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Recent Trials in Hypertension

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1. Introduction

There are numerous trials in hypertension many of which have focused on cardiovascular (CV) outcomes (death, non–fatal Myocardial Infarction, stroke, congestive heart failure). These trials have influenced our clinical practice in terms of setting out guidelines in the treatment of Hypertension. However, the last three years have seen newer trials emerge which we feel will influence the new upcoming guidelines.

Making sense of these trials and applying their conclusions into clinical practice remains a formidable challenge to physicians. In this chapter we will not only review landmark trials, but also attempt to analyse them and suggest recommendations to be applied in daily practice. The trials will be evaluated according to the following three major categories:

1. **Trials in Patients with Essential Hypertension (Hypertension Trials)**
2. **Trials in patients with renal disease and renal outcomes (Renal Trials)**

a. Non-Diabetic
b. Diabetic

3. **Trials in patients with high cardiovascular risk and focusing on cardiovascular outcomes. (Cardiovascular Trials)**

2. Hypertension trials

All physicians are faced with the dilemma of which drug is the best choice for patients with essential hypertension. By best choice we mean, the drug that is most economical, has a high safety profile and improves cardiovascular mortality. Our drug choice has been influenced over time by various published trials that will be reviewed. However, it is important to start first by evaluating a trial looking at lifestyle modification in essential hypertension.

TOHP Trial (Trial of Hypertension Prevention) (1) and its long-term follow-up **TOHP-2**(2) were the main studies on lifestyle modification. This randomized, placebo controlled trial of 2812 patients demonstrated that weight loss is the most effective lifestyle modification, reducing SBP and DBP on average by 2.9/2.3 mm Hg for every 4 kilogram weight loss. Dietary sodium restriction reduced BP by 2/1 mm Hg for every 44-meq/ day decreasing salt intake. All other arms, reductions in calcium or magnesium, fish oil and stress management failed to achieve sustained blood pressure improvement. Though non-pharmacologic measures lead to modest BP effects, it nevertheless has great clinical significance. This was also shown in large trials such as ALLHAT and VALUE, where even

small differences of -4/-3 mm Hg were associated with significant reduction in stroke (23%), coronary heart disease (15%) and mortality (14%).

As monotherapy most of the drugs produce effective response in about 30 percent of cases (3,4). However there is wide inter-patient and inter-racial variability. Black patients for instance, respond better to CCBs and diuretics, whereas white patients have better response to ACE/ARBs and Beta-blockers. This variability may be related to low renin-high volume conditions in the former and high renin-low volume in the latter. Hence results of individual trials are not generalizable and apply only to the specific study population.

TOMHS Trial (Treatment of Mild Hypertension Study) attempted to evaluate the response of 5 major first line drugs in a predominant white population (5). The efficacy of the drugs was essentially similar although the CCB group (Amlodipine) had the highest percentage of patients responding to monotherapy.

ALLHAT Trial (Antihypertensive and Lipid Lowering to prevent Heart Attack Trial) is a randomised prospective trial of 45,000 patients with hypertension and one additional risk factor for coronary heart disease (6). ALLHAT compared primary (fatal coronary heart disease and non fatal myocardial infarction) and secondary (congestive heart failure, stroke etc.) cardiovascular outcomes among those randomly assigned chlorthalidone (12.5-25 mg/day) to one of three other arms: CCB (Amlodipine), ACEI (Lisinopril) and alpha adregenic blocker (Doxazosin). The initial mean untreated and treated blood pressures were similar (156/89 and 145/83). The Doxazosin arm was prematurely terminated due to increased risk of heart failure compared to diuretics. It should be noted that though the Doxazosin arm was stopped in February 2000, the primary end point, reduction in cardiovascular mortality from myocardial infarction was not different between two groups. This occurred despite the thiazide diuretic groups having a SBP 3 mm Hg lower than the alpha-blocker group.

The incidence of primary outcome (fatal coronary heart disease and non fatal myocardial infarction) was similar for all three agents. The CCB arm compared to diuretic had a higher rate of heart failure but other secondary outcomes were similar. The ACEI arm compared to diuretic had higher combined cardiovascular outcomes, stroke and heart failure. Blacks and non-diabetics in the ACEI arm had higher rates of these unfavourable outcomes. The higher risk of heart failure seen with Amlodipine and Lisinopril was greatest in the first year. This was attributed mainly to better blood pressure control in the diuretic arm. The risk was greatly attenuated after the first year when blood pressures were similar. The mean increase in fasting glucose in non-diabetics was higher in diuretic arm versus ACEI or CCB. The ALLHAT Trial showed that in patients with hypertension and high risk for cardiovascular disease, diuretics (chlorthalidone), CCB (Amlodipine) and ACEI (Lisinopril) had same protection from fatal coronary heart disease and nonfatal myocardial infarction. Amlodipine was not associated with excessive cardiac deaths as suggested by INSIGHT trial though the higher rate of congestive heart failure is consistent with other trials (7).

ANBP2 Trial (Second Australian National Blood Pressure) compared an ACEI (Lisinopril) with diuretic (Hydrochlorothiazide) in elderly hypertensive patients (8). The ANBP2 trial was a prospective trial of 6000 participants. The primary outcome was all cardiovascular events. These included coronary events (myocardial infarction, sudden death from cardiac events), cardiovascular events (heart failure, vascular cause of death) and cerebrovascular (stroke or transient ischemic episode). At the end of the study both arms had similar reductions of blood pressure of 26/12 mm Hg. Approximately 65 percent of patients in both arms needed monotherapy while the rest needed two or more agents. The ACEI arm had

better cardiovascular outcomes as compared to the diuretic arm. While fatal events were the same in both arms, the incidence of non-fatal cardiovascular events was less in the ACEI arm. This was in contradiction to the ALLHAT trial that showed that diuretics were more effective in cardiovascular outcomes.

Stop-Hypertension 2 Trial comparing ACEI (Lisinopril) vs. dihydropyridine CCB (DHP-CCB) in this case Felodipine or Isradipinevs. Beta-blocker and /or diuretic, found no difference in cardiovascular end points (9). **NORDIL Trial (Nordic Diltiazem Trial)** comparing CCB (Diltiazem) combined with either a diuretic or Beta-blockers or both showed no cardiovascular outcome differences between the three groups at similar level of blood pressure control (10). The conclusion of Stop-Hypertension 2 study and NORDIL study show that CCBs are equally effective in cardiovascular outcome trials of low- medium risk patients.

MRC Trial (Medical Research Council Trial) (11) found no difference in cardiovascular outcomes between thiazide diuretic and Propanolol, but there was a significant increased risk of stroke in the Propanolol arm. This trial was predominantly in middle aged men with mean diastolic pressure 99-109 mm Hg. A subsequent MRC trial (12) comparing Atenolol to Hydrochlorothiazide plus Amiloride suggested Beta-blockers did not reduce cardiovascular mortality or coronary events but did reduce the incidence of cerebrovascular incidents, while diuretics reduced all of these endpoints.

In the **ACCOMPLISH trial (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension)**, 11,500 patients with hypertension and mean baseline BP 145/80, who are at high risk of cardiovascular events, were randomly assigned to a combination therapy with Benazepril plus either Amlodipine or hydrochlorthiazide (12.5 to 25 mg/day) (13). At 36 months, the trial was terminated early. Benazepril- Amlodipine therapy was associated with significant reductions in the primary composite end point of fatal or non fatal cardiovascular events (9.6 versus 11.8 percent) and the secondary end point of cardiovascular death or non fatal MI or stroke (5.0 versus 6.3 percent). The mean blood pressure was slightly (about 1mm Hg) lower in the Benazepril-Amlodipine arm (132/73 versus 133/74), a difference that was too small to account for the large difference in outcomes. In a subset of 573 patients with 24 hour Ambulatory BP monitoring there was a non-significantly higher BP (1.3/0.3 mm Hg) in the Benazepril-Amlodipine group. The benefits seen in the Benazepril-Amlodipine arm appear to be independent of blood pressure lowering. The study also cannot distinguish benefit from Benazepril-Amlodipine and harm from Benazepril-hydrochlorthiazide arms.

2.1 Choice of antihypertensive medications in essential hypertension

The 2007 American heart Association and 2007 European Society of Hypertension (14) and European Heart Association (15) concluded that it is the amount of Blood Pressure reduction and not the class of drug used which determines the reduction in Cardiovascular risk in patients with Hypertension.

The initial choice recommended by the Joint National Commission 7(JNC7) for uncomplicated essential hypertension is thiazide diuretics (16) If thiazides fail to control blood pressure then ACEI/ARBs, CCBs or BB can be added. The use of these drugs is guided by cost or comorbid conditions for specific therapies. Post-ACCOMPLISH trial, since most patients with mild hypertension end up using more than one drug, either long acting ACE inhibitor/ARB or dihydropyridine calcium channel blocker could be recommended as first line therapy. Those with moderate to severe hypertension (Stage II) as defined by JNC7

having blood pressures greater than 20/10 mm Hg above goal should be considered initially for dual therapy. The combination of long acting ACEI/ARB with a dihydropyridine CCB would probably be the therapy of choice given the favourable results in the ACCOMPLISH trial.

Trial	Population Studied	Intervention	Outcome	Comments
TOHP Trial (Hypertension Prevention)	placebo controlled trial of 2812 hypertensive patients	Lifestyle modification on BP control.	Weight loss most effective Calcium, Magnesium, fish oil – no effect. Small BP differences (-4/-3 mm Hg) associated with significant reduction in stroke (23%), coronary disease (15%) & mortality (14%).	
TOMHS Trial (Treatment of Mild Hypertension)	predominant white population	Efficacy of 5 major first line drugs on BP control	Efficacy similar But Amlodipine had highest percentage of responders to monotherapy	
ALLHAT Trial (Antihypertensive and Lipid Lowering to prevent Heart Attack)	45,000 patients with hypertension and one additional coronary disease risk factor	Randomly assigned chlorthalidone (12.5-25 mg/day) to one of three other arms: CCB (Amlodipine), ACEI (Lisinopril) and alpha adregenic blocker (Doxazosin)	Primary outcome (fatal coronary disease, non fatal myocardial infarction) similar for all three agents. **Doxazosin arm prematurely terminated due to increased risk of heart failure vs diuretics a) CCB vs diuretic - higher rate of heart failure but other secondary CV outcomes similar b) ACEI vs diuretic- higher combined cardiovascular outcomes, stroke and heart failure *a) & b) attributed to better BP control in diuretic arm*	For hypertensives at high risk for cardiovascular disease, diuretics, CCB and ACEI offer similar in protection vs fatal coronary disease & nonfatal myocardial infarction
ANBP2 Trial (Second Australian National Blood Pressure)	Prospective trial of 6000 elderly hypertensive patients	ACEI (Lisinopril) vs diuretic (Hydrochlorothiazide)	Primary outcome: all cardiovascular events (myocardial infarction, sudden death from cardiac events)- ACEI arm had better outcomes vs diuretic Fatal events same in both arms, but non-fatal cardiovascular events were less in ACEI arm	

Stop-Hypertension 2 Trial	Low-medium CV risk hypertensive patients	ACEI (Lisinopril) vs. dihydropyridine CCB Felodipine or Isradipine vs Beta-blocker and /or diuretic	No difference in cardiovascular end points	CCBs equally effective in cardiovascular outcome
NORDIL Trial (Nordic Diltiazem Trial)	Low-medium CV risk hypertensive patients.	Comparing CCB (Diltiazem) combined with either diuretic or Beta-blockers or both.	No cardiovascular outcome differences	CCBs equally effective in cardiovascular outcome
MRC Trial (Medical Research Council Trial)	Middle aged men with mean diastolic BP 99-109.	Thiazide diuretic vs Propanolol. Second MRC trial comparing Atenolol to Hydrochlorothiazide plus Amiloride	No difference in cardiovascular outcomes but significant increased stroke risk in Propanolol arm Beta-blockers did not reduce cardiovascular mortality or coronary events but reduced cerebrovascular incidents, while diuretics reduced all these endpoints	
ACCOMPLISH trial (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension	11,500 patients with hypertension and baseline BP 145/80, high risk of cardiovascular events	Benazepril plus either Amlodipine or hydrochlorthiazide (12.5 to 25 mg/day).	Terminated early Benazepril- Amlodipine showed significant reductions in primary composite end point (fatal or non fatal cardiovascular events) and secondary end point (cardiovascular death or non fatal MI or stroke)	Cannot distinguish benefit from Benazepril-Amlodipine vs. harm from Benazepril-hydrochlorthiazide

Table 1. Summary of Trials in Patients with Essential Hypertension

3. Renal trials

Renal outcome trials can be divided into those pertaining to patients with diabetic versus non- diabetic kidney disease. In the latter, the focus has been on short-term reduction of proteinuria and long term delay in progression of kidney disease. On the other hand, in diabetic kidney disease trials have focused on reduction of protein excretion as a surrogate end point since it correlates directly with the rate of decline in renal function.

a. Non- Diabetic kidney disease:

Most trials on reduction of proteinuria have focused on ACEI. This class of drugs has been known to reduce intraglomerular pressure mainly by inhibition of Angiotensin II- mediated efferent arteriole vasoconstriction. In addition, ACEI alter the permaselective properties of

the glomerular basement membrane and have antifibrotic effects that are thought to further reduce proteinuria.

How do other drugs compare with ACEI in proteinuria reduction?

In a trial (17) comparing non-dihydropyridine CCBs (Verapamil and Diltiazem) versus dihydropyridine CCBs (Amlodipine and Nifedipine), the former were found to have a significant (30%) reduction in proteinuria while the latter had no decrease or even an increase in protein excretion. It is postulated that DHP CCBs cause afferent arteriole dilatation allowing more of the aortic pressure to be transmitted to the glomerulus. Hence despite lowering of systemic blood pressure the intraglomerular pressure (IGP) remains elevated without significant decrease in proteinuria. Similarly Beta-blockers, diuretics, alpha-blockers have no effect on reducing IGP and hence proteinuria (18,19,20). Studies have also examined the comparative effectiveness of Angiotensin II receptor blockers (21). In one study of patients with IgA nephropathy Enalapril and Irbesartan had similar effects on proteinuria (22). The antiprotenuric effect of ACEI and A2RBs increases when used at supramaximal doses. For instance, Temlisartan 80 mg when used twice vs. once daily had significantly greater decline in proteinuria and progression of kidney disease, despite similar BP reduction. Additionally, combination therapy with ACEI and A2RBs has shown significant beneficial effect on proteinuria and kidney disease progression, more so when used in maximal or submaximal doses than maximum dose of either drug alone (23). This meta-analysis comparing combination therapy at submaximal doses to either agent alone at maximal doses confirmed these findings with greater reduction in proteinuria.

While the above trials focused on reduction of proteinuria, other trials in non-diabetics have shown benefits of ACEI in reducing progression to chronic kidney disease.

Though, the **ALLHAT Trial** (24) of more than 44,000 hypertensive patients failed to show superiority of ACEI, DHP-CCBs and alpha-blockers over a thiazide diuretic with respect to cardiovascular outcomes. In post hoc analysis neither ACEI nor CCB was superior to thiazide diuretic with respect to renal outcomes. This trial was contradictory to other primary renal outcome trials that showed benefit of ACEI over other drug classes. Some of the factors responsible for this controversy will be explored.The ALLHAT did not select patients with renal disease as an inclusion criterion, since it was not mainly a renal outcome trial. Blood pressure was also lower in thiazide arm as compared to the other arms hence equivalency of blood pressure was not achieved. Furthermore, no urine tests were performed even though renal outcomes were studied thus failing to identify those who were at highest risk for progression and most likely to derive benefit from ACEI i.e. patients with proteinuric diabetic kidney disease. Hence, in the ALLHAT trial little or no attention was paid to kidney function, consequently the results of ALLHAT regarding renal outcomes remain unresolved.

REIN Trial (Ramipril Efficacy in Nephropathy) of non-diabetic chronic kidney disease patients treated with Ramipril or placebo plus other medications to a target diastolic pressure less than 90 mm Hg. At same level of blood pressure control, the Ramipril group had a significant decrease in rate of decline of GFR (25). The disparity was predominantly so significant in groups excreting > 3 grams/day, necessitating premature termination of the study in favour of the Ramipril group. As a follow-up to this study patients excreting > 3grams/day on Ramipril were continued on same drug, but those on placebo were also switched to Ramipril. Analysis of this follow-up revealed that patients assigned as well as those shifted to Ramipril, had significant attenuation in the rate of deterioration of renal

function compared to the conventional therapy group. Longer follow-up at 5 years showed that some patients in the Ramipril group actually had an increase in GFR. Further analysis also revealed that Ramipril was efficious in patients with less severe proteinuria (>1 gram but < 3 grams/day) and also decreased the rate of decline in GFR in all tertiles of GFR (low: 11-33 ml/min/1.73m2, middle: 33-51 ml/min/1.73 m2, high: 51-101 ml/min/1.73m2).In the REIN 2 Trial (26), DHP CCB's were once again found to be non efficacious in patients with chronic kidney disease. In this trial patients on Ramipril (up to 5 mg) were randomly assigned to conventional (DBP<90) or intensive BP control (DBP<80) groups. Felodipine was added for intensive blood pressure control. After 19 months there was no significant difference in proteinuria, decline in GFR or progression to ESRD in the intensive Felodipine treated group despite lower blood pressure.

MDRD Trial (Modification of Diet in Renal Disease) compared two groups: one with usual blood pressure control (target 140/90) and one with aggressive control (target 125/75) over a three-year period. The achieved blood pressures were 130/80 and 125/75 respectively. The patients were further subdivided into 3 groups by severity of proteinuria, i.e.: < 1 gram, 1-3 grams and > 3 grams of protein excretion per day. More than half the patients were treated with ACEI and the mean GFR of the approximately 600 patients was 39 ml/min (27). The patients with <1 gram/day proteinuria had the slowest decline in GFR of the three groups (approximately 3 ml/year). No difference was seen in the low blood pressure group. Patients in 1-3 gram/day group had a more rapid deterioration in GFR with mild benefit in lower BP group. Those in >3 gram/day group had the fastest rate of loss in GFR but at the same time there was a substantial attenuation in rate of GFR decline in the low blood pressure group. This study showed that the greater the proteinuria, the faster is the decline in GFR. However with blood pressure control the rate of decline in GFR can be attenuated. While this trial did not evaluate the efficacy of ACEI, the Benazepril Trial did. 600 patients with chronic kidney disease (diabetic and non diabetic but not hypertensive nephrosclerosis) on treatment for blood pressure control were randomised to either Benazepril or placebo (28). The Benazepril group had significantly lower proteinuria, greater reduction in blood pressure, less doubling of serum creatinine and progression to dialysis. Though the drug was compared to placebo, it did show the efficacy of ACEI.

The role of combination ACEI with A2RB's was addressed in the COOPERATE Trial (Combination Treatment of Angiotensin II receptor blocker and Angiotensin converting enzyme inhibitor in non diabetic renal disease) where Losartan 100mg/day, Trandolapril 3mg/day or a combination of the two were compared (29). All the three arms of the trial had the same blood pressure reduction. However the largest decrease in proteinuria was seen in the combination group (77 percent) versus Losartan (42 percent) or Trandolapril (44 percent). The composite end point of doubling serum creatinine or progression to ESRD was less with combination (11 percent) therapy than either Losartan (23 percent) or Trandolapril (23 percent). In the COOPERATE trial, those who could not tolerate maximum doses of combination therapy were treated with sub-maximal doses. Even then the antiprotenuric effects were greater than with either of the single agents. This was further verified in another trial (30) comparing Losartan 50 mg/day, Benzalapril 10 mg/day, Losartan (25mg/day) plus Benzalapril 5 mg/day. Although similar blood pressure lowering was observed, combination therapy at half the dose resulted in significantly lower proteinuria than either drug alone.

Non-Diabetic Trial	Population Studied	Intervention	Outcome	Comments
REIN Trial (Ramipril Efficacy in Nephropathy)	Non-diabetic chronic kidney disease patients	Ramipril or placebo	Ramipril group had significant decrease in rate of GFR decline especially significant in groups excreting > 3 g/d but also in less severe proteinuria DHP CCB's non efficacious	ACEi significant attenuation in rate of deterioration of renal function
MDRD Trial (Modification of Diet in Renal Disease)		Usual (140/90) vs aggressive BP control (125/75)	The greater the proteinuria, the faster is the decline in GFR With BP control rate of GFR decline attenuated	
Benazepril Trial	600 patients with chronic kidney disease (diabetic and non diabetic but not hypertensive nephrosclerosis)	Benazepril or placebo	Benazepril significantly lower proteinuria, greater reduction in BP, less doubling of serum creatinine and progression to dialysis	Trial demonstrates efficacy of ACEI
COOPERATE Trial (Combination Treatment of Angiotensin II receptor blocker & Angiotensin converting enzyme inhibitor in non diabetic renal disease)	Non-diabetic renal disease	Losartan Trandolapril or a combination	Doubling serum creatinine or progression to ESRD was less with combination than either Losartan or Trandolapril Even with sub-maximal doses of combination therapy, antiprotenuric effects greater than with either of the single agents	Largest decrease in proteinuria seen in combination group

Table 2. A. Summary of Trials in patients with renal disease and renal outcomes (Renal Trials). NON-DIABETIC

b. Trials in Diabetic kidney disease:

These are divided into three major groups.

i. Prevention of Incipient Diabetic Nephropathy- BENEDICT Trial
ii. Trials on microalbuminuric Diabetic Nephropathy- HOPE, IRMA, MARVAAL Trials
iii. Trials on overt Diabetic nephropathy-IDNT, RENAAL, DETAIL, AVOID, ONTARGET Trials

i. Prevention of Incipient Diabetic Nephropathy

BENEDICT Trial (Bergamo Diabetic Nephrogenic Trial) is a prospective (31), randomised trial in 1209 hypertensive patients with type 2 diabetes mellitus and normal urine albumin excretion whose aim was to prevent the progression to microalbuminuria. Patients were randomised to a 3-year trial of non DHP CCB (Verapamil 240 mg/day), ACEI (Trandolapril 2 mg/day), combination (Verapamil 180 mg/day and Trandolapril 2mg/day) and placebo. The primary outcome was the development of persistent microalbuminuria, which occurred at a rate of 11.9% in Verapamil only group, 6 %in Trandolapril group, 5.7 % in the combination group and 10% in the placebo. The study showed that Verapamil was similar

to placebo and the use of ACEI was effective in reducing the incidence of microalbuminuria whereas the addition of non DHP CCB did not decrease the risk of its development. It can be concluded that ACEIs are the medication of choice in reducing microalbuminuria in diabetic nonmoalbuminuric hypertensive patients.

ii. Trials on microalbuminuric Diabetic Nephropathy

PRIME Trial (Program for Irbesartan Mortality and Morbidity Evaluation) consisted of two large trials comparing IDNT (Irbesartan in Diabetic Nephropathy Trial) (32,33,34) and IRMA (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria), which evaluated the renal and cardiovascular effects of Irbesartan on hypertensive patients with diabetes (40). In particular, these two large trials addressed the question of whether ARB can prevent the development of clinical proteinuria (IRMA) or delay the progression of nephropathy (IDNT) in type2 diabetes. The latter will be discussed with the trials on overt nephropathy.

IRMA Trial (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group), a multicentre, randomized, double-blind, placebo-controlled trial, evaluated the effect of Irbesartan in preventing the onset of clinical proteinuria in patients with type 2 diabetes, hypertension and microalbuminuria (35). A total of 590 patients were randomized to receive therapy with Irbesartan 150 mg, Irbesartan300 mg, or placebo. Additional antihypertensive agents (excluding ACE-I, ARB, and Dihydropyridine calcium-channel blockers) were allowed in each arm of the study to achieve the target BP of<135/85 mmHg. The primary end point of the study was the onset of overt nephropathy, defined as the occurrence of a urinary albumin excretion rate >200 μg/min and at least 30%higher than baseline. Secondary outcomes were the regression to normoalbuminuria and changes in albuminuria and renal function.

The mean duration of follow-up was 2 yr. The average BP during the course of the study was 143/83 mmHg in the 150-mg group, 141/83 mmHg in the 300-mg group, and 144/83 mmHg in the placebo group. Although the difference in systolic pressure between the Irbesartan 300-mg group and the placebo group was only 3mmHg, it was statistically significant. With respect to the primary end point, Irbesartan 150and 300 mg showed a reduction of 44 and 68%, respectively versus placebo. Moreover, albuminuria was reduced by 38% in the 300-mg group, 24% in the150-mg group, and remained unchanged in the usual care group. In this last group, the reduction in BP from 153/90 to 144/83mmHg resulted in stabilization of albuminuria. In addition, regression to normoalbuminuria was more frequent in the patients who were treated with the higher dose of Irbesartan (17, 12, and 10.5/100 patient-years in the 300-mg, 150-mg, and placebo group, respectively). On the basis of these data, Irbesartan seems to be much more effective in preventing the development of clinical proteinuria and in favouring the regression to normoalbuminuria than conventional therapy. The renoprotective, dose-dependent effect of Irbesartan seems to be independent of its BP-lowering effect, even though the 3-mmHg difference in systolic pressure may have played a role. Similar findings were shown in other trials as discussed below.

HOPE Trial (Heart Outcomes and Prevention Evaluation) and MICRO-HOPE (Microalbuminuria and Renal Outcomes) Trial retrospectively analysed changes of proteinuria over4.5 yrs., and compared Ramipril's effects to placebo in9297 participants, including 3577 with diabetes and 1956 with microalbuminuria. In particular, one of every three participants with diabetes developed new microalbuminuria, and one of five diabetic participants with microalbuminuria developed overt nephropathy (36,37). We know little about the development of new microalbuminuria in type 2 diabetes; these data indicate that

it develops ata surprisingly high rate. Assuming a constant rate of appearance of new overt nephropathy over time, the **HOPE** study also confirms that approximately 50% of microalbuminuric people with type2 diabetes will develop overt nephropathy in 10 years (38). ACE inhibition was shown to be effective in reducing the progression of albuminuria in all participants including the subgroups with and without diabetes mellitus.

MARVAL Trial (Microalbuminuria Reduction with Valsartan) compared Valsartan 80mg/day versus Amlodipine 5 mg/day in type 2 diabetic microalbuminuric patients (39). A target BP of 135/85 mm Hg was aimed for by double dosing after four weeks followed by addition of bendrofluazide and Doxazosinas needed. The primary end point of percentage reduction in proteinuria was 44 percent with Valsartan and 8 percent with Amlodipine. For the same level of attained BP, Valsartan lowered albuminuria more effectively than Amlodipine in patients with type 2 diabetes and microalbuminuria, including the subgroup with baseline normotension. This indicates BP-independent antiprotenuric effect of Valsartan. Moreover, more patients reverted to normoalbuminuria with Valsartan.

Recommendations clinical pearl The above three studies clearly show that blocking of the Renin Angiotensin Aldosterone System (RAAS) with ACEI or ARBs in patient with type II diabetes mellitus reduces the risk of progression of microalbuminuria to overt proteinuria and may even revert it back to normoalbuminuria, both in hypertensive and normotensive patients.

iii. Trials on overt Diabetic nephropathy

For patients who already have overt nephropathy, trials in type 1 and type 2 diabetics show benefits of ACEI and ARBs in reducing progression to end stage renal disease (ESRD) as will be discussed. In Type 1 DM the largest trials (40,41) were in patients who already had overt nephropathy with serum creatinine less than 2.5 mg/dl who were randomised to either Captopril or placebo. After four years there was significant decrease in rate of decline in renal function in the Captopril arm versus placebo. This rate was reduced from 1.4 mg/dl in the placebo group to 0.6 mg/dl in the Captopril group. The beneficial effect was seen mainly in patients whose initial serum creatinine was greater than 1.5 mg/dl, while no benefit was seen with lower baseline serum creatinine likely because the rate of progression was very slow in this group (0.1-0.2 mg/dl/year). The beneficial effect of Captopril was seen in both normotensive and hypertensive patients. However, it has been suggested that reducing BP to less than 120/75 regardless of the agent may slow progression of kidney disease (42).

In another study (43) of 301 patients with overt nephropathy of whom 271 were hypertensive and 30 were normotensive, the remission rates (defined as proteinuria less 300 mg/day) and regression rates (defined as rate of decline in GFR< 1 ml/min/year) were significantly greater in the lower blood pressure groups. The main antihypertensive drugs were ACEI in about 179 patients. The lower blood pressure group (mean arterial pressure 93 mm Hg) had remission and regression rates of 58 and 42 percent while the higher blood pressure group (mean arterial pressure 113 mm Hg) had rates of only 17 and 7 percent, after a mean follow up of 7 years. Thus aggressive blood pressure control in patients with overt nephropathy will induce greater remission and regression rates, especially when ACEI are used.

In Type 2 diabetics with overt nephropathy much of the prevailing evidence is with ARBs. Similar to the trials described above, control of blood pressure is essential to limit progression to ESRD however the optimal lower limit is not defined. **The UKPDS Trial (United Kingdom Prospective Diabetes Study)** showed that every 10 mm Hg decrease in systolic blood pressure reduced diabetic complications by 12 percent, with the lowest risk

below 120 mm Hg (43). However in the IDNT Trial (Irbesartan Diabetic Nephropathy Trial) lowering SBP less than 120 mm Hg was associated with increased risk of all cause cardiovascular mortality (33,34). However in the group with increased cardiovascular mortality there was a higher incidence of underlying heart disease and heart failure. Moreover, the number of patients was too low to determine if the effect of low blood pressure was independent of prior cardiac disease. The two major trials which have clearly shown the benefits of ARBs in patients with proven nephropathy due to Type 2 DM will be reviewed.

The IDNT Trial (Irbesartan Diabetic Nephropathy Trial) of 1715 patients with diabetic nephropathy who were randomly assigned to Irbesartan 300 mg/day versus Amlodipine 10 mg/day versus placebo (33,34). After 30 months of follow up, the composite end points of development of ESRD or death from any cause were 23% and 20 % lower with Irbesartan than Amlodipine and placebo respectively. The rates for doubling serum creatinine were also 37% and 30 % lower for Irbesartan than Amlodipine and placebo respectively (33,34,35).

The RENAAL Trial (Reductions of endpoints in NIDDM with the Angiotensin II Antagonist Losartan) of 1513 patients with type 2 diabetic nephropathy, in which patients were assigned Losartan (50-100 mg/day) versus placebo with additional drugs added for further blood pressure control (except ACEI). The composite end points of doubling serum creatinine or ESRD were 25% and 28 % lower with Losartan than placebo (44). Both the above studies underline the positive effect of ARBs on progression of diabetic nephropathy.

The DETAIL Trial is the only study which offered head to head comparisons between ACEI and ARBs for diabetic nephropathy in type 2 diabetics (45). Temlisartan versus Enalapril were compared in patients with albuminuria (defined as micro and macroalbuminuria). After five years of follow-up there was a smaller but non-significant decline in GFR with Enalapril versus Temlisartan (14.9 ml/min versus 17.9 ml/min per 1.73 m2). Both arms had similar secondary end points of urine albumin excretion, doubling serum creatinine, progression to ESRD and cardiovascular events.

Combination ACEI and ARBs in diabetic proteinuric kidney disease have not been studied in large trials. Nevertheless, three small studies (46,47,48) have shown benefit of combination therapy over either ACEI or ARBs (the latter two used at either maximal or sub-maximal dose).

While diuretics are not known to have antiprotenuric effects despite lowering blood pressure, Aldosterone antagonists either used alone or in combination with ACEI or ARBs have been shown to reduce proteinuria. In a trial of 59 patients with Type 2 diabetes and nephropathy on ACE or A2RBs, the addition of Spironolactone 50 mg/day versus placebo was associated with a 40% reduction in proteinuria and 7/3 mm Hg decrease in BP (49). Eplernone 50 mg/day when added to ACEI in patients with type 2 diabetes was associated with a significant 40% reduction in proteinuria compared to placebo (50). While no long term studies have shown a benefit of Aldosterone blockers in reducing the rate of loss of GFR, their antiprotenuric and BP lowering effects would be expected to translate into nephroprotection.

GEMINI Trial (Metabolic Effects of Carvedilol vs. Metoprolol in Patients with Type 2 Diabetes Mellitus and Hypertension)1200 participants with type 2 diabetes mellitus showed that when Carvedilol was added to blockers of RAAS improvements not only in glycaemic control but also in risk of developing microalbuminuria were seen. These were markedly reduced over Metoprololat similar levels of blood pressure control. (51). It was also noted that those without microalbuminuria had a 7/4 mm Hg greater reduction in

blood pressure as compared to those with microalbuminuria (52). This observation supports previous data of a blunted vascular response associated with microalbuminuria. It also suggests that not all have the same detrimental effect on diabetes and the risk of its development.

The **AVOID Trial (Aliskerin in the Evaluation of Proteinuria in Diabetes)** of 599 patients with Type 2 diabetes and nephropathy, evaluated the renoprotective effects of dual blockade of the renin angiotensin aldosterone system (RAAS) by adding treatment with Aliskerin (maximum dose 300 mg daily), an oral direct renin inhibitor, to treatment with the maximal recommended dose of Losartan (100 mg daily) (53). At 6 months the primary end point of reduction in albumin- creatinine ratio was a mean of 20% in Aliskerin group versus placebo with over 50% reduction in 25% of patients in Aliskerin group versus 12.5% in placebo. This was despite a small difference in BP between the two groups (systolic 2mm Hg/ diastolic 1 mm Hg) favouring Aliskerin. Clinical pearl This suggests Aliskerin may have renoprotective effects that are independent of blood pressure lowering effects in hypertensive patients with type 2 diabetes and nephropathy who are already receiving the recommended therapy.

The ONTARGET trial (The Ongoing Telmisartan alone and in combination with Ramipril Global Endpoint Trial), in which 25,620 patients with vascular disease or diabetes were randomized to the ACE inhibitor Ramipril, ARB Telmisartanor the combination of the two drugs (54). The primary renal outcome was a composite of dialysis, doubling of serum creatinine and death. The number of events of primary composite outcomes was similar for Ramipril and Temlisartan but was increased with combination therapy. Although the combination therapy reduced proteinuria more than either single therapy, overall it worsened major renal outcomes.

Finally, the controversial meta-analysis by Casas (55) will be discussed. This included thirteen trials with 37,089 subjects. Casas concluded that drugs which inhibit the Renin Angiotensin Aldosterone system (RAAS) provide only marginal benefit for nondiabetic kidney disease and no benefit in diabetic renal disease. The authors state that if there is a benefit of ACEI or ARBs in diabetics, it is simply due to better blood pressure control, which was 2 to 7 mm Hg lower in the ACEI groups. When their analysis was limited to studies with no evident blood pressure difference, no benefit was identified. Similar findings were noted in the ABCD trial (Appropriate Blood Pressure Control Trial) in patients with microalbuminuria and mean baseline GFR of 84 ml/min. No difference in renal outcomes at 5 years was observed between ACEI and calcium channel blockers when their BP was lowered to below 130/80 mm Hg (56).

Trial Diabetic	**Population Studied**	**Intervention**	**Outcome**	**Comments**
BENEDICT Trial (Bergamo Diabetic Nephrogenic Trial)	1209 hypertensive patients with type 2 diabetes mellitus and normal urine albumin excretion	Non DHP CCB Verapamil vs ACEI Trandolapril vs combination vs placebo	Primary outcome: Development of persistent microalbuminuria. Verapamil similar to placebo ACEI effective in reducing incidence of microalbuminuria	ACEIs are of choice in reducing microalbuminuria in diabetic nonmo-albuminuric hypertensive patients
PRIME	Consisted of	Whether ARB can		

Trial(Program for Irbesartan Mortality and Morbidity Evaluation)	two large trials on type 2 diabetics: IDNT (Irbesartan in Diabetic Nephropathy Trial) IRMA (Irbesartan in Patients with Type 2 Diabetes & Microalbuminuria)	prevent development of clinical proteinuria (IRMA) or delay progression of nephropathy (IDNT)		
IRMA Trial (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group)	**Patients with Type 2 Diabetes and Microalbuminuria.**	Irbesartan 150 mg or Irbesartan 300 mg vs placebo	Primary end point: Onset of overt nephropathy- Irbesartan 150and 300 mg showed a reduction vs placebo Secondary outcomes: Regression to normoalbuminuria and changes in albuminuria & renal function- Regression more frequent with higher Irbesartan dose	Irbesartan more effective in preventing development of clinical proteinuria and regression to normoalbuminuria than conventional therapy
HOPE Trial (Heart Outcomes and Prevention Evaluation) and MICRO-HOPE (Micro-albuminuria and Renal Outcomes) Trial	9297 participants, including 3577 with diabetes and 1956 with Microalbuminuria	Follow changes of proteinuria and compare Ramipril's vs placebo	Approximately 50% of microalbuminuric people with type2 diabetes will develop overt nephropathy in 10 years ACE inhibition effective in reducing progression of albuminuria in all, including subgroups with and without diabetes mellitus	
MARVAL Trial (Microalbuminuria Reduction with Valsartan)	Patients with type 2 diabetes and microalbuminuria	Valsartan vs Amlodipine	Primary end point: reduction in proteinuria- Valsartan more effective including subgroup with baseline normotension & more patients reverted to normo-albuminuria	BP-independent antiprotenuric effect of Valsartan

Trials on Overt Diabetic Nephropathy	Type 1 DM with overt nephropathy & serum creatinine < 2.5 mg/dl 301 Patients with overt nephropathy, 271 hypertensive & 30 normotensive	Randomised to either Captopril or placebo Normal vs lower BP groups Main antihypertensive drugs were ACEI in 179 patients	Significant decrease in rate of decline in renal function in the Captopril arm Beneficial effect of Captopril in both normotensive & hypertensive patients Significantly greater nephropathy remission & regression rates in lower BP group	Aggressive BP control in patients with overt nephropathy will induce greater remission & regression rates, especially when ACEI are used
The UKPDS Trial (United Kingdom Prospective Diabetes Study)		Showed that every 10 mm Hg decrease in systolic BP reduced diabetic complications by 12 %, with lowest risk below 120 mm Hg		
IDNT Trial(Irbesartan Diabetic Nephropathy Trial	1715 patients with diabetic nephropathy	Irbesartan vs Amlodipine vs placebo	Composite end points: development of ESRD or death from any cause- lower with Irbesartan than Amlodipine and placebo Doubling serum creatinine lower for Irbesartan.	Positive effect of ARBs on progression of diabetic nephropathy Of note: lowering SBP < 120 mm Hg associated with increased risk of all cause cardiovascular mortality. However this group had higher incidence of underlying heart disease & heart failure and number of patients was too low to determine if lower BP effect was independent of prior cardiac disease
RENAAL Trial (Reductions of endpoints in NIDDM with	Type 2 diabetic nephropathy	Effect of Losartan (50-100 mg/day) vs placebo	Composite end points of doubling serum creatinine or ESRD: lower with Losartan	Positive effect of ARBs on progression of diabetic nephropathy

the Angiotensin II Antagonist Losartan)				
DETAIL Trial	Type 2 diabetics with diabetic nephropathy (micro and macro albuminuria)	Temlisartan vs Enalapril on diabetic nephropathy progression	A smaller but non-significant decline in GFR with Enalapril vs Temlisartan Similar secondary end points of urine albumin excretion, doubling serum creatinine, progression to ESRD & cardiovascular events	
GEMINI Trial(Metaboli c Effects of Carvedilol vs. Metoprolol in Patients with Type 2 Diabetes Mellitus and Hypertension)	1200 participants with type 2 diabetes mellitus	Carvedilol vs Metoprolol was added to RAAS blockers	Improvements in glycaemic control & risk of developing microalbuminuria with carvedilol vs Metoprolol	Confirms blunted vascular response associated with microalbuminuria Suggests that not all beta Blockers have same detrimