channel Blocker

ACEi – Angiotensin Converting Enzyme inhibitor

RCTs – Randomized Controlled Trials

ARB – Angiotensin Receptor Blocker

UAE – Urinary Albumin Excretion

eGFR – Estimated Glomerular Filtration Rate

CVD – Cardiovascular Disease

CAD – Coronary Artery Disease

HF – Heart Failure

MI – Myocardial Infarction

PICO – Population, Intervention, Comparator and Outcome

NHANES – National Health and Nutrition Examination Survey

NICE – National Institute for Care and Excellence

RRR – Relative Risk Reduction

RR – Relative Risk

HR – Hazard Ratio

NKF – National Kidney Foundation

CHAPTER –1: INTRODUCTION

According to World Health Organization, nearly 1 in 4 adults have HTN across developing and developed nations (1). The burden of HTN at global level accounts for 7.5 million deaths equivalent to about 12.8% of all deaths and 57 million Disability Adjusted Life years (DALYs), which is equivalent to 3.7% of total DALYS (2,3). It was estimated that overall epidemiological burden for the adults aged ≥ 25 are equivalent to 40% in 2008 (4). The proportion of patients with HTN worldwide increased from 600mn in 1980 to nearly 1 billion in 2008 due to ageing and population growth (3). Amongst the WHO regions, the prevalence of HTN (in both male and female) is found to be the highest in Africa (46%) and the lowest in America (35%) (1,3).

HTN is a significant risk factor for cardiovascular disease and plays an eminent role in contributing to the incidence of chronic heart disease, stroke and kidney failure (5). Uncontrolled BP can also cause vascular dementia, peripheral artery disease, aneurysms as well as eye damage (1). Although Chronic Kidney Disease (CKD) is one of the byproducts of HTN, diabetes and family history which are responsible for 2 in 3 of the CKD cases, it is reciprocal as it can cause HTN as well (6). There is no solid evidence that CKD can be reversed, due to which it is vital to diagnose early for preventing its exacerbation (7).

HTN has been tackled in various ways and the pharmacological therapeutic choices are divided into five major classes of drugs (8). They are: (1) Calcium channel blockers (CCBs) such as Amlodipine (Norvasc), Diltiazem, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil; (2) Angiotensin-converting enzyme inhibitors (ACEIs) such as Perindopril, Ramipril, Captopril, benazepril, trandolapril, fosinopril, Lisinopril, moexipril, enalapril; (3)Angiotensin II receptor blockers (ARBs) such as

Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan; (4) Beta-blockers (BBs) such as Acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, timolol, and (5) Thiazide type Diuretics such as Chlorthalidone, hydrochlorothiazide, metolazone, indapamide (5).

Furthermore, ACE inhibitors and ARBs are commonly called Renin Angiotensin System (RAS) blockers which is also known as Renin Angiotensin Aldosterone System (RAAS) blockers, because of the functions of ACE inhibitors and ARBs (9,10). ACE inhibitors usually inhibit the renin angiotensin I from forming into more potent angiotensin II which can narrow the blood vessels and likewise, ARBs inhibits angiotensin II from binding on its receptors (11,12). According to American Diabetes Association guidelines, these RAS blockers are considered as the first line treatment for those with HTN (13,14)

Recently done trials has shown that BP lowering capacity by RAS blockers has benefit of renal protection in diabetic and non-diabetic kidney diseases and specifically in non-diabetic patients, studies such as AIPRI and REIN trials confirm the added long term reno-protective effect by use of ACE inhibitors (Wolf &Risler, 2004). Studies also advocate that CCBs and ACE inhibitors have a synergistic effect on BP control and CVDs (16). Consequently, it has been shown that if it is used appropriately, it can result in better health outcomes including Reno-protective effect (16–18). Guidelines had placed both CCB and RAS at same levels as initial therapies in patients with HTN without compelling indications; like diabetes or established CAD, stroke or CKD; with preference of CCB in blacks and elderly as more efficacious than other drugs (19).

In addition to above mentioned individual studies, there are several Systematic reviews and meta-analysis on the effects of either RAS blockers, CCBs or both on the

progression towards CKD (20–22). Moreover, several other studies linked across all antihypertensive drugs and its effect on renal outcomes (22–25). Some of them focused on either of the RAS blockers such as ARBs or ACEis and its progression towards CKD (22,26–31). These studies encompassed effect of renal disease progression amongst those with diabetes as well as non-diabetes. On the other hand, there are several other systematic reviews and meta-analysis that emphasized on the effect of CCBs on CKD outcomes (32,33).

Besides, some of the systematic reviews and meta-analysis were covering RAS blockers in direct comparison with CCBs and its effects on renal outcomes (34–37). Out of those four SR and MA that were done in the similar topic, two of them found that there were no significant differences between RAS blockers and CCBs in terms of renal and blood pressure outcomes in addition various other outcomes including stroke, heart failure, cerebrovascular events and all cause mortality (34,35). However, two other very recent ones showed that RAS is superior over CCB for retarding the progression towards CKD and reducing blood pressure (36,37). Nonetheless, all of these studies are quite distinct due to discrepancies in the study PICO from the existing literature. For instance, two of the recent meta-analysis, which was similar in title but different by the population group as they covered only diabetic and CKD Stage 3-5 patients (34). As for clinical trials with direct comparison, majority of them showed that RAS blocker are more effective in slower progression of CKD except two trials. (38–42). On the other hand, one of those two trials showed similar renal outcomes in both the arms while the other one showed that CCB is superior to RAS blockers.

Despite a number of studies and clinical trials are conducted to investigate the

effectiveness of all classes of hypertensive drugs in terms of CKD, CVDs and mortality outcomes, unparalalled evidence on the actual impact of RAS blockers versus Calcium channel blockers based treatment approach on the decline in estimated GFRor increase in UAE for all the hypertensive patients with any CKD stage from I-IV (eGFR≥15 ml/min/1.73m^2 or UAE<300 mg/d) amongst diabetes as well as non-diabetics (43).

1.1. Aim:

To study the relative effect of any Renin angiotensin system blockers (RAS) and any Calcium channel blockers as monotherapy amongst non-diabetic as well as diabetic patients with any CKD stage from 1-4 based on the further decline in eGFR or rise in Urinary albumin excretion levels than at the baseline.

1.2. Objectives:

- To examine the relative risk for progression towards decline in eGFR or rise in Urinary albumin excretion levels with RAS blockers (ACE inhibitors or ARBs) compared to any CCB as an initial therapy amongst non-diabetic as well as diabetic hypertensive CKD patients.
- To investigate the effect of Renin Angiotensin System blockers (RAS) and Calcium Channel Blockers (CCBs) based monotherapies on BP control (SBP/DBP) by pooling mean differences in SBP and DBP.

CHAPTER –2: LITERATURE REVIEW

2.1. Burden of HTN:

According National Institute of Health, one in three adults in US have HTN and it is known as silent killer as it can occur without showing any apparent symptoms (44). Due to its asymptomatic nature, if it is left undiagnosed or untreated, it can place one at greater risk of developing cardiovascular diseases (CVDs) including stroke, heart failure (HF), heart attack (HA) as well as vision loss, CKD or failure, and sexual dysfunction(45–47).

As per projections from NHANES in 2013, prevalence of high BP in the US, will increase 7.2% by the year of 2030. It was found that until the age of 45, men have more burden of HTN than women, followed by similar burden across both the genders between 45-65 years of age and, when the age increases over 65, a higher percentage of women have more prevalence compared to men (4,48).

According to the American Heart Association (AHA) in 2009, 44.8% of male deaths and 55.2% of female deaths were caused due to HTN in the US (48). It was estimated that from 1999 to 2009, there had been an increase by 17.9% in terms of death rates from HTN and the actual number of deaths was found to have risen by 43.6%. As for the economic burden of high blood pressure, it was shown as 51.9 billion dollars in the year 2009 (4).

2.2. Burden of CKD:

According to Center for Disease Control and Prevention (CDC), nearly one in three adults with diabetes and almost one in five adults with HTN are likely to have CKD (49). It was shown that CKD were of high chances when they had hypertension, diabetes or family history(43). When a person is suspected to have decreased renal functions, fluids

accumulate in the body causing excess fluids in the lungs resulting in HTN (50,51).

Studies shows that around 30 million people in United States are having CKD. There are around 48% of those with severely poor renal function do not undergo dialysis are unknown about their CKD Status. Almost every person with mild or moderately poor renal function are unaware of the presence of CKD (51). Studies also indicate that prevalence of CKD is more among women (16%) than in men (13%) in US (50).

According to CDC, risk of premature death from heart disease as well as all-cause mortality is higher in patients with CKD compared to those without (51). However, for end-stage renal disease in which eGFR drops below 15 ml/min/1.73 m2, men are found to have more likelihood than women and African Americans had more risk than whites in US (43,52).

There are multiple studies that indicate the advantages of controlling BP in patients with and without renal disease including slowed progression of CKD and reduction in risk of developing cardiovascular disease as well as mortality (53). Patients with and without diabetic CKD also known as nephropathy with decline in eGFR than normal level of higher than 90 ml/min/1.73 m2 or the presence of proteinuria are shown to benefit particularly from pharmacological approach with RAS blockers using ACE inhibitors or ARBs (53).

2.3. Antihypertensive treatment regimens on CKD and BP control:

In terms of Antihypertensive drugs, ARBs and ACEis are commonly known to be the best of medications for treating HTN as well as due to its independent effect on CVD, CKD and mortality outcomes(19). Several other studies also confirmed that Telmisartan, a type of ARBs and ACEis are highly effective as well as widely prescribed as antihypertensive drugs due to its efficacy and safety profile (54,55). However, many large

studies including meta-analysis have showed that ARBs are sometimes considered to be superior than ACEis with fewer adverse events such as dry persistent cough unlike ACEis (47,54–58). Nevertheless, ACEis are well tolerated as well and was considered to be the first line treatment by various guidelines due to reduced risk of having CKDs, CVDs and Myocardial infarction associated with ACEis (59).

On the other hand, ARBs are known to be costly than ACEis, although these days, ARBs are made available as generic drug which makes the cost difference minimal(19). However, based on numerous studies, both are still recommended equally as they both stay highly superior in terms of its favourable effects (19,60,61).

As for CCBs, various systematic reviews and meta-analysis has shown that amlodipine, a type of calcium channel blockers is beneficial in BP control as well as in protecting against various major complications including CVD and CKD outcomes (32,62,63). Moreover, several significant guidelines also recommend CCBs and RAS blockers including ACEis and ARBs in treating HTN and preventing various major consequences (19,60).

Based on previous studies, guidelines recommend either of RAS based therapy for the patients with nephropathy and without CKDs but has higher risk of developing renal impairment due to diabetes, abnormal level of micro albumin in urine and HTN as ACEis and ARBs has highly superior Reno-protective effects compared to other antihypertensive drugs (64).

Findings based on a large meta-analysis of eleven clinical trials with sample size of 84, 363 patients, demonstrated that RAS blockers including ACEis or ARBs, must be recommended in patients who has high risk of new onset of diabetes (NOD) as these are

helpful in reducing the incidence of NOD and in having desirable effects in Cardiovascular with OR and non-cardiovascular mortality amongst those patients with high risk for CVDs (65).

In addition, numerous clinical trials has indicated that RAS has a significant role in protecting renal function along lowering of BP amongst both diabetic as well as non-diabetic patients with renal diseases due to the antiproteinuric action of RAS (66).

On the contrary, based on an ecological study, it is shown that ARBs and ACEis are the most commonly prescribed medication for high blood pressure, heart and kidney diseases for people with and without diabetes, and there was an increase kidney problems with increasing prescription of RAS blockers which could potentially be due to lack of patient level data (67,68).

Some studies comparing CCBs to RAS blockers stated that their effects are similar in terms of protecting against major complications except that RAS blockers are particularly superior in case of reducing risk of heart failure (13). However, the majority of the recommendation from guidelines considers RAS blockers as a better first line therapy for non-diabetic CKD patients (69).

Concerning RAS blockers' impact on CKD outcomes, there are several systematic reviews or/and meta-analysis that have been done previously. One of the meta analysis that looked at progression of CKD and its association with the factors such as BP control and lower UAE during antihypertensive therapy with or without ACEi, had found that SBP control between 110-129mmHg as well as UAE <2.0 g/d have association with lowest risk for progression of CKD. However, the study also tried to estimate the risk after adjusting for these factors and RR was shown to be 0.67 [95% CI of 0.53-0.84] (21).

Moreover, systematic review showed that ACEi and ARB are being beneficial for treating CKD in Albuminuric patients with diabetes or CVD (28).

Another meta-analysis that looked at the effect of ACEi on progression of non-diabetic renal disease had found that HTN treatment regimens that included ACEi was effective in controlling BP as well as for delaying renal disease progression (70). The mean decrease in SBP as well as DBP was by 4.5 mmHg [95%CI of 3.0 to 6.1mmHg] and 2.3 mmHg [95% CI of 1.4 to 3.2 mmHg] respectively in addition to mean in UAE level by 0.46g/d [95%CI of 0.33 to 0.59 g/d]. After adjusting for baseline factors including changes in BP and UAE levels, ACEi had demonstrated more protective effect in slowing down the progression of CKD towards stage V with RR of 0.69 [95% CI of 0.51-0.94]. Moreover, it was noticed that patients with baseline UAE levels ≥ 0.5 g/d were more advantageous of ACEi therapy. However, study added that their data were inconclusive to suggest whether benefit of ACEi therapy remained same for the patients with baseline UAE levels <0.5 g/d.

Another meta-analysis of randomized controlled trials on the effect of ACEi for the non-diabetic renal disease progression indicated that,BP that was evidently controlled by ACEi. Also, it was shown to have reduced risk for end stage renal disease as well as mortality with RR of 0.70 [95% CI of 0.51 to 0.97] and RR of 1.24 [95% CI of 0.55 to 2.83] respectively (71). The study concluded that ACEi are greatly effective than any other antihypertensive treatment regimens. However, they could not determine if this effect was mediated by its effect on BP or any other related factors.

One of the systematic review and meta-analysis that compared RAS blockers such as ARB/ACEi with other antihypertensive drugs on kidney outcomes, has shown that there

was only small benefit in terms of progression towards CKD Stage V with RR of 0.87 [95%CI of 0.75 to 0.99] (27). The study indicated that the benefit of ACEi/ARB on renal outcome is resultant of its BP lowering effect. However, the study also added that the additional Renoprotective actions of these treatment regimens beyond BP control in diabetic renal disease patients remains unproven. Moreover, they stated there is uncertainty about greater Renoprotective effects seen among non-diabetic renal disease patients. Last but not least, they also stated that placebo controlled trials of ACEi/ARBs showed greater reduction in progression of CKD than those trials that compared ACE/ARBs with other antihypertensive drugs.

According to CASE-J and several other trials, it also indicated that RAS blockers play an essential role in pathological process of elevated blood pressure, kidney and cardiac diseases (40–42) . Besides that, many trials suggest that ARB as a RAS inhibitor is a quite protective first line therapy in diabetic and non-diabetic patients(72–74).

Nonetheless, CCBs as a therapy in the progression of CKD was found to contradicting findings as some trials supporting that it is beneficial while some states that it has no benefit(38,75–77). One of the existing study indicated that CCB is not beneficial in lowering BP and had OR of 1.67 [95% CI of 1.22 to 2.28] for microalbuminuria but favored RAS blockers on its effect in BP control and microalbuminuria with OR of 0.99 [95% CI of 0.73 to 1.35] (78).

Based on several CKD based trials, RAS blockers were known to reduce UAE by 35-40% compared to other antihypertensive drugs after adjusting for BP control effect. However, CCBs were found to have variation in its effects as some studies indicated that Non-dihydropyridine CCBs can be effective for BP control amongst diabetic patients in

comparison to other type of CCBs such as dihydropyridine agents. Lately, studies as well as NICE guidelines showed that CCBs are specifically better in terms of effects for African Americans (19,79).

Besides, several clinical trials had made comparison between RAS antagonists and CCBs in particular. One of the biggest trial by ALLHAT indicate that renal events are similar in both the arms with RR of 0.99 [95% CI 0.77, 1.26] (41). Multiple studies comparing CCB vs ACEi based regimens found no differences in rate of decline in GFR between either of the drug or BP control groups. Another study comparing ARB vs CCB also had shown the same result in terms of GFR reduction (80,81). Moreover, several significant guidelines also recommend CCBs and RAS blockers including ACEis and ARBs in treating hypertension and preventing various major consequences (19,60). Another trial has shown no statistically significant risk reduction between ARB and CCB with HR of 0.40 [95% CI 0.13, 1.29] (42). However, one of the major trials by AASK revealed that there is 38% risk reduction in ACEi group compared to those in CCB [95% CI 10, 58](38).

Another indicated that the proportion of those who had normal albumin status after being microalbuminuric at baseline were relatively higher in ACEi group (46%) than CCB arm (33%) (40). Also, eGFR reduction was found to be higher in ACEi group than CCB based on Nephros and ALLHAT study (39,41). Another study has shown that UAE levels reduction was greater in CCB (Mean change in UAE level of 9.49 mg/d) over ARB group (Mean change in UAE level of 0.29mg/d) (82).

In regard to SR and MA in this context, a recent meta-analysis that had direct head to head comparison indicated that CCBs has higher probability of having renal events

compared to RAS with OR of 1.25 [95% CI, 1.05–1.48] among CKD patients (35). Meanwhile, another study published this year has shown that there is no statistically significant mean difference between CCBs and ACEi with regard to BP, UAE levels as well as GFR of diabetic CKD (37). Similar was the finding based on a study that was published earlier with RR of 1.14 [95% CI, 0.95-1.37] (34). All of these trials had implied similar BP reduction in both the groups (38–42,80,82).

All of these inconsistent results based on numerous studies considering the burden of CKD and the fact that CKD is irreversible, were the driving force behind the rationale of this study as it is important to understand if both of treatments stands equally in achieving better renal outcomes.

CHAPTER –3: METHODS

3.1. Study design

A systematic review and Meta-analysis of randomized controlled trials

3.2. Search Strategy

3.2.1. Data sources

The sources of the data for this study are (a) Electronic databases such as PubMed, the Cochrane Library Central, WHO, Embase, Scopus and ProQuest, (b) Grey Literature such as Clinical Registry of unpublished Trials, International Clinical Trials Registry Platform (ICTRP) and Open Grey, and (c) hand search of reference lists including backward as well as forward citation search and (d) expert contact up to September 2019, for relevant articles in all languages by using the Keywords and synonyms as given below. I also used MeSH terms for PubMed.

I screened the reference lists of included studies and related publications, and corresponding authors were contacted for clarifications regarding the relevant articles that had potential for inclusion. For instance, As for large studies by Research study groups such as AASK and ALLHAT had done multiple trials over the years that used same population but not clearly mentioned in the trial, its authors were contacted to confirm population group they employed and asked them if they used same kind of population but from different locality, in which case, studies can be eligible. These were required to be understood to make a decision on selection of such trials because if it is found to be same population, it is not possible to include more than one trial by AASK or ALLHAT. Also, some of the authors were contacted for the purpose of retrieving the data that I need as it was not mentioned in the study. In addition, I had looked for existing meta-analyses and

systematic reviews in the context of antihypertensive drugs and its impact on CKD outcomes, to ensure that no studies, that meets criteria, were missed out during study selection from the above-mentioned data sources.

3.2.2. Search terms

Table 1: Keywords used in the search engines

Population	Intervention	Comparator	Outcome
HTN , high BP , elevated blood pressure	Angiotensin-receptor-blockers, arbs, losartan, valsartan, irbesartan, candesartan, telmisartan, eprosartan, olmesartan, Angiotensin-converting enzyme inhibitors*, aceis, perindopril, ramipril, captopril, benazepril, trandolapril, fosinopril, lisinopril, moexipril, enalapril	Calcium channel blockers, ccbs, amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, Lercadipine , verapamil , diltiazem	Glomerular filtration rate, GFR, proteinuria, microalbuminuria, urinary excretion levels, non-diabetic nephropathies, renal impairment , renal failure, stage 3 chronic kidney disease, stage 4 chronic kidney disease, stage 5 chronic kidney disease*, CKD*, Chronic kidney disease*

3.2.3. Search String(s)

The search thread used for screening title or abstracts was angiotensin converting enzyme inhibitor* OR Perindopril OR Ramipril OR Captopril OR benazepril OR trandolapril OR fosinopril OR Lisinopril OR moexipril OR enalapril OR angiotensin recptor blocker* OR losartan OR valsartan OR irbesartan OR candesartan OR telmisartan OR eprosartan OR olmesartan AND calcium channel blocker* OR Amlodipine OR

Diltiazem OR Felodipine OR Isradipine OR Nicardipine OR Nifedipine OR Nisoldipine OR lercadipine OR Verapamil OR diltiazem AND Glomerular filtration rate OR GFR OR CKD OR Chronic kidney disease* OR nephroprathies OR renal impairment OR proteinuria OR Albuminuria.

Search restriction were none but humans based studies. Also, primarily I focused retrieving only experimental studies as I was aiming to do Meta-analysis and ended up with 3-4 studies that were meta-analyzable. However, since Meta-Analysis of less than 5 studies is not preferable due to flawed error estimation, I included studies that were not meta-analyzable in terms of CKD measures to pool more studies with an aim to do Systematic review alone (83).

Some of the major databases along with search strings that were used in retrieving the relatively relevant articles from three of the major databases are given in Appendix A, to enable replication by other researchers.

3.3. Study Selection

This study has a well-defined PICO based on which the set of eligibility criteria, were followed and met. In our study, the population (P) are non-diabetic as well as diabetic hypertensive adults aged ≥18 years with CKD of any Stage except V, I (Intervention) as RAS blockers based treatment approach (ACE inhibitors or ARBs), C (Comparator) as CCB based treatment approach, and O (Outcome) as progression towards further CKD in terms of further reduction in estimated glomerular filtration rate (eGFR)or added increase in UAE levels than at the baseline. In terms of treatment strategies, the studies must be looking at a single pill therapy for both RAS blockers as well as CCBs.

The inclusion criteria had included all the full text articles that studied non-diabetic

and/or diabetic hypertensive patients with either eGFR ≥ 15ml/min/1.73 m^2 or UAE ≤ 300mg/d during RAS based treatment approach in direct comparison with calcium channel blockers treatment based approach. Thereby, I included patients with and without CKD (Stage I-IV) to discern the progression of CKD in terms of decline in GFR and increase in UAE than at the baseline after taking the medications.

In other words, aim was to assess those studies that begin with RAS blockers based monotherapy or any add on other than CCBs as well as any CCB based monotherapy that had any add on other than any of RAS blockers amongst non-diabetic and diabetic adults aged ≥18 with eGFR ≥15 ml/min/1.73 m^2 or UAE ≤ 300mg/d. Moreover, included studies must have direct head-to-head comparison between intervention and comparator and must not be of less than 3 months in terms of patients' follow-up.

This study had excluded those studies that had patients with renal transplantation, any degree of abnormal urinary protein excretion of more than 300mg/d or reduced eGFR of less than 15 ml/min per 1.73m^2, duration of less than 3 months, and the ones who had undergone dialysis and pregnant women. Pregnant women are excluded as their management of HTN varies from that of a normal adult in general and according to NKF, pregnant women should not be included in antihypertensive drug based trials as it can negatively affect the fetus (79,84). I chose 3 months as minimum study duration because according to American Society of Nephrology (2011) and National Kidney Foundation (2004), it was mentioned that initiation of study medication can take 3-4 months to show decrease in renal function depending on the GFR observed at the baseline (79).

Moreover, the studies with RAS based combination therapy, to which any CCB was being added or vice versa, were excluded, as that could potentially confound the actual

impact of each monotherapy. Concomitantly, the studies that had any RAS based first line monotherapy, which was later combined by either of RAS blockers, were excluded. As a matter of fact, there were a large number of studies that indicated that ARBs in combination with ACEis has very limited and contradicting evidence on the safety and efficacy in regard to combining these two prominent antihypertensive drugs (10). In addition, various international guidelines on medication use including NICE (National Institute for Care and Excellence) guidelines generally recommends to avoid using combination of ARBs with ACEis (9,19,53,85)

Based on the criteria as aforementioned, selected studies had either any ACE inhibitor versus any kind of CCB being the first line monotherapy OR the ones has any ARBs versus any CCB as the monotherapy being prescribed for hypertensive patients with all stages of kidney disease except Stage V (eGFR≥15 ml/min/1.73 m^2 or UAE <300 mg/d) and for patients with or with diabetes.

In overall, I screened titles and abstracts for the studies based on this topic and retrieved all the articles that can potentially meet inclusion criteria based on Population, Intervention, Comparator and outcomes as well as methodology the studies have employed. In terms of study design, I had searched for all kinds of study designs including experimental as well as non-experimental studies such as cohort and case control.

Apart from all that, the Study had an intention to include an independent reviewer for study selection. However, independent reviewer could not complete the task, given the tight schedule of the thesis completion. Nevertheless, Quality of our selected studies for this Systematic review and Meta-Analysis were independently assessed by another separate reviewer. There were no disagreements with reviewer.

3.4. Study outcomes

The three main outcomes of this study are RR for proportion with further progressed CKD and WMD for changes in BP measurements including SBP as well as DBP. All the outcome values were expressed in terms of Mean ±SD unless it is stated as median with 25^{th} and 75^{th} percentiles.

3.4.1. Primary Outcome

The primary outcome of this study is further progression of CKD in terms of added decline in GFR values or by further increase in UAE levels than at the baseline. I chose these two measures as they were more reliable measures based on NIDDK (43). Estimated GFR levels is a measure that will be calculated based on blood creatinine test, age, gender and body size according to National Kidney Foundation (86). It can be calculated based on Plasma clearance and cystatin C as well (86). It was expressed in ml/min/1.73m^2. Studies with estimated GFR are based on any of the existing equation with components such as iothalamate clearance, inulin, Cr-EDTA, Tc-DTPA, or iohexel, were included as part of this study because GFR equation according to KDOQI guidelines is relatively new and most of the studies that met the study criteria were done earlier than 2015. Based on eGFR, a person is said to be normal level of having eGFR when one is having eGFR of more than 90 ml/min/1.73 m2, he/she is considered to be in Stage I, 90-60 ml/min/1.73m^3 being considered as CKD Stage II and lower than 60 ml/min/1.73 m^2 is the stage III CKD at which it is considered to have actual impairment in the renal function and lower than 15 ml/min/1.73 m^2 are suspected to have developed kidney failure (43).

In regards to UAE as an alternative measure of outcome, same condition was applied as there is no one unified way of determining it. I accepted all the studies with any of the

immunochemical methods for ascertaining UAE levels such as immuno-nephelometry, radioimmunoassay and immuno-turbidimetry (87).

Based on these aforementioned measures for CKD, I was interested in estimating the overall pooled RR for the proportion with progressed CKD that was based on further decline in GFR/increase in UAE levels.

3.4.2. Secondary Outcomes

BP control is the secondary endpoint of this study, which was calculated based on change in SBP as well as DBP by the end of the study duration in relation to the BP at the baseline. Any device that assess BP were included for this study without any restriction such as Hawksley random zero sphygmomanometer, mercury sphygmomanometer (Korotkoff I and V), or using any certified equipment (Spacelabs 90207, Redmond, WA, USA) like mentioned in of the included studies. This is because comparative studies done on devices used for assessing BP, indicated that they were all more or less same with each other (88). BP measurements taken in any position including sitting, supine and standing, were considered as a part of this study.

Concerning BP outcomes, it included (a) mean SBP change and (b) mean DBP change, which were both ascertained in the form of WMD during quantitative analysis. For both the secondary outcomes including WMD in SBP and WMD DBP, I estimated mean differences to calculate WMD based on the differences observed at the end of follow up in relation to the observed value at the baseline (89).

In other words, formula was as following:

Mean differences = Baseline mean – Final mean or the mean at the end of Follow up

Apart from aforementioned study outcomes, I had an intention to look at additional CKD outcomes such as mean change in GFR rates as well as mean differences in UAE levels, and additional BP outcome such as the proportion with controlled BP. However, there were no sufficient data in regards to those additional CKD outcomes as only two studies reported required data and BP outcome from neither of the included studies. Due to these issues, I dropped the idea of doing meta-analysis on these additional BP and CKD outcomes.

3.5. Data Extraction

Data extraction from selected studies has been confirmed independently by another reviewer. It includes a section with baseline characterstics such as mean age, gender, race, origin of the study, history of Heart diseases as either Yes or No, type and dosage of ARBs, ACE inhibitors and CCBs; duration of therapy, co-interventions such as concurrent use of sodium restriction or diuretics, doses given, primary as well as secondary outcomes of the included studies and summary of each study findings given in following section with measurements of SBP and DBP levels in mmHg, and eGFR in ml/min/1.73 m2 or urinary albumin excretion levels at baseline and follow-up,

In regard to mean age based on all the selected studies, I calculated manually based on the mean age of each study. In other words, mean age of the included studies was the average taken from the sum of averages of each study.

Apart from all that, there was a study that had only median and Interquartile range instead of Mean and Standard deviation (SD), I contacted authors in this case for the mean and SD of BP measurements, GFR values or UAE levels. However, one of the two authors responded that they do not wish to provide the data. Another study had not reported

aggregate mean and SD but across subgroups such as race and gender in which case I had contacted Author for providing us with aggregate mean for which I did not receive any response.

When comparison of studies are made and doses are varying, the studies with highest dose are usually considered (90). However, I had included all doses to examine if it has differential impact on the outcomes. Moreover, I also chose studies with add on therapies as per our inclusion criteria. I also examined if intention to treat analysis was done for those with high loss to follow-up in relation to the number of events occurred.

As for our quantitative analysis, I determined overall pooled estimates for all three outcomes including CKD and BP outcomes using meta-analysis such as (i) Relative risk for CKD progression, as our primary outcome, and (ii) Weighted mean differences (WMD) in SBP and (iii) Weighted mean differences in DBP as our secondary outcomes. With regard to Meta-analysis for CKD outcome, which is to determine RR, I retrieved the data such as number of total participants, cases, and non-cases for each group. In regards to our meta-analysis that were done for secondary BP outcomes, which are to determine (i) WMD in SBP, and (ii) WMD in DBP change separately, I extracted the data regarding sample size, mean differences from baseline by the end of follow-up (FU), and its respective standard deviation (SD) for both the treatment groups.

As a matter of the fact, none of the studies had reported Standard deviation explicitly, for mean differences for both the intervention arms. However, I had managed to calculate the standard deviation manually using the given standard deviation for baseline as well as for the end of follow-up and the sample size (n). The formula of SD for mean differences that was used in this study was following:

$$SD = \sqrt{(SE \text{ at the baseline})^2 + (SE \text{ at the end of follow-up})^2}$$

Where, SE = SD of baseline or end of follow-up divided by $\sqrt{n}$

This formula was used to calculate the SD for mean differences in both the groups –RAS as well as CCB. It is important to note that I had an assumption for this study regarding the SD. I assumed that the SD at the baseline were to remain same until the end of FU in an ideal situation (89). So, whichever study that did not report SD at the end of follow-up, I used the SD at baseline for the end of FU as well. Concomitantly, I do acknowledge that the precise SD at the end of the follow-up must have been different due to sampling error for those studies that did not report them. However, I made an assumption to enable inclusion of those studies by considering them as an ideal case.

3.6. Quality Assessment

In this study, risk of bias assessment for methodological quality was done using Cochrane Collaboration tool (91). It is based on seven items such as random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases such as funding bias if manufacturer of medication is the source of fund for the study trial (91). These domains cover various prominent biases such as selection biases, performance bias, attrition bias and detection bias. For instance, first two domains affects selection bias as without randomization, individuals might be selected selectively for each of the interventions. In addition, without allocation concealment, individuals can know which medication they are assigned to and potentially tried to change if it is not of their choice, which can create bias. In terms of other biases, it can include funding or any other bias that are not covered in other domains (91,92).

Biases under each of those eight domains can be judged as either low, high or unclear. If information is sufficient, I have reported it as low, unclear in case of lack of details reported and high risk if the method adopted was unsatisfactory or insufficient that has high likelihood to alter the results. These justifications for judgements as any of these options, are based on Chapter 8 of the Cochrane handbook (91,93).

Any discrepancies in the assessment with independent reviewer were resolved without conflicts. Cochrane collaboration tool was executed with the help of RevMan 5.3 to produce Risk of bias plot and summary graph based on the studies selected as a part of this review.

3.7. Data Synthesis and Analysis

This study primarily began with exploring baseline characteristics and summary of findings of the included studies followed by the detailed description tables for each single study, which was provided in the Appendix B.

With regard to quantitative analysis, I used MetaXL software v5.3 to determine overall pooled estimate of RR for primary CKD outcome and WMD for secondary BP outcomes using IVhet (Inverse variance heterogeneity) model. I preferred IVhet to other models because it has been considered as optimal for the meta-analysis with few numbers of studies and high heterogeneity (83,94). Furthermore, it is proven to be better than Random effects model and that it covers issues concerning underestimation of standard error, CI's poor coverage and elevated MSE (83,94–96). However, I had executed Fixed effects and Random effects model as well for CKD outcome for exploratory purpose (95). In regard to BP outcome, quantitative analysis was done based on 4 studies that reported mean values at the baseline and end of follow-up along with SD to produce weighted mean

differences (WMD) using IVhet model, for which each study will be weighted by its sample size (97,98). As for publication bias, I assessed Doi plot that measures the bias based on LFK (Luis Furuya Kanamori) Index that will provide us with a value that can show the indication for bias (95,99). If the value less than -1 and 1, it is considered as "no asymmetry" which states that there is no publication bias. In addition, when the values are between |1| and |2|, it shows there is "minor asymmetry". Moreover, if the LFK index goes beyond |2|, it is said to be having "major asymmetry". The advantage of this plot is that it is more sensitive than funnel plot and was proven to be well suited for meta-analysis with fewer than 10 studies unlike Funnel plot (99). Hence, I preferred Doi plot over funnel plot (95,99,100). For those Meta-analyses with more than 25% heterogeneity, I wanted to do sub-group analysis or Meta-regression to identify source of variation in effects across various subgroups. However, I could not do further heterogeneity assessment as there were only very few meta-analyzable studies with which quantitative synthesis were done (101). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guides reporting of this study and its checklist has been enclosed as Appendix C (102,103).

3.8. Ethical considerations

This study did not require any primary or secondary data collected from individual or group of patients' data that would demand confidentiality, privacy and protection since it was a systematic review and meta-analysis based on published experimental studies from the literature. However, a QU IRB approval was sought, and it was approved with an exemption.

3.9. Funding source

This project was not funded by any source.

CHAPTER –4: RESULTS

4.1. Results of the search

As for producing this review, the search was seemingly comprehensive with results based on multiple databases and by hand search of all potential and included studies. Overall, the search that included a time window up to September 2019 resulted in 5826 citations. Out of which, 4579 citations were retrieved from three major databases with 1090, 1799, and 1720 being identified through PubMed, Embase and Cochrane Library respectively. In addition to that, 1247 of additional search results were being identified through other sources including reference lists, Clinical Registry of Unpublished trials, WHO, Scopus and ProQuest. Majority of the results were by hand search and only less than 10% of it constituted the results from the other sources. After reading titles, 2689 duplicated were identified and thereby removed which then resulted in total of 1569 records that met the criteria by title and majority of them comprising of 1462 results were then excluded after reading Abstracts.

A total number of 107 were, consequently selected for full text articles assessed for Eligibility. However, 100 results were excluded due to several reasons such as outcomes of interest not reported either BP or CKD outcome(n= 67) as the study must include both of its main outcomes, insufficient duration of study (n= 21), wrong add-on therapy/ crossover (n = 9) and studies that used same population (n=3).

Besides, since its systematic review, I tried hand searching the reference lists and all the databases as mentioned earlier except Embase for observational studies as well. However, there were no non-experimental studies in the context of my topic that met my study criteria. I eventually had only seven studies that met our inclusion criteria for our

qualitative synthesis. However, not every study had required values to estimate the pooled effect sizes such as cases and controls from each arm due to which our Meta-Analysis was done on 3 studies only for CKD outcome. Correspondingly, only 4 studies were suitable for meta-analysis for secondary outcome. The study flow diagram based on the PRISMA checklist was shown in Figure 1.

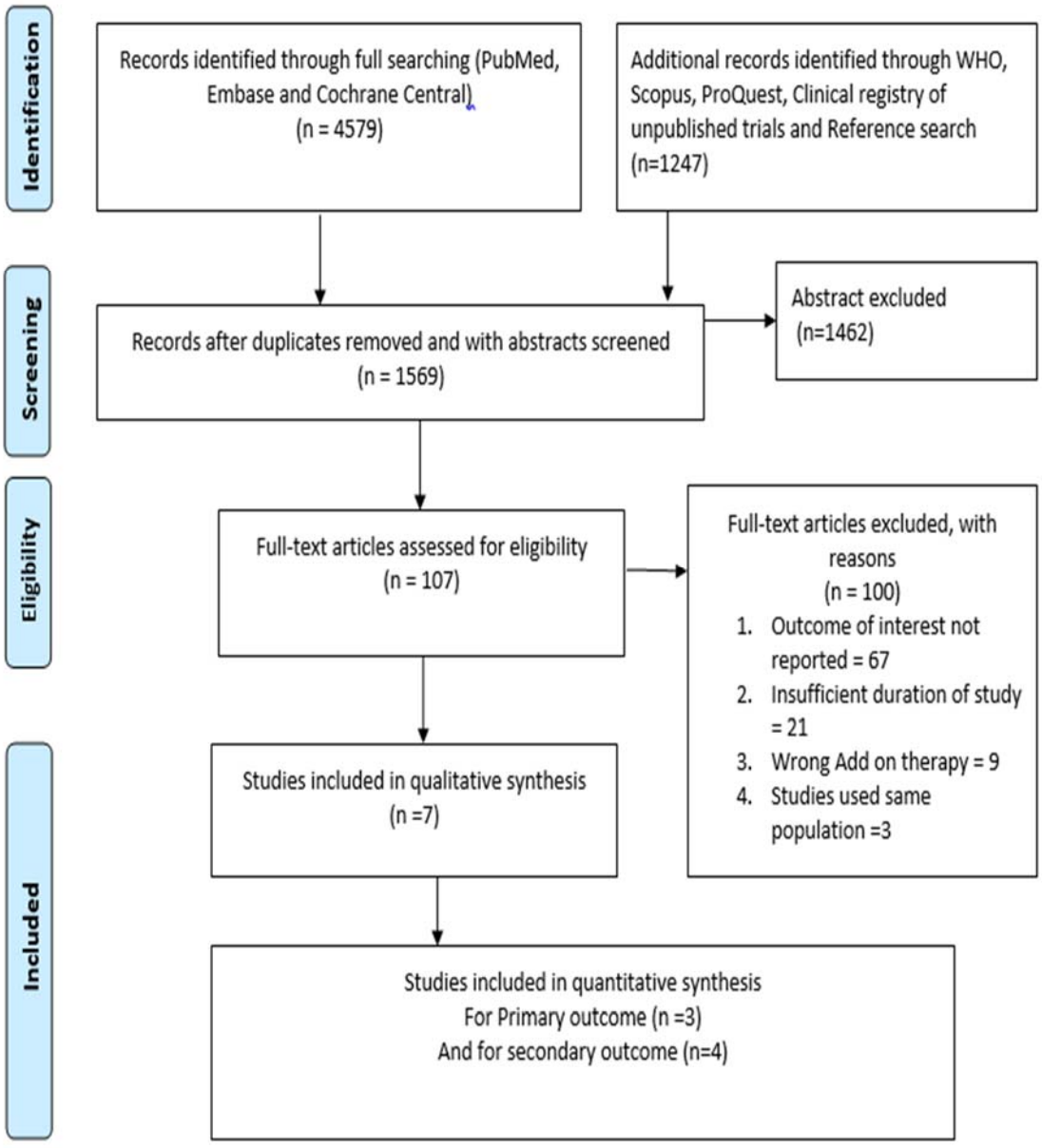

Figure 1: Study flow diagram

4.2. Characteristics of Included studies

Baseline characteristics of the included studies were shown in table 2. I identified seven randomized controlled trials that met our inclusion criteria. Despite of a search without restriction to experimental studies alone, only RCTs were found to meet the criteria of this study. That is the reason why study has been entitled as "Systematic review and meta-analysis of RCTs", even though search was not restricted to RCTs alone.. All of them comprised of direct head-to-head comparison with RAS inhibitors either ACEi or ARB compared against CCB. Out of seven included trials (n=24446), four of them (57.1%) were based on ACEi compared with CCB with 19663 participants (38–41). Rest of the three trials constituting 42.8% were done based on comparison between ARB and CCB with a total of 4783 participants (42,80,104). Trials that did a comparison with placebo were not identified for this study.

4.2.1. Age:

Based on the table 2, the mean age of participants across all the included trials was 56.6 years. Most of the trials had an age range between 50 and70 years (38–42). Nonetheless, two of the included trials were limited to an average age of patients less than 50 years (80,82). Mean age of population in trials that had a direct comparison between ACEi and CCB was 59.12 years with a range of 50-70. On the other hand, the average age of patients in trials that investigated ARB versus CCB was 53.3 years with a range of 45-65.

4.2.2. Country or the origin of the study:

Two of the trials recruited participants from USA with 19196 participants constituting 78.5% of total participants (38,41). One of the remaining trials was from Turkey

with 20 participants (<1%) (82); another one from Japan with 4703 participants (19.2%) (42). Rest of them (42.8%) were found to recruit from European countries such as Sweden, Italy, and Greece with a total of 527 participants accounting for 2% (39,40,80).

4.2.3. Male proportion:

As for the gender of the participants, three of the studies (42.8%) had reported around 50-55% of male population in their study (40–42). While three other studies (42.8%) reported around 60-65% of men in their trial (38,39,80). Nevertheless, the smallest of all included trial, had not reported the gender proportion (82).

Furthermore, HTN can be said as either primary or secondary, wherein primary is the one with HTN due to non-identifiable cause while secondary is the one with several secondary causes (105,106). In this study, patients in all the trials were considered to have eGFR >15 ml/min per 1.73^2 or urinary albumin excretion levels <300mg/24h. In other words, included trials comprised of patients without CKD (82) or with CKD of any stage from 1-4 but with exception of stage 5 (38–42,80), which represents Kidney failure or need for kidney transplantation or dialysis. Hence, this study assessed alternative therapies used in treating patients with primary as well as secondary causes of HTN as it includes people with or without CKD, with or without diabetes and patients with low and high-risk hypertension.

4.2.4. Length of the follow-up:

Study duration of all the included trials was of 3 months at minimum. Trial by Ay et al (2013) was the one with smallest duration and trial by Leneen et al (2006) had the highest length of the follow-up with 4.9 years.

Table 2: Characteristics of included studies

Author	Year	Country	P	I	LoFU	History of Heart Diseases	CoI	Study endpoints
Agodoa et al.	2001	USA	Non-diabetic (100%) African Americans with mean age of 54.3 and GFR of 65-20 ml/min per 1.73^2 (n=1094)	CCB vs ACEi vs BB	3 years	NR	NR	Primary: Rate of change in GFR Secondary:Composite Index of the clinical endpoints of reduction in GFR of more than 50% or 25ml/min per $1.73m^2$
Herlitz et al.	2001	Sweden	Non diabetic patients (100%) with uncontrolled HTN with mean age of 53 years and GFR >20 ml/min/ 1.73 m^3 (n=158)	CCB vs ACEi vs CCB+ ACEi	1.73 years**	NR	NR	Change in BP measurements and renal function
Fogari et al.	2002	Italy	Diabetic outpatients with mean age of 62.5 years and microalbuminuria (n=309)	CCB vs ACEi vs CCB+ ACEi	4 years	NR	NR	Primary: Effect on Microalbuminuria, Secondary: cardiovascular outcomes
Leneen et al.	2006	USA	Diabetic participants (41.2%) with mean age of 66.7 years (n=18102)	CCB vs ACEi	4.9 years	Y	Y	Primary: Composite of fatal CHD or non-fatal MI Secondary: All-cause mortality, fatal and non-fatal stroke, combined CHD, combined CVD. Other pre-specified secondary outcomes such as end-stage renal disease [ESRD], cancer, hospitalization for GI bleeding, angioedema, and ECG-left ventricular hypertrophy (LVH)

Author	Year	Country	P	I	LoFU	History of Heart Diseases	CoI	Study endpoints
Ogihara et al.	2008	Japan	Hypertensive diabetic Japanese patients (42.9%) with mean age of 63.8 years (n=4703)	ARB vs CCB	3.2 years**	Y	Y	Primary: Sudden death, Cerebrovascular, cardiac, renal and vascular events Secondary: All-cause deaths, new-onset diabetes and discontinuance of treatment due to adverse events
Liakos et al.	2012	Greece	Non diabetic Caucasian hypertensive patients with mean age of 46.9 (n=60)	ARB vs CCB	9 months	NR	NR	Effect on acute exercise induced inflammatory and thrombotic response
Ay et al.	2013	Turkey	Non diabetic patients with mean age of 49.4 years (n=20)	ARB vs CCB	3 months	NR	NR	Effect on Microalbuminuria

*ACEi – Angiotensin converting enzyme inhibitor; CCB – Calcium channel blocker; CVD – Cardiovascular Disease; UAE – Urinary Albumin excretion; CHD – Coronary Heart Disease; HF- heart failure; ARB – Angiotensin receptor blockers; MI – Myocardial Infarction; RRR – Relative risk reduction; P-Population; I-Interventions in the study; NR-Not reported; LoFU-Length of the Follow-up; CoI- Cointervention such as concomitant use of sodium restriction/diuretics/beta blockers; Y indicates YES, and N indicates NO;

**LoFU expressed in terms of mean

4.2.5. Race/ ethnicity of the population:

In terms of ethnicity, one of the studies was based on African Americans in which study focused on Blacks alone (38). While another study comprised of blacks as well as non-blacks (41). Two of the other studies (28.5%) reported that their study were based on Japanese and Caucasian patients only, respectively (42,80). Three trials constituting almost 43% had not reported ethnicity of their participants in their respective studies (39,40,82).

All trials had sought informed consent from their participants prior to their trial initiation. I had included all the participants with any stage of hypertension, any stage of CKD except Stage 5, which is in state of kidney failure seeking transplantation or dialysis. I also included those studies for which patients had diabetes as well as non-diabetes to compile the evidence on Hypertensive patients progressing to further decline in GFR or rise in Albumin levels regardless of the history of any CVD events. Trials that were already taking RAS inhibitors or CCBs were not included as it would over or underestimate the effect of medication if any effect is actually present. Also, trials with crossover design was excluded to avoid biased estimate; however, any add on therapy other RAS inhibitors for CCBs and any add on therapy for either of the RAS inhibitors other than CCBs were included in this review.

4.2.6. Diabetic status of the population group:

Majority of the trials were of non-diabetic participants (38,39,80,82). Participants in three of the trials (42.8%) were comprising of high-risk hypertensive patients due to which they had reported prevalence of diabetes at baseline and specifically controlled by diet, or by medication of metformin or its combination with sulfonylurea in case of study by Fogari et al (2002) (40–42).

4.2.7. Co-interventions:

Concomitant use of sodium restriction or diuretics has the potential to confound the true effect of the study based on the existing literature (107,108) As shown in table, none of the included trials reported either of co-interventions except for two studies that showed use of diuretics simultaneously (41,42).

4.2.8. Endpoints of the included studies:

Primary outcome of most of the trials (57.1%) were renal outcome based, including decline in eGFR ml/min per 1.73m^2 and change in urinary excretion levels (mg/d) (38,40,42,80). One of the trials (14.1%) did not specify renal outcome neither as primary nor secondary (80). Another one included trial had end-stage renal disease as secondary outcome (41). The studies with high risk hypertensive patients with diabetes and history of Cerebrovascular, cardiac and/or vascular related events at baseline had different heart events including stroke, heart failure, angina, CVD, CHD as either primary or secondary outcome (40–42). Moreover, two of those three trials (66.6%) with high hypertensive patients, all cause mortality or sudden death events were mentioned as secondary outcome (41,42).

4.2.9. Interventions in the included studies:

Only four (57.1%) of the included trials considered interventions as monotherapies such as any of RAS blockers vs any of CCBs (41,42,80,82). On the contrary, rest of the three trials (42.8%) had three arms in the study such as a combination therapy of the respective RAS inhibitor with that specific CCB in addition to two arms of monotherapies (38–40).

4.2.10. Doses of the medications:

Based on Appendix B, it is very apparent that doses of study drugs across studies are quite varying ranging from 2.5mg/d to 300 mg/d. However, in trials that compared ACEi vs CCB, it was worth noting that regardless of dose variation, GFR decline is found to be higher in ACEi compared to CCB (38,39,41). In terms of UAE as well, ACEi dropped better than CCB (40).

In case of trials that compared ARBs with CCBs, ARB and CCB seemed to show quite similar GFR throughout the study duration (80). As for renal events based on proteinuria or Albuminuria, there were no significant difference with no regard to varying doses (42). Nonetheless, one of the trials (14.1%) showed that CCB has higher level of decrease in UAE levels than ARB (82). Apart from that, three out of trials in this review were seen to have been given with add on therapies when BP goal was not achieved (38,41,80). Moreover, One trial indicated that it increased its doses whenever needed or target was not met for BP (42).

In one of the trials (14.1%), even though medications were randomly assigned, before analysis of the study, 9.3% and 48.7% from ARB and CCB arms respectively were withdrawn due to either loss of interest, pregnancy, side effects, non-compliance or adverse events such as coronary artery disease. Intention to treat analysis was not done due to which analysis was done on the remaining participants who were verified for inclusion based on study criteria.

Two of the included trials seemingly had washout period of 2-4 weeks prior to treatment assignment (39,40). Reasons for withdrawal were reported in two of seven trials constituting 28.5% of the trials (39,40,80). Additionally, two of the trials indicated the adverse events in their study (39,40).

4.3. Risk of bias assessment

In this study, all of the included studies were based on randomized controlled trials, which were selected for this review after assessing its eligibility criteria. Risk of bias assessment were presented in Figure 2 and 3. Most of the studies (71.4%) reported that it was randomized, computer generated or with a code in which case, risk was assessed as low (38–42). While for those trials with no details (28.5%), it has been reported as unclear (80,82).

Two (28.5%) of the trials mentioned that they were open label which can introduce bias (40,42). One of the trials (14.1%) mentioned that study medications were supplied by manufacturer but reported that were not involved in any part of the study such as design and conduct, collection, analysis and interpretation due to which other bias was reported as unclear as I are not certain if they had interfered (41).

Another trial (14.1%) had clearly reported that pharmaceuticals granted them unrestricted funding for which I reported other bias as high because funding bias is likely in that case (42). Three of the trials (42.8%) that had loss to follow-up greater than 20% was reported as high risk (39,40,80).

Based on these above given figures, two studies were considered to be with low risk of bias (38,41). While two studies seemed to have high risk of bias (40,42). One of the studies were apparently having unclear risk of bias (82). Rest of the studies seemed to have moderate risk of bias (39,80).

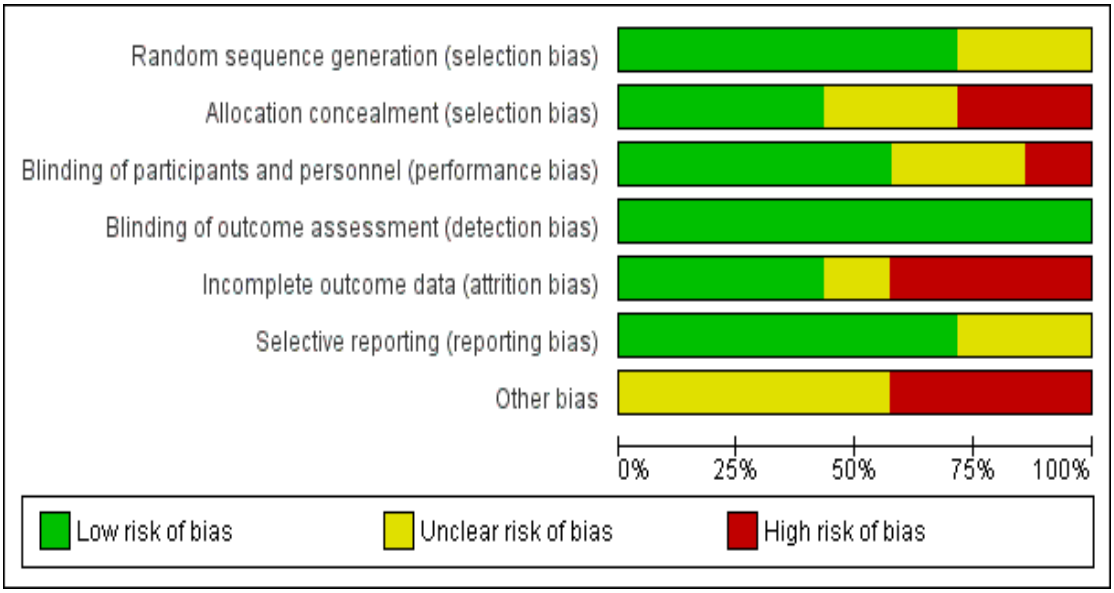

Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

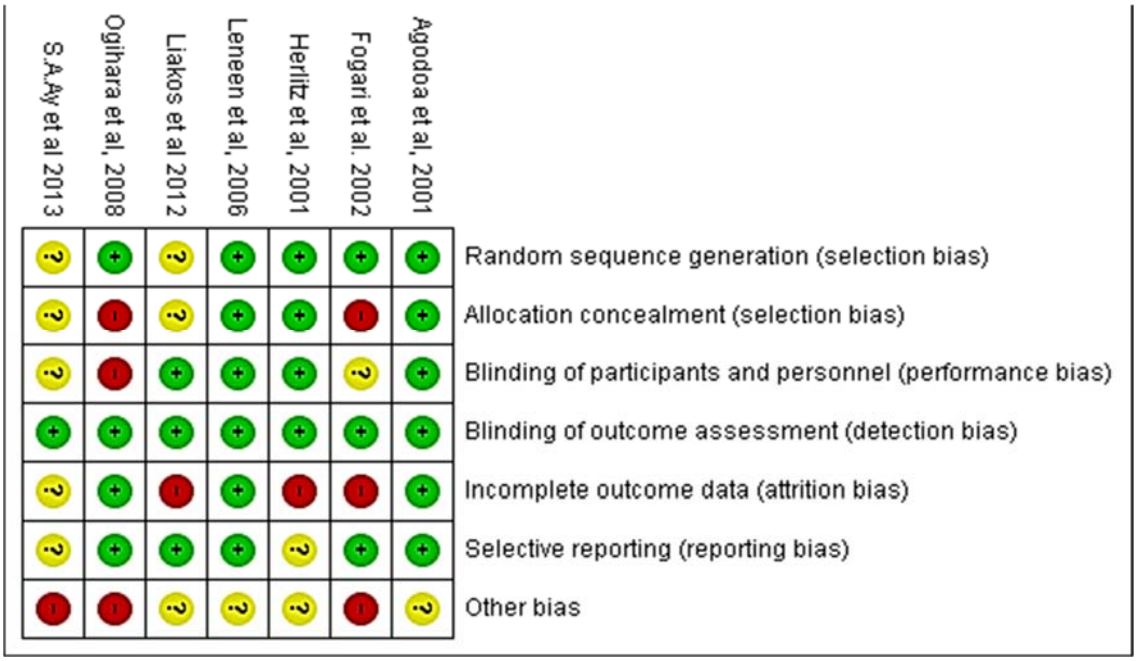

Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

4.4. Main Study Outcomes:

Table 6 shows Summary of findings based on all the included studies. There were three trials with no diabetes and CKD stage 3 (38,39,82) and a trial with no diabetes but CKD stage 1 (80). Two trials with diabetes as well as CKD stage 3 (40,42) and a trial with diabetes as well as CKD stage 2 (41). Out of seven, three trials reported CKD outcome measures in terms of UAE levels (40,42,82). Rest of the trials measured CKD in terms of GFR (38,39,41,80).

4.4.1. CKD

4.4.1.1. Narrative:

In terms of CKD outcomes as shown in Table 6, only one trial (14.2%) measured eGFR and it had similar reduction in both the arms (80). As for the other two trials (28.5%) that were reported in terms of UAE levels, one study showed greater reduction in UAE for CCB than ARB arm while the other remaining trial showed that UAE levels reduction was somewhat similar in both the regimens. only one of four trials were mentioned in UAE levels for which there was decrease but reduction in ACEi was slightly higher than CCB (40). On the other hand, for the trials with GFR, there was a decline in both groups but the decrease was greater in ACEi compared to CCB in one trial, and another one showed higher reduction in CCB than ACEI in the long term (38,41). In case of study by Agodoa et al (2001), they reported that in the short term, the decrease in GFR was higher in CCB than ACEi (38).

4.4.1.2. Overall Relative Risk for CKD progression:

There were only 3 studies that were meta-analyzable as the other included studies did not provide the number of participants that were reported to further progress in terms

of CKD. Each study showed different level of incidence of CKD progression amongst those who used RAS vs. those who had CCB. The total number of participants from both the arms were 23458, out of which cases were found to be 382 constituting 1.62% of participants having progressed to further CKD from both the treatment groups as shown in table 3.

Table 3: Input table for pooled RR for CKD progression

Study name	**RAS**			**CCB**		
	N1	**Cases**	**Non-cases**	**N2**	**Cases**	**Non-cases**
Agodoa et al, 2001	436	70	366	217	43	174
Leneen et al, 2006	9054	126	8928	9048	129	8919
Ogihara et al, 2008	2354	4	2350	2349	10	2339
Total	**11844**	**200**	**11644**	**11614**	**182**	**11432**

With the help of MetaXL software as mentioned in the Methods section, I yielded forest plots for overall RR using IVhet model in addition to conventional models such as fixed and random. Based on Figure 4 that has shown the IVhet model, overall pooled estimate of RR for CKD progression was found to be 0.90 [95% CI of 0.69, 1.16]. This means that pooled estimate favours RAS (Intervention) over CCB (Control). Thereby, forest plot shown in Figure 4 has indicated that there is 10% lower risk for further CKD progression for those with RAS compared to those with CCB. In to regard to 95% CI, I are 95% confident that RR lies between 0.69 and 1.16, but it was not presented to be statistically significant as the interval contained null value of 1.

Based on forest plots for Fixed effects as shown in Figure 5, pooled estimate of RR was shown to be 0.90 [95% CI of 0.74, 1.09]. This RR was same as that of IVhet model

and interpreted that there was seemingly 10% lesser risk for further progressed CKD amongst those who have taken RAS blockers compared to those with CCB. The heterogeneity was seen as low with I2= 25% and was not significant as they reported p value as 0.26 which was greater than 0.05, indicating a fair amount of consistency between studies. Also, this is evident from overlapping of confidence intervals for individual study point estimates, which again confirms that there is no statistically significant difference between studies. In addition, when I executed Random effects model as shown in Figure, the pooled estimate was similar to other two models mentioned above, with RR of 0.87 [95% CI of 0.68, 1.13]. This means there was 13% lower risk for progressed CKD for those with RAS drug compared to CCB users. However, both the pooled risk ratios are not statistically significant as their CI contains 1.

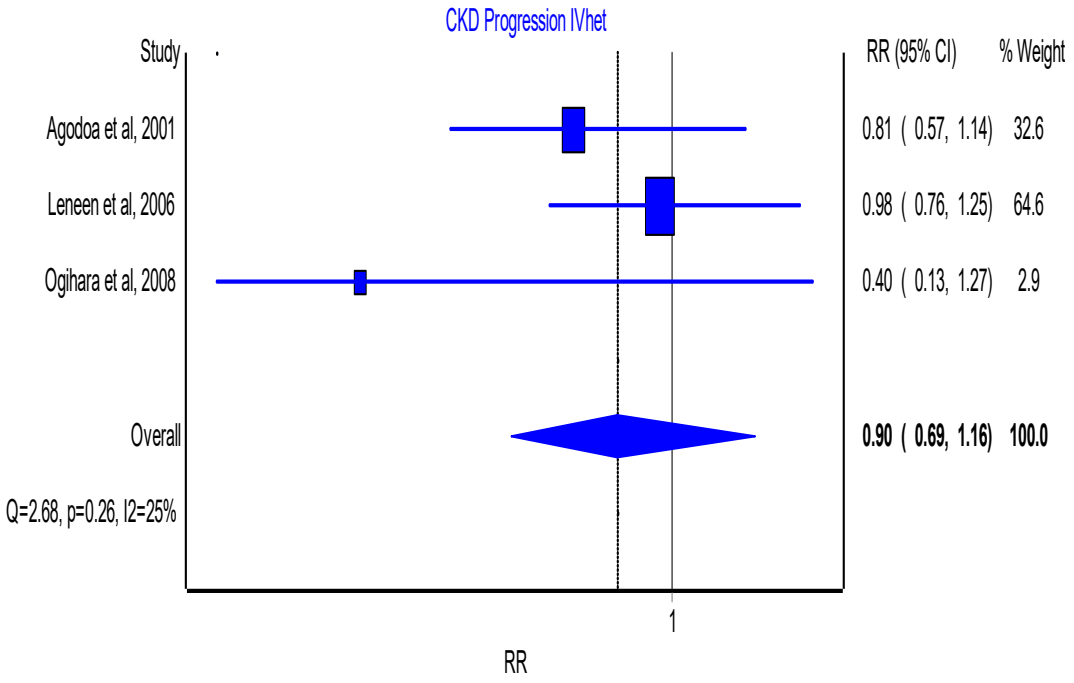

Figure 4: Relative risk estimate for CKD progression using IVhet Model

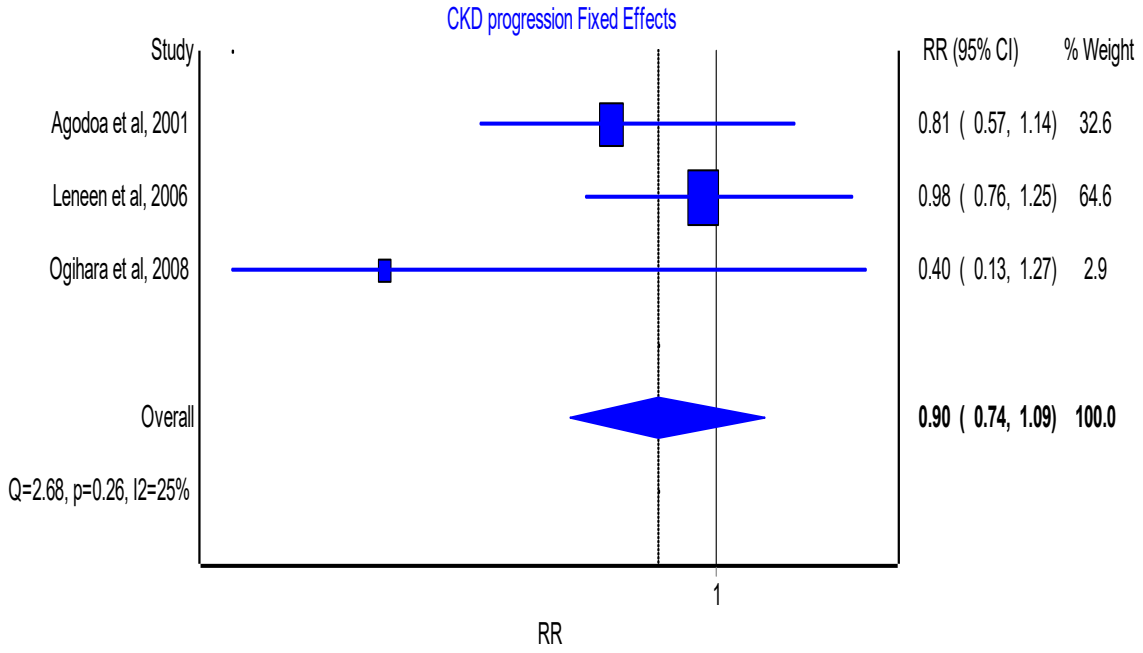

Figure 5: Relative risk estimate for CKD progression using Fixed Effects Model

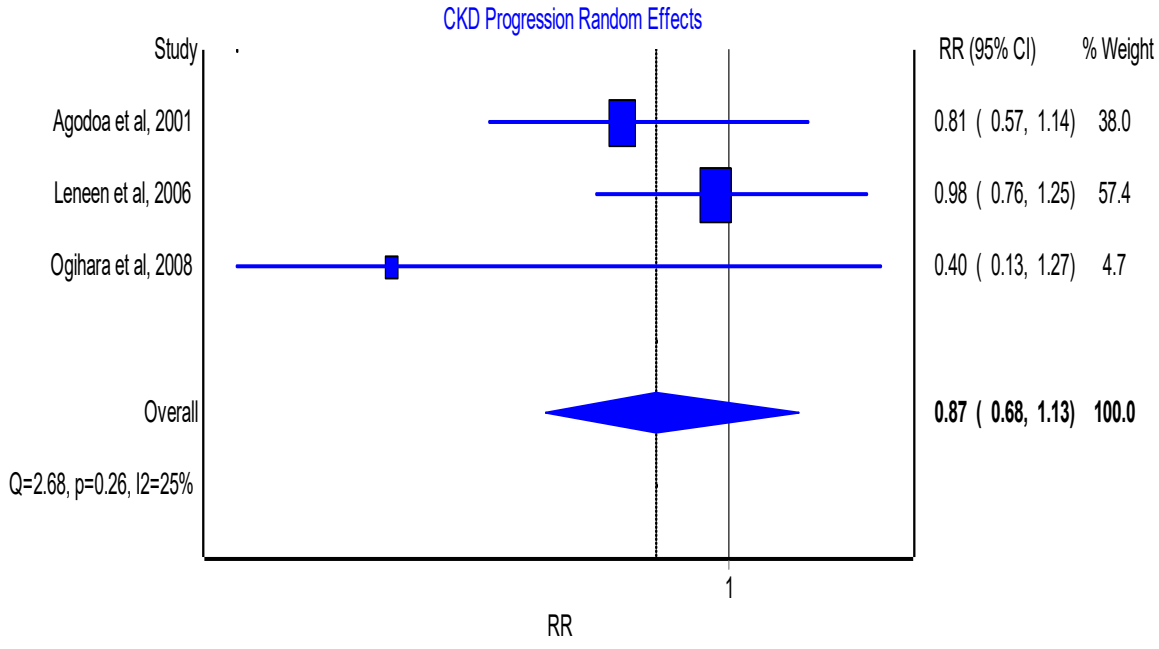

Figure 6: Relative risk estimate for CKD progression using Random Effects Model

4.4.1.3. Publication bias:

As for detection of publication bias using IVhet model, I assessed Doi plot as well as funnel plot. I detected major asymmetry with LFK index of -4.84, which was farther away from 0, indicating the presence of publication bias, as shown in Figure 7. In other words, this plot indicates that study effects were not homogenous and that it was potentially affected by selection or other types of bias.

In addition, I also estimated funnel plot as given in Figure 8 and it showed that all the studies were under the "funnel" indicating that there is no publication bias. Thus, it is not conclusive about bias as it was based on just three studies even though I believe that there is major bias as detected by Doi plot.

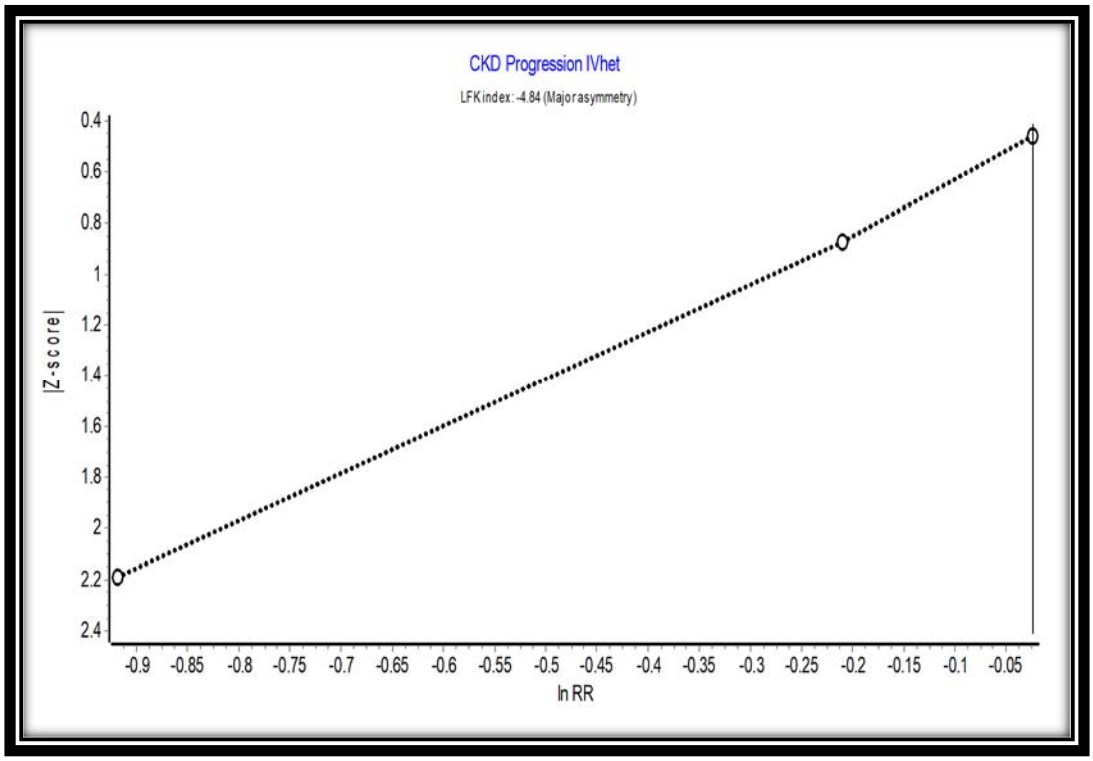

Figure 7: Doi plot for detecting Publication bias for CKD progression using IVhet model

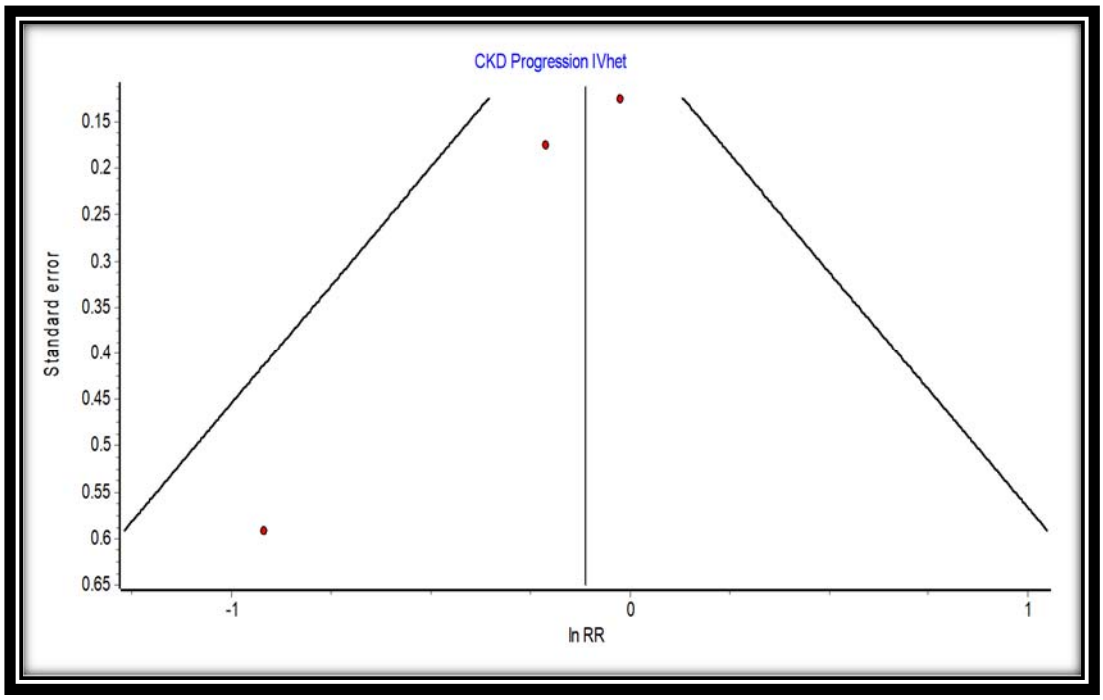

Figure 8: Funnel plot for publication bias for CKD progression using IVhet model

4.4.2. BP control

4.4.2.1. Narrative

Based on the information presented in Table 6 given, it is understandable that in those three trials (42.8%) with ARB vs CCB, BP outcome was found to decrease but similar in both the regimens for two trials even though one of those trials consists of diabetic while other consist of non-diabetic participants with CKD stage 3 (42,82). However, the reduction is slightly higher in ARB than CCB for the remaining one trial (14.2%) and it comprises of non-diabetic but CKD stage 1 patients (80).

Meanwhile, for the rest of the four trials (57.1%) that had made a head to head comparison between ACEi and CCB, reduction in the BP level was similar in three trials,

of which two of them are with non-diabetic participants (38–40). However, all of those three trials (42.8%) had CKD stage 3. In case of the remaining one trial (14.2) with ACEi vs CCB comparison, BP decrease was higher in CCB than in ACEi arm (41).

Based on the trials that reported mean SBP and DBP values at the baseline and end of follow-up, I executed a meta-analysis with 4 studies with total participants of 1538, out of which 874 (56.8%) in RAS and 664 (43.2%) in CCB arm as shown in Table 4 and 5. I produced forest plots for mean differences in SBP as well as DBP using IVhet model from MetaXL software as mentioned earlier.

Table 4: Input table for pooled estimate for Mean SBP change

Study name	RAS			CCB		
	N1	Mean diff	StDev	N2	Mean diff	StDev
Agodoa et al, 2001	417	16.5	1.595	209	17.1	2.452
Fogari et al, 2004	102	17.2	1.671	103	19.9	1.733
Ogihara et al, 2008	306	26.4	0.862	321	28.8	0.847
Liakos et al, 2012	39	26.3	2.504	21	16.9	1.867

Table 5: Input table for pooled estimate for Mean DBP change

Study name	RAS			CCB		
	N1	Mean diff	StDev	N2	Mean diff	StDev
Agodoa et al, 2001	417	13.8	0.993	209	14.3	1.366
Fogari et al, 2004	102	11.8	0.864	103	12.8	0.878
Ogihara et al, 2008	306	14.3	0.668	321	15.1	0.680
Liakos et al, 2012	39	19.3	1.916	21	11.7	1.981

4.4.2.2. Mean SBP change

4.4.2.2.1. Overall WMD in SBP

With WMD of -2.09 mmHg [95% CI of -5.96, 1.79], the forest plot apparently

favours the RAS (Intervention) over CCB (Control) for achieving a better reduction in mean SBP change. Since the summarized estimate had crossed a line of no effect, WMD of -2.09 mmHg is not statistically significant with CI containing 0.

Based on qualitative visual analysis for the results of the studies, there seemed to be between-study heterogeneity. In addition, WMD for each study were found to be away from each other, appearing to be scattered on forest plot and were not lined up on a vertical axis, indicating a variability in the WMD among studies. In addition, there was no overlapping of confidence intervals in overall, which indicates that there is statistically significant differences between individual study point estimates. All of these confirms that there is fair amount of heterogeneity in the results.

Based on quantitative tests for heterogeneity, with I2 of 99%, high level of heterogeneity is apparent. Moreover, Q statistics of 494.75 with p value of 0.00, which is lesser than 0.05 again suggests the inconsistency that apparent across studies.

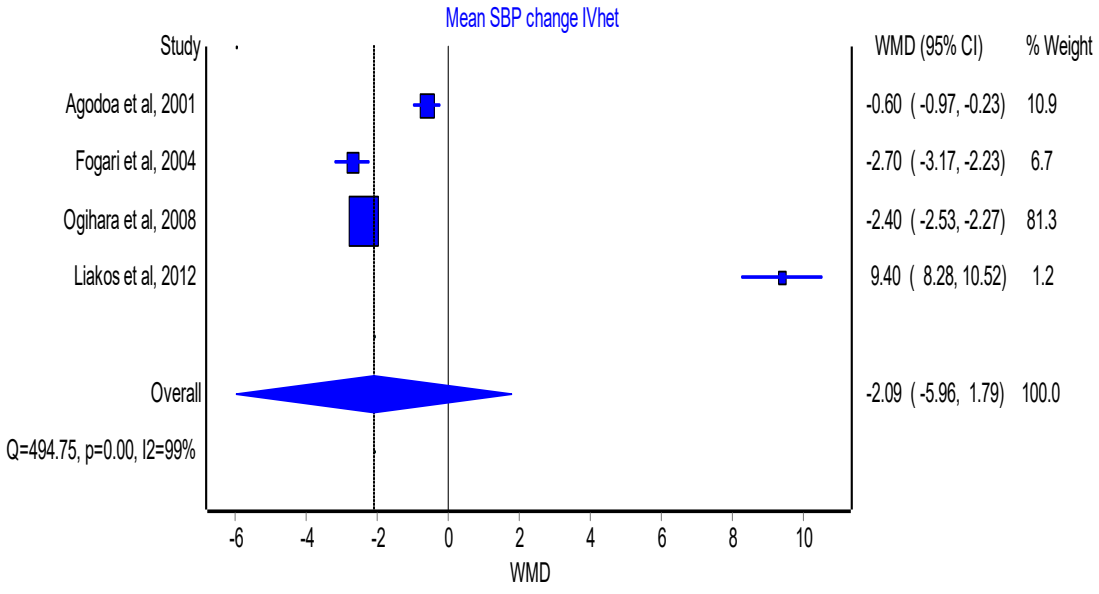

Figure 9: Weighted mean differences for SBP using IVhet Model

4.4.2.2.2. Publication bias

As per LFK index of 4.32 from Doi plot as shown in Figure 10, it is important to understand that the major asymmetry and skewed to right; thereby denoting the possibility of publication bias as it is beyond 0. While on the other hand, Figure 11 of funnel plot indicated the likelihood for the publication bias in the study results as studies are slightly away the funnel.

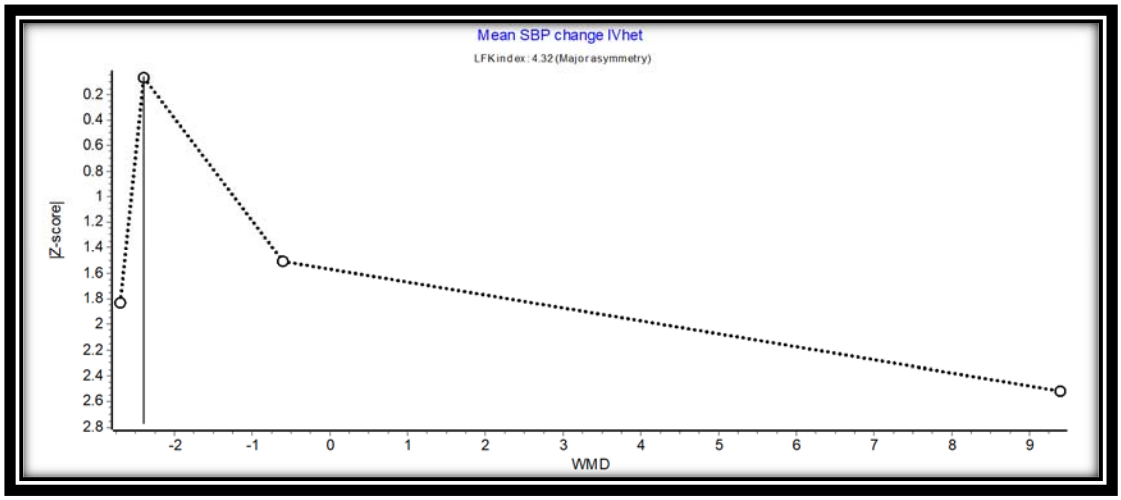

Figure 10: Doi plot for publication bias in Mean differences in SBP

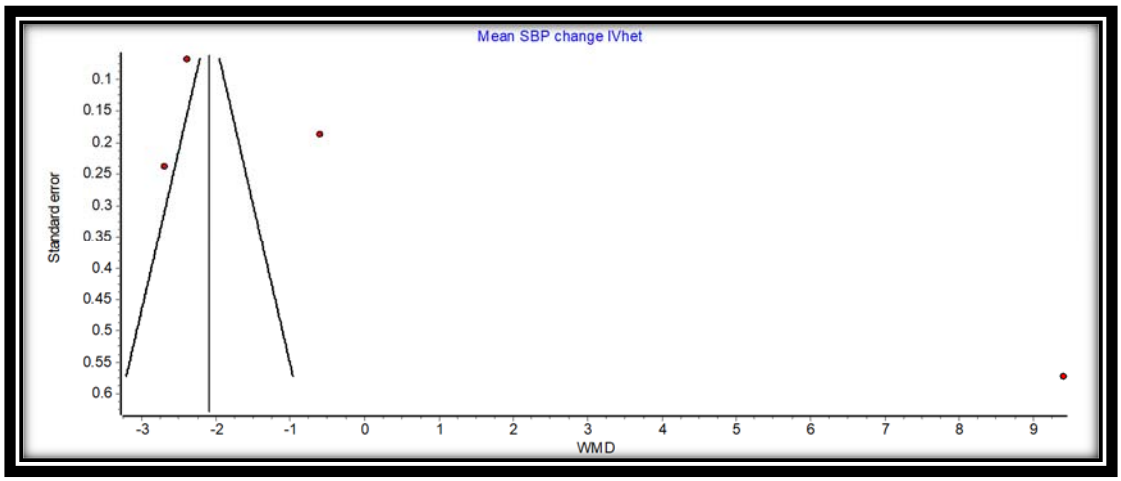

Figure 11: Funnel plot for publication bias in Mean differences in SBP

4.4.2.3. Mean DBP Change

4.4.2.3.1. Overall WMD in DBP:

With WMD of -0.71 mmHg [95% CI of -2.16, 0.73], the forest plot apparently favoured the RAS (Intervention) over CCB (Control) for achieving a better reduction in mean DBP change. Since the summarized estimate had crossed a line of no effect, WMD of -0.71 mmHg was not statistically significant with CI containing 0.

Based on qualitative visual analysis for the results of the studies, there seemed to be between-study heterogeneity as studies were there on both the sides of scale. In other words, WMD for each study were found to be away from each other, appearing to be scattered on forest plot and were not lined up on a vertical axis, indicating a variability in the WMD among studies. In addition, there was not many overlapping of confidence intervals in overall, which indicates that there was statistically significant differences between individual study point estimates. All of these confirms that there is fair amount of heterogeneity in the results.

Based on quantitative tests for heterogeneity, with I2 of 99%, there is high level of heterogeneity. Moreover, Q statistics of 258.06 with p value of 0.00 which is lesser than 0.05 again suggests the inconsistency that apparent across studies.

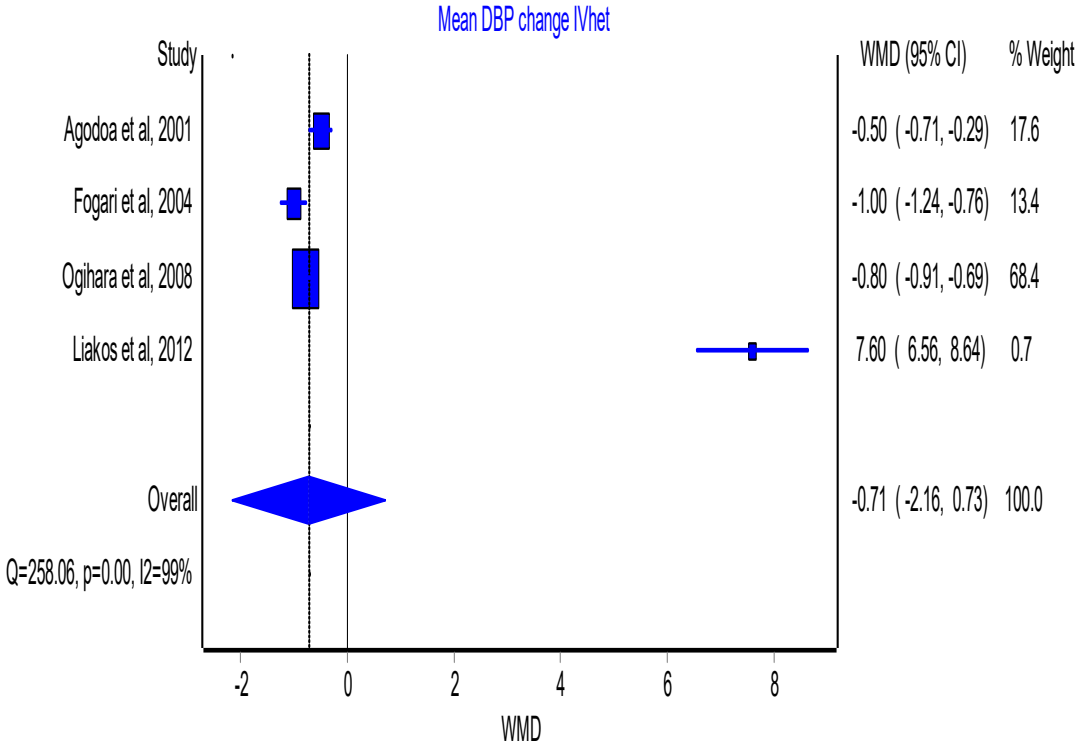

Figure 12: Weighted mean differences for DBP using IVhet Model

4.4.2.3.2. Publication bias

With regard to Doi plot as shown in Figure 13, there was major asymmetry seen with LFK index of 4.11, which implied that there is publication bias as it is farther away from 0 and skewed to right. Meanwhile, Figure 14 shows funnel plot, and it denoted the likelihood for no publication bias in the study results as studies are fitted on the funnel with all the studies being scattered on the top of the inverted funnel. However, it is proven that Doi plots are better off with fewer than 10 studies due to which I conclude that there is possibly publication bias.

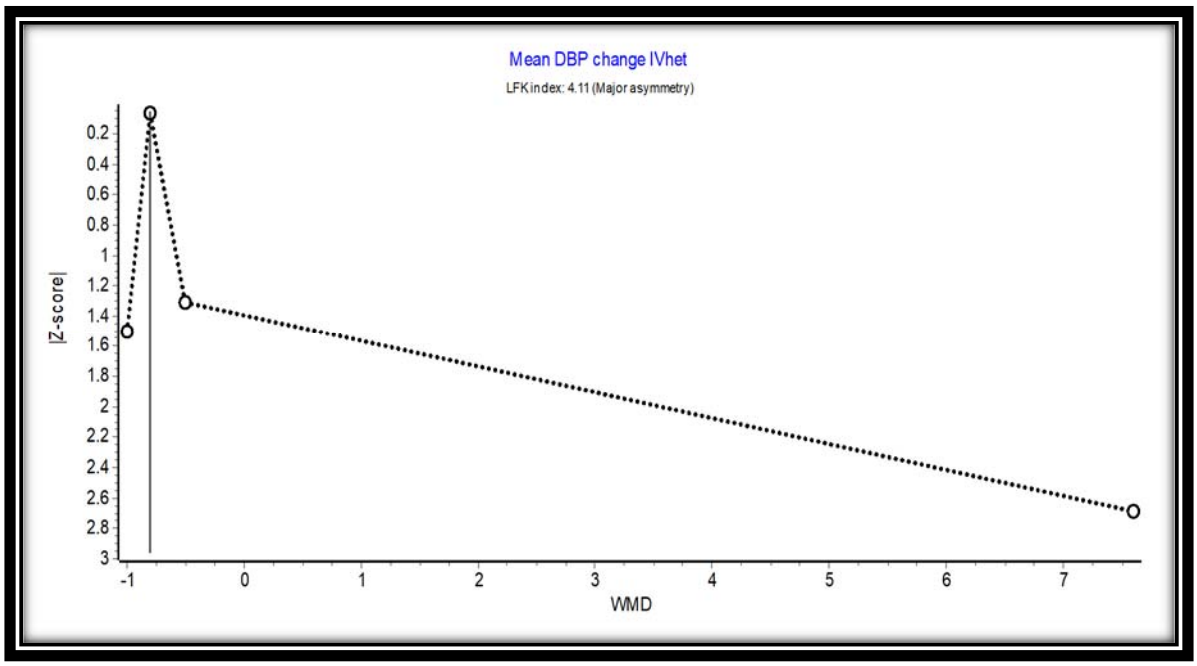

Figure 13: Doi plot for publication bias in Mean differences in DBP

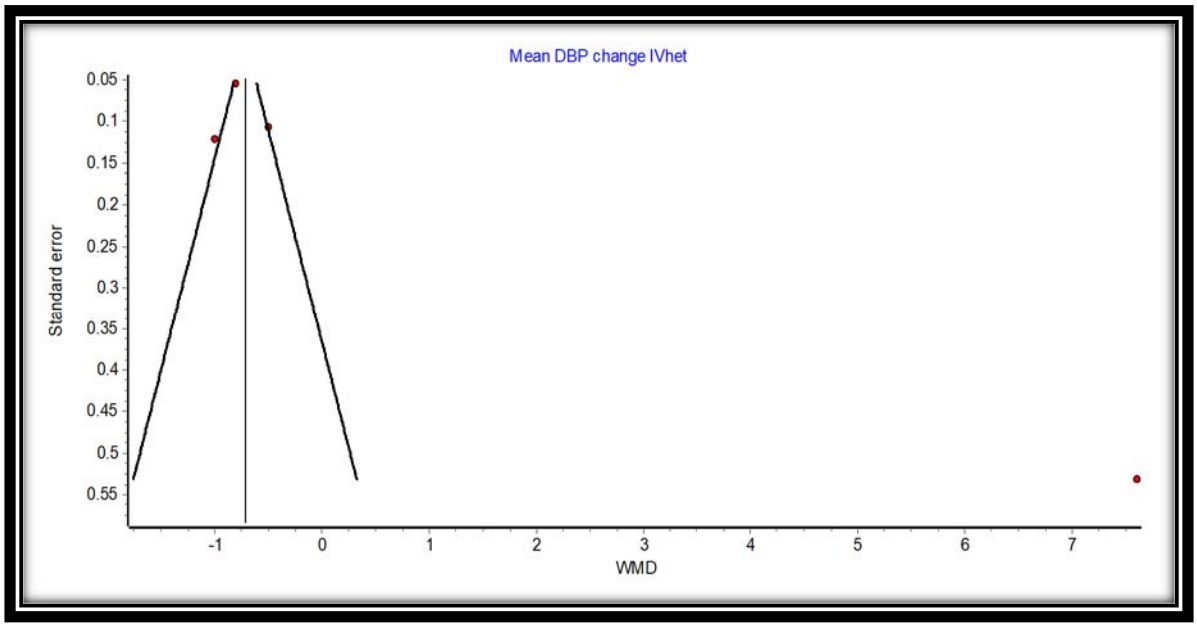

Figure 14: Funnel plot for publication bias in Mean differences in DBP

Table 6: Summary Findings of Included Studies

Author, year	Study medications	Effect on BP (mean, SD)	Effect on CKD (eGFR/UAE level(s))
Agodoa et al, 2001	Ramirpil vs Amlodipine	BP results, at the end of follow up were considerably lower than at baseline with no significant reduction across treatment groups (with p value >.10). In ramipril group, BP was 151.0/96.0 mmHg at baseline and was decreased to 134.5/82.2 mmHg. Meanwhile in amlodipine group, it was 150.0/95.7 mmHg at baseline and was reduced to 132.9/81.4 mmHg.	Patients who were on Ramipril group was shown having mean decline in GFR of 1.15ml/min per 1.73m^2 or 36% slower decline in GFR than amlodipine group with p value of 0.002 during chronic phase or over the study duration. Nonetheless, during acute phase or within the first 3 months of drugs assignment, It was seen that GFR increased by 4.19ml/min per 1.73m^2 more in amlodipine compared to Ramipril group with p value <0.001. However, the mean total slope which includes chronic as well as acute phase seemingly did not vary between both the groups with difference in total mean slopes=0.34 mL/min per 1.73 m^2, 95% CI,−0.41 to 1.08 and a p value of 0.38. Based on clinical end point analysis, unadjusted risk reduction for all the three endpoints such as GFR event, ESRD and death was 26% in Ramipril group when compared with amlodipine (95% CI of -4% to 47% with p value of 0.09). However, after adjusting for pre-specified covariates such as log transformed values of Urinary protein to creatinine ratios, history of heart disease, mean arterial pressure, age and sex, as per study's analysis plan, it was shown that there was 38% RRR in Ramipril group compared to Amlodipine with 95% CI of 13-56% and p value of 0.005 for ESRD and death, and with 95% CI of 10%-58% and p value of 0.01 for eGFR event as one of the clinical end points.

Author, year	Study medications	Effect on BP (mean, SD)	Effect on CKD (eGFR/UAE level(s))
Herlitz et al, 2001	Felodipine vs Ramipril	Mean Change in BP over the study duration was -14.3/-15.0 mmHg and -13.5/-13.3 mmHg in Ramipril and felodipine groups respectively.	Study tried to differentiate between Acute effect on eGFR or 1/serum creatinine levels which is based on overall effect calculated from baseline to first 3 months after randomization and longer term effects based on calculating regression coefficient from 3 months until the end of follow-up. It was found that substantial acute reduction in eGFR was apparent in Ramipril group with -3.2±7.0 ml/min and a p value <0.01 but no significant difference was seen in Felodipine group with 0.4±8.0 ml/min. It was also shown that with regard to longer term effects that was evident that Ramipril group (P value >0.20) had a slower progression rate in comparison to Felodipine group (p value <0.05) In monotherapy group OF Ramipril, mean ±sd of GFR was -2.1±10.0 vs -9.0±22 in amlodipine group. Adverse events amongst both the groups were similar.
Fogari et al, 2002	Amlodipine vs Fosinopril	BP changes were similar in both the groups with reduction being evident in the first 3 months followed by persistence over the years. In fosinopril group, mean reduction was 17.2/11.8 mm Hg while it was 19.9/12.8 mm Hg in Amlodipine group (with p value of 0.001 vs placebo).	Patients who were assigned to fosinopril therapy seemed to have significant decrease in UAE levels after only 3 months (Mean±SD of 98.2±67.3 to 63.8±38.4 mg/d with P value <0.01), and further slight decrease was observed in 6 and 12 months of treatment and then remained to stay stable over the remaining study duration. On the contrary, Amlodipine seemed to take 18 months to show significant decrease in UAE levels (mean±SD of 95.51±64.1 to 70.9±41.2 mg/d with P value <0.01) which was lesser than what was observed in fosinopril treatment after first 3 months. In overall, by the end of the study, fosinopril (98.2 ±67.3 to 45.5 ± 25.2) shown greater reduction than amlodipine (95.5 ± 64.1 to 62.3 ± 33) in terms of UAE levels.

Author, year	Study medications	Effect on BP (mean, SD)	Effect on CKD (eGFR/UAE level(s))
Leneen et al, 2006	Amlodipine vs Lisinopril	Mean BP at baseline was 146/84mmHg across both the treatment regimens. It was observed that during the follow up, BP was shown to decrease but BP higher on average by 1.5/1.1mmHg in Lisinopril group than amlodipine. Based on BP assessed by race and gender, it was shown in both male and female non-blacks even though there was rapid decrease in treatment groups, Lisinopril arm was still kind of having higher BP when compared to amlodipine by 0.0/0.5 mmHg in men and 1.3/0.9mmHg in women. On the contrary, decrease in BP was somewhat lesser in blacks than in non-blacks and it was higher under Lisinopril arm vs amlodipine arm for mean follow-up BP difference of 3.9/2.1 mmHg and 2.7/1.6 mmHg in black women and black men respectively. In case of two subgroups of age, non-diabetics and CHD patients at baseline, there was no major difference in BP between groups with only less than or equal 1 mmHg higher in Lisinopril arm. In diabetic patients, SBP was found to rise from 1.4 to 2.0 mmHg in the ACEi arm.	In overall, eGFR was shown to decrease in both the groups; however, the decrease in Lisinopril arm (77.7 to 70.7 ml/min per $1.73m^2$) was higher than in amlodipine arm (78.1 to 75.1 ml/min per $1.73m^2$). In terms of Clinical outcomes, ESRD events were similar in both the arms with RR of 0.99 with CI of 0.77 -1.26 and a p value of 0.929.
Ogihara et al, 2008	Candesartan vs Amlodipine	In overall, BP was well controlled in CASE J trial with both the medications. In case of Candesartan group, mean BP was 162.5/91.6 mmHg at baseline and was decreased to 136.1/77.3 mmHg and in Amlodipine group, it	At baseline, it was mentioned that around 24.3% in Candesartan group and 23% in Amlodipine group had history of renal events, which is presence of proteinuria and serum creatinine levels ≥1.3mg/Dl. In terms of renal events across both the groups, there was no statistically significant interval

		was 163.2/91.8 at baseline and was reduced to 134.4/76.7 mmHg.	risk ratios across both the treatment regimens with CI containing 1 for HR. ESRD had HR of 0.40 with CI of 0.13-1.29 and a p value of 0.112.
Liakos et al, 2012	Irbesartan vs Diltiazem	In overall, mean BP at baseline was 141.4/94.0 mmHg and was under control at the end of follow up with 118.4/77.4 mmHg (with p value <0.001 vs baseline). In case of Irbesartan group, mean BP was 142.7/94.8 mmHg at baseline and was decreased to 1116.4/75.5 mmHg. Meanwhile in diltiazem group, it was 139.1/92.6 mmHg at baseline and was reduced to 122.2/80.9 mmHg.	In overall, eGFR seemingly did not have any significant difference from both the groups, which were found to be similar in the baseline (111.1± 30.3) and at the end of follow-up (110.4± 28.4).
Ay et al, 2013	Valsartan vs Amlodipine	BP had shown significant decrease post treatment in both the groups. At baseline, Mean SBP and DBP were 155.2± 8.3 and 94.5 ± 10.6 mmHg in the amlodipine group and 156.5±12.6 and 92.7 ± 5.8 mmHg in the valsartan group. After treatment, mean SBP before and after treatment were 155.8± 10.4 and 127.3± 5.9 mmHg respectively and mean DBP observed at baseline and at the end of follow-up were 93.6 ± 8.3 and 77.4± 6.4 mmHg, respectively (with p value <0.001).	Amlodipine group showed reduction in UAE levels from 18.4±14.2 mg/d to 8.96 mg/d while valsartan group which had lower levels of UAE in the baseline with 9.2±5.2 was reduced to 8.91 mg/d. In other words, there wasreduction shown in both the groups but the decrease was higher in CCB group than ARB arm.

CHAPTER –5: DISCUSSION

5.1. Summary of the main results

After completion of a comprehensive and systematic search, and selection process as per the eligibility criteria that was set, tototal of seven trials for SR were included in the systematic review of this study.These trials comprised of 24446 participants in total and assessed two treatment strategies of interests - any RAS inhibitors vs any CCB amongst diabetic as well as non diabetics, and with either of CKD 1-4 stages (38–42,80,82). . The two prominent outcomes of this review are changes in BP measurements and effect of those specific antihypertensive drugs on progression of CKD ranging from stage 1-4. These outcomes are vital from patients perspective for their understanding about their own health (22).

As for quantitative analysis of CKD outcome, 3 trials with n= 11844 were included Based on the findings of this study, thereby states that there is no statistically significant difference based on pooled estimate of RR of 0.90 [95% CI 0.69, 1.16] using IVhet model for the proportion who progressed to further CKD as the summarized estimate has its CI containing null value. And in case of BP outcome, MA was based on 4 trials with n= 6166. In regard to BP outcomes, the mean difference in SBP as well as DBP were -2.09 [95% CI -5.96, 1.79] and -0.71 [95% CI -2.16, 0.73] respectively with its confidence interval containing 1. This is closely aligned with the existing literature regarding the study drugs as both of them were proven with renoprotective and BP lowering effects, even though RAS blockers are established as reno-protective antihypertensive agents based on NICE guidelines.

With the help of medications, it can only aid in slowing down the progression of

CKD (20,22). As a consequence, this review looked at such empirical studies to comprehend the effect that these drugs has on the aforementioned endpoints of this study.

This study indicated that there is always a fall in BP with any of the antihypertensive medications of study interest which is in line with the other studies that were previously done (20,22,109). In terms of comparison made with ARB vs CCB as well as in case of ACEi vs CCB, it was evident that the BP-level decreases across all the medications, which appeared to be similar in both groups, except in two trials (38–40,42,82). These two trials were distinct in terms of its characteristics. One of them was with non-diabetic and CKD stage 1 participants assessing CCB vs ARB with only 60 participants over study duration of 9 months, which showed that reduction in ARB is slightly higher than that in CCB.

On the contrary, the other one consisted of diabetic with CKD stage 2 patients assessing CCB vs ACEi with 18102 participants over the study duration of 4.9 years, which found that reduction in CCB is quite higher than the ACEi arm (41,80). This shows that there could be some external validity issues in existence in case of the former one with small sample size within less than a year. However, the latter could be projecting true results as it had a very large sample size including blacks and non blacks, and diabetic and non-diabetic and was held for almost 5 years (41). In addition to that, it was worth noting that the latter was studied on high-risk hypertensive patients which means that it cannot be applied for all the patients affecting the external validity of the study, which is concerned with applicability of evidence to other settings (41,110,111). Although all the other five trials showed comparable BP decrease in both the treatment regimens, they are distinct and has variation between studies. Some of those trials had large sample size, low vs high-risk

hypertension, presence of diabetes or heart events, sociodemographic characteristics of the population including age and sex are all varying across those studies (38–40,42,82,110).

Based on this study review, it was found that most of the studies with ARB vs CCB either had similar effect in both the arms or better decrease in UAE levels amongst CCB group when compared to ARB (42,80,82) which was later confirmed by quantitative analysis based on meta-analyzable studies.

Undoubtedly, the trials showing effect was based on a one large trial with 4703 participants while the other one was smallest of trials with only 20 participants (42,82). Also, one of them is based on diabetic and another one is based on non-diabetic participants with varying stages of CKD. This again confirms that despite of the results it shows, studies are not promising enough to conclude based on these findings (22,112).

In this review, I also compared ACEi vs CCB, and based on narrative summary, majority of the studies shown that patients with ACEi are more likely to progress to further CKD with higher decline in the eGFR. On long term basis, ACEi seems to have higher decline in GFR, while CCBs were found to have higher decline in the first three months or in the short run (38–41). These studies are with and without diabetic participants. However, meta-analysis showed that there was no statistically significant differences between both the treatment regimens. Nevertheless, since the meta-analysis was based on few number of studies, further research with more larger studies with large sample size are required for those with and without diabetes to confirm findings extracted from this review.

Combination therapy in those trials either as ACEi plus CCB or ARB plus CCB although not of our interest, it was quite appealing to know that it has better effect in terms of outcomes of our interest. Nevertheless, previously done systematic review and meta-

analysis on combination therapy seems to have conflicting results and has stated no additional benefit can be retrieved by using combination therapy for reno-protection (29,40,109,113).

Based on narrative, most of the trials indicated that rate of progression is higher in RAS inhibitors when compared dihydropyridine such as felodipine and amlodipine, and non-dihydropyridine calcium channel antagonists such as diltiazem. This seemed to be not aligned with the findings of Meta-analysis which had reported RR 0.90 [95% CI of 0.69, 1.16] indicating that risk for CKD progression is lower in RAS users, even though this was not statistically significant. However, since some trials had less than 100 participants and had a length of follow-up as less than a year, study demands more larger studies to be conducted over longer year in the context of these study medications as direct comparison to make more meaningful inferences. Also, not all the studies used the same unified way of measuring BP and CKD outcomes in terms of eGFR (with varying equations). This also emphasizes that need for more studies with unified measures for outcome is just as important as having larger studies for better judgement of findings.

As for results of other SR and MA in relation to my study results, it was quite unmatching. A similar systematic review and meta-analysis based of 8 trials with n=25,647 done on the Renoprotective effect of RAS vs CCB showed CCBs to be weaker in terms of renal protection compared to RAS but for CKD patients (35). Their findings on CKD related outcomes demonstrated that higher probability for ESRD was linked with CCB compared with RAS based therapy with OR of 1.25 [95% CI, 1.05,1.48]. In terms of BP outcomes, However, they added that reduction was similar in both treatment regimens. My study seems to have conflicting results with their study as they have indicated highly

statistically significant OR in CCB groups while our study remained to show no difference between the Intervention and the comparator.

As for one of the recent meta-analysis based on 7 trials with n=403which is quite similar to this study that compares CCB vs ACEis shows no benefit over the other and didn't incude both RAS, only ACEI was compared (37). Their CKD related findings were MD in UAE levels =1.91µg/min [95% CI: -10.3, 14.12] and MD in GFR=0.01 [95% CI: -0.38 to 0.41]. Their BP related results showed MD in SBP=1.05 mmHg [95% CI: -0.97, 3.08], MD in DBP= -0.34 mmHg [95% CI: -1.2, 0.51]. This study shows similar results as this study with no statistically significant difference in outcomes between intervention and the comparator.

Another yet to be published meta-analysis based on 23 trials with n=1805, its abstract had shown superiority of RAS over CCB on improving UAE levels but not considered other CKD measures such as GFR (36). Their CKD based results were MD in UAE levels of -0.442 [95% CI -0.660, -0.225]. Their study was done on diabetic CKD patients and their results were apparently statistically significant. In relation to this study findings, there were evident difference as they both seem to contradict based on their results. However, it is important to note that this study was consisting of both CKD and non CKD as well as Diabetic and Non diabetics.

Hence, even though there were systematic reviews and met-analysis done on these direct head to head comparisons, PICO were quite distinct as most of them were based on CKD patients of stage 3 or more. However, their findings were similar that both RAS inhibitors as well as CCB can be good at reducing BP and UAE levels with no special reno-protective effect for ACEis or ARBs which contradicts other findings based on

previous literature except two (34,36,37,37).

Study findings were also compared against individual trials that had head to head comparison. As for those with GFR as a CKD measure, ALLHAT trial (14.2%) had similar reduction in both the arms while other 3 studies showed ACE as favourable over CCB (41). However, it is quite important to note that ALLHAT trial had participants of 18102. Concerning those studies with UAE as a measure, one of 3 trials showed decrease in both but reduction in ACEi was slightly higher than CCB, while another trial showed that reduction was somewhat similar in both the regimens (40,42,104). In addition, one study showed greater reduction for CCB than ARB arm. Nonetheless,it is indeed worth noting that this one trial that favoured CCB had only 20 participants which indirectly implies low statistical power of the study due to small sample size. Furthermore, ALL seven RCTs showed similar reduction in BP measurements for both the arms except for trial that indicated higher reduction in CCB over RAS but it only had 60 participants.

In overall, trials were all in harmony with our findings and this possibly indicated that even though favoring RAS was not statistically different, there is greater support from existing literature for our findings to be clinically significant. Also, if meta-analysis was done with more studies, there seems to be chance of having statistical significance.

5.2. Overall completeness and applicability of evidence

Most of the trials were not reporting about all the times ranging from motality to BP difference post treatment. Also, studies did not report measures using unified method. However, studies had included high risk as well as low risk hypertensive patients.

In addition, diabetes as well as non-diabetic patients were included. In addition, progression of CKD from all 1-4 stages were part of this review. All of this can,

consequently, can be addressed to any hypertensive patients with any CKD stage regardless of their diabetic status. Moreover, majority of the studies collated for this review does not report RR, HR or OR due to which complete, sensible and consistent conclusion cannot be drawn from this regard to study medications effects on outcome of our interest. However, with the available data, I had done an exploratory MA for determining the RR for CKD progression, Weighted mean differences in SBP as well as for DBP using IVhet model from MetaXL software.

Finally yet importantly, Some studies had add on therapy in addition to randomly assigned study medications of our interest for which effect could be different than without add on therapy. Moreover, one of the studies despite of having more than 20% loss to follow up after random assignment but before analysis, they did not use intention to treat analysis. However, all their participants were considered who met inclusion criteria after removing the withdrawn participants for the analysis.

5.3. Strengths of this study

Firstly,this study is quite novel in terms of its PICO which includes patients with any CKD stage from 1-4 amongst diabetic and non-diabetic population groups.. Furthermore, meta-analysis for primary as well as secondary outcomes in this study was executed using IVhet model, which is far better than conventional RE models that can cause over dispersion of the study effects.Since this meta-analysis was based on less than 5 studies, using IVhet has certainly helped us produce as accurate as possible overall pooled estimate for our study outcomes. Moreover, using Doi plot also indicated proper assessment of publication bias as it is more optimal for MA with fewer studies and is more sensitive enough to detect better than funnel plot. Besides, most of the included studies had

large sample size which means that each of the included study had a higher statistical power to detect the differences between treatment arms. Also, we used PRISMA for reporting using PRISMA which enables replication by other researchers and more structured reporting pattern. .

5.4. Limitations in the review

This is undoubtedly a novel review that looks at effect of RAS blockers and CCB on the BP level as well as renal disease progression amongst diabetic as well as non diabetic hypertensive patients. However, this review has its own set of limitations. The included trials in this review have heterogeneity in terms of methods, BP measurement at baseline and BP target for the study, study populations and medications that will altogether increase the likelihood for potential limitations in the study. In addition, the study took account of sample size as small as 20, and studies with longer length of follow-up as less as 3 months, which implies that included studies, does not have sufficient statistical power to verify the summarised evidence.

Due to insufficient number of studies with appropriate effect size such as HR, RR (or the required information to calculate those), meta analysis could not be done on all the studies included for Systematic review. As for those with which MA was done, subgroup analysis or meta-regression was not feasible due to the low number of included studies. Hence, I could not assess and address the heterogeneity. Additionally, the studies included were not necessarily the studies with outcomes of interest as I included any study that reported values for CKD outcome and BP measures. Moreover, the studies were quite heterogeneous with some studies with participants over 18,000 while the other included trial has only 20 participants, which again implies that this review is not sufficient to make

an inference for the effect of RAS vs CCB on BP measurements and progression of CKD. Furthermore, the dose variation was quite apparent across studies, which makes it less comparable despite of lack of difference seen in groups with high doses vs low doses. Finally yet importantly, estimation of GFR was evidently heterogeneous across studies and on top of that, few trials even did not mention how it was being calculated in their study. Apart from all that mentioned, due to the search strategy that included search terms for outcome, it is possible that I have missed to retrieve those studies that had CKD stage 1 or 2 as some studies might have considered it as those with normal renal function and might not have defined it as CKD stage 1 or 2.

CHAPTER –6: CONCLUSION

To sum up, this study evidence finds no benefit over the other. Both RAS antagonists and CCBs showed no statistically significant difference neither for primary CKD outcome nor in terms of secondary BP endpoints in the study. However, the study have its own set of limitations due to which more well designed and well conducted RCTs with robust findings are required to confirm the inferences based on this review.

6.1. Implications for Practice

Based on findings of this study, clinical practice can adopt either RAS blockers or CCBs as an intial therapy for hypertensive patients with any CKD stage from I-IV as there is no difference between both of those treatment regimens.

6.2. Implications for Research

Despite of the evidence indicating no difference between RAS blockers and CCBs, more number of well-designed and larger randomized controlled studies that are aimed at examining the effect of antihypertensive drugs on CKD outcomes, including both diabetic as well as non-diabetic patients, are required to confirm the findings of this review due to study limitations.

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APPENDICES

Appendix A: Search strings for each of the major databases

1. PubMed

(((((((calcium channel blocker*[Title/Abstract] OR Amlodipine[Title/Abstract] OR Diltiazem[Title/Abstract] OR Felodipine[Title/Abstract] OR Isradipine[Title/Abstract] OR Nicardipine[Title/Abstract] OR Nifedipine[Title/Abstract] OR Nisoldipine[Title/Abstract] OR lercadipine[Title/Abstract] OR Verapamil[Title/Abstract] OR diltiazem[Title/Abstract])) AND (angiotensin converting enzyme inhibitor*[Title/Abstract] OR Perindopril[Title/Abstract] OR Ramipril[Title/Abstract] OR Captopril[Title/Abstract] OR benazepril[Title/Abstract] OR trandolapril[Title/Abstract] OR fosinopril[Title/Abstract] OR Lisinopril[Title/Abstract] OR moexipril[Title/Abstract] OR enalapril[Title/Abstract])) OR (angiotensin recptor blocker*[Title/Abstract] OR losartan[Title/Abstract] OR valsartan[Title/Abstract] OR irbesartan[Title/Abstract] OR candesartan[Title/Abstract] OR telmisartan[Title/Abstract] OR eprosartan[Title/Abstract] OR olmesartan[Title/Abstract])) AND chronic kidney disease*[MeSH Terms]) OR (glomerular filtration rate[Title/Abstract] or GFR[Title/Abstract])) OR (Urinary albumin excretion[Title/Abstract] or UAE[Title/Abstract] or albuminuria[Title/Abstract])). Such was restricted to Humans and Study designs such as observational study and RCTs.

2. Cochrane Library

(calcium channel blockers OR CCBs OR amlodipine OR Diltiazem OR Felodipine OR Isradipine OR Nicardipine OR Nifedipine OR Nisoldipine OR lercadipine OR Verapamil OR diltiazem):ti,ab,kw AND (angiotensin-receptor-blocker OR ARBs

OR losartan OR valsartan OR irbesartan OR candesartan OR telmisartan OR eprosartan OR olmesartan):ti,ab,kw AND (angiotensin-converting enzyme inhibitors OR ACEIs OR Perindopril OR Ramipril OR Captopril OR benazepril OR trandolapril OR fosinopril OR Lisinopril OR moexipril OR enalapril):ti,ab,kw

3. Embase

The search string used in this database that could retrieve relevant articles were ((((('calcium'/exp OR calcium) AND channel AND blockers OR ccbs OR 'amlodipine'/exp OR amlodipine OR 'felodipine'/exp OR felodipine OR 'isradipine'/exp OR isradipine OR 'nicardipine'/exp OR nicardipine OR 'nifedipine'/exp OR nifedipine OR 'nisoldipine'/exp OR nisoldipine OR lercadipine OR 'verapamil'/exp OR verapamil OR 'diltiazem'/exp OR diltiazem) AND ('angiotensin receptor blocker'/exp OR 'angiotensin receptor blocker' OR arbs OR 'losartan'/exp OR losartan OR 'valsartan'/exp OR valsartan OR 'irbesartan'/exp OR irbesartan OR 'candesartan'/exp OR candesartan OR 'telmisartan'/exp OR telmisartan OR 'eprosartan'/exp OR eprosartan OR 'olmesartan'/exp OR olmesartan) OR (angiotensin-converting AND ('enzyme'/exp OR enzyme) AND ('inhibitors'/exp OR inhibitors)) OR aceis OR 'perindopril'/exp OR perindopril OR 'ramipril'/exp OR ramipril OR 'captopril'/exp OR captopril OR 'benazepril'/exp OR benazepril OR 'trandolapril'/exp OR trandolapril OR 'fosinopril'/exp OR fosinopril OR 'lisinopril'/exp OR lisinopril OR 'moexipril'/exp OR moexipril OR 'enalapril'/exp OR enalapril) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [clinical study]/lim AND ([embase]/lim OR [medline]/lim OR [pubmed-not-medline]/lim) AND [2008-2018]/py AND [medline]/lim) AND ('clinical article'/de OR

'clinical study'/de OR 'clinical trial'/de OR 'clinical trial (topic)'/de OR 'comparative effectiveness'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled clinical trial (topic)'/de OR 'controlled study'/de OR 'crossover procedure'/de OR 'dosage schedule comparison'/de OR 'double blind procedure'/de OR 'drug dosage form comparison'/de OR 'drug dose comparison'/de OR 'evidence based medicine'/de OR 'evidence based practice'/de OR 'experimental design'/de OR 'experimental study'/de OR 'factorial design'/de OR 'good clinical practice'/de OR 'human'/de OR 'human experiment'/de OR 'intention to treat analysis'/de OR 'intervention study'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'meta analysis (topic)'/de OR 'multicenter study'/de OR 'multicenter study (topic)'/de OR 'normal human'/de OR 'open study'/de OR 'outcomes research'/de OR 'parallel design'/de OR 'phase 1 clinical trial'/de OR 'phase 2 clinical trial'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'single blind procedure'/de OR 'study design'/de OR 'systematic review'/de) AND ([adult]/lim OR [aged]/lim OR [middle aged]/lim OR [very elderly]/lim OR [young adult]/lim) AND ('amlodipine'/dd OR 'amlodipine besylate'/dd OR 'amlodipine camsylate' OR 'amlodipine plus atenolol'/dd OR 'amlodipine plus hydrochlorothiazide'/dd OR 'amlodipine plus metoprolol' OR 'angiotensin 1 receptor antagonist'/dd OR 'angiotensin 2 receptor antagonist'/dd OR 'angiotensin receptor antagonist'/dd OR 'antihypertensive agent'/dd OR 'atorvastatin'/dd OR 'azelnidipine'/dd OR 'benazapril' OR 'benazepril'/dd OR 'benazepril plus hydrochlorothiazide'/dd OR 'benidipine'/dd OR 'benzodiazepine'/dd OR 'benzodiazepine derivative'/dd OR 'calcium channel blocking agent'/dd OR 'calcium channel blocking agent receptor'/dd OR 'candesartan'/dd OR 'candesartan hexetil'/dd OR

'candesartan hexetil plus hydrochlorothiazide'/dd OR 'cilazapril'/dd OR 'cilazapril plus hydrochlorothiazide'/dd OR 'cilnidipine'/dd OR 'delapril'/dd OR 'dihydropyridine'/dd OR 'dihydropyridine derivative'/dd OR 'diltiazem'/dd OR 'enalapril'/dd OR 'enalapril maleate plus hydrochlorothiazide'/dd OR 'enalapril plus hydrochlorothiazide'/dd OR 'enalopril' OR 'eprosartan'/dd OR 'felodipine'/dd OR 'felodipine plus ramipril'/dd OR 'fimasartan'/dd OR 'hydrochlorothiazide plus irbesartan'/dd OR 'hydrochlorothiazide plus lisinopril'/dd OR 'hydrochlorothiazide plus losartan'/dd OR 'hydrochlorothiazide plus losartan plus amlodipine' OR 'hydrochlorothiazide plus olmesartan'/dd OR 'hydrochlorothiazide plus quinapril'/dd OR 'hydrochlorothiazide plus telmisartan'/dd OR 'hydrochlorothiazide plus valsartan'/dd OR 'hydrochlorothiazide, lisinopril drug combination' OR 'hydrochlorthiazide plus valsartan' OR 'imidapril'/dd OR 'indapamide plus perindopril'/dd OR 'irbesartan'/dd OR 'irbesartan plus amlodipine' OR 'lisinopril'/dd OR 'lisinopril plus amlodipine' OR 'lisinopril plus manidipine' OR 'losartan'/dd OR 'manidipine'/dd OR 'nanopril' OR 'nicardipine'/dd OR 'nifedipine'/dd OR 'nimodipine'/dd OR 'nisoldipine'/dd OR 'nitrendipine'/dd OR 'olanzapine'/dd OR 'olmesartan'/dd OR 'olmesartan plus atenolol' OR 'peduopril' OR 'perindopril'/dd OR 'perindopril plus lindapamide' OR 'perindopril tert butylamine'/dd OR 'pitavastatin'/dd OR 'pravastatin'/dd OR 'prescription drug'/dd OR 'quinapril'/dd OR 'ramipril'/dd OR 'renin'/dd OR 'renin angiotensin system blocking drug' OR 'renin angiotensin system inhibitor'/dd OR 'renin inhibitor'/dd OR 'rilmenidine'/dd OR 'sacubitril'/dd OR 'telmisartan'/dd OR 'ticlopidine'/dd OR 'trandolapril'/dd OR 'trandolapril plus verapamil'/dd OR 'valnidipine' OR 'valsartan'/dd OR 'verapamil'/dd.

Appendix B: Table for Detailed Description of Included Studies

Agodoa et al, 2001

Methods	A randomized, doubleblind, 3x2 factorial trial
Participants	Non-diabetic African Americans who were aged 18 to 70 years with glomerular filtration rate [GFR] of 20-65 mL/min per 1.73 m^2 and no other diagnosed causes for renal impairment. Individuals with DBP <95mmHg, Urinary protein to creatinine ratio greater than 2.5, malignant HTN within 6 months, identified non BP related causes for renal disease, serious systemic disease, history of heart failure and those with specific indication to study drug were excluded.
Interventions	Amlodipine (5 to 10mg/d), Ramipril (2.5 to 10 mg/d) or metoprolol (50 to 200 mg/d)
Outcomes	The primary outcome measure was the rate of change in GFR; the main secondary outcome was a composite index of the clinical end points of reduction in GFR of more than 50% or 25 mL/min per 1.73 m2, end-stage renal disease, or death.
Notes	Additional unmasked drugs such as furosemide, doxazosin mesylate, clonidine hydrochloride, hydralazine hydrochloride and

	minoxidil were given if BP goal was not achieved with randomly assigned treatment.

Herlitz et al, 2001

Methods	Open long-term randomized prospective multicenter study with 28 centers in Sweden, UK, Germany, France and Israel.
Participants	Non diabetic patients who are aged 18-74 years with uncontrolled HTN and are on treatment with a diuretic and beta blocker were included in the study. Individuals with History of Heart diseases, diabetes, renal transplantation, known bladder dysfunction, nephrectomy and those on corticosteroids, steroidal anti-inflammatory and immunosuppressive drugs, as well as those with known intolerance to ACEi or CCB were excluded from the study.
Interventions	Ramipril (2.5-20mg/d), Felodipine (2.5-20mg/d) and half doses in combination group of Ramipril with Felodipine
Outcomes	Change in BP control and progression of renal insufficiency
Notes	Follow up of 1.73 years on average based on three groups

Fogari et al, 2002

Methods	Multicenter, open labeled, randomized, prospective, parallel group study which started with 4 week placebo washout period for the selected participants, checked them for inclusion criteria using computerized randomization by an external investigator who is not part of participants' recruitment, assigned interventions such monotherapy of ACEi and CCBs as well as combination therapy of both during 3 month titration period. People with side effects or non-responders discontinued and rest of the patients being enrolled and was followed over 4 years. BP being monitored monthly for first three months for three times with 5 minutes rest and its average were taken as their BP level. Patients were then checked every 6 months for BP and UAE levels, which was assessed by radioimmunoassay.
Participants	Outpatients including both the genders, with essential hypertension, Diabetes mellitus (type 1), microalbuminuric with 30-300mg/24hr in two different 24-h urine collections taken 7 days prior to enrollment, BMI<30 kg/m^2 and Serum creatinine <1.5mg/Dl. Patients with history of CVD and Cancer, total cholesterol >240 mg/dL, ECG showing left ventricular hypertrophy and those who smoke as well as those using Diuretics or Beta blockers were excluded from the study.

Interventions	Amlodipine (5 to 15 mg/day), Fosinopril (10 to 30 mg/day), and Amlodipine with fosinopril (5/10 to 15/30 mg/day)
Outcomes	Changes on BP and Microalbuminuria as well as cardiovascular outcomes
Notes	Patients were on diabetes control either by diet, metformin or metformin with sulfonylurea which could act as co-intervention. Adverse events were found to be more or less same in both the groups.

Leneen et al, 2006

Methods	Randomized trial with intention to treat analysis and statistical methods using z test for continuous variables and contingency table analysis for categorical values, cumulative event rates based on Kaplan Meier and Cox proportional model for estimation of Hazards ratios.
Participants	Participants aged greater than or equal to 55 years, with untreated or treated HTN and diabetes, and with at least one risk factor for CHD were included for the study.
Interventions	Amlodipine (2.5,5 and 10 mg/d) and Lisinopril (10,20 and 40mg/d)
Outcomes	The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction, analyzed by intention-to-treat.

	Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease (CVD), end-stage renal disease (ESRD), cancer, and gastrointestinal bleeding.
Notes	If study drugs were not able to achieve BP target, step 2 drugs such as atenolol, clonidine or reserpine or step 3 drug such as hydrazaline will be given if needed.

Ogihara et al, 2008

Methods	A prospective, randomized, open label study with blinded assessment of the endpoint and analysis done using incidence proportions with the help of Kaplan Meier Method and comparison made based on log rank test and cox regression analysis for estimating Hazard ratios.
Participants	Diabetic Patients with high-risk HTN aged <70 years were joined in the study.
Interventions	Candesartan cilexitil (4- 8 mg/d) and Amlodipine besylate (2.5-5.0mg/d)
Outcomes	Primary end points including Sudden death which is unexpected death that happened within 24 hours without external causes; Cerebrovascular events including stroke or transient ischemic

	attack; Cardiac events such as heart failure, angina pectoris, or acute myocardial infarction; Renal events such as serum creatinine concentration 4.0 mg/dL, doubling of the serum creatinine concentration (however, creatinine 2.0 mg/dL is not regarded as an event), or end-stage renal disease, and Vascular events like dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery. Secondary and pre-specified end points are All-cause deaths, New-onset of diabetes and stopping of treatment sue to adverse events
Notes	Candesartan cilexitil is increased to dose of 12 mg/d when necessary and Amlodipine besylate can be increased to the dose of 10mg/d when necessary.

Liakos et al, 2012

Methods	A prospective trial with analysis done using students' t test or non-parametric test for continuous variates and Chisquare or fishers test for categorical variates and a general linear model for multivariate analysis of covariance

Participants	Non-diabetic Caucasian patients, aged 30–65 years, with uncomplicated and never treated hypertension, were included in this study.
Interventions	Irbesartan (300mg/d) and Diltiazem (300mg/d)
Outcomes	Effect on the inflammatory and thrombotic response
Notes	Renal outcomes was none of their study outcomes due to which renal function was ascertained based on the GFR estimate given at baseline and end of the follow-up. Also, in case of drugs, diuretics (Hydrochlorothiazide with dose of 25mg/d) will be given if needed

Ay. Et al, 2013

Methods	Randomized trial with analysis done using ANCOVA and Pearson correlation
Participants	Newly diagnosed hypertensive patients applying to the internal medicine and cardiology outpatient clinics with n=20 were included in the study and Patients with any damaged organ due to HTN diabetes, alcohol intake, smoking habits and those on any medications were excluded.
Interventions	Valsartan (80–320 mg/day) or Amlodipine (5–10 mg/day)
Outcomes	Changes on BP and Microalbuminuria
Notes	Patient of two groups were matched for age and BMI.

Appendix C: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3&4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	15&16
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	17
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NIL
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	28-30
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	25-26
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	85-89

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	25-30
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	33-36
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	25-38
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	36-37
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	32-36,37-38
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	37-38
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	37-38
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	38
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	39-40
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	41-48
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	47-49
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	50-61

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	50-61
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	50-61
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	66-71
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	71-72
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	73
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	38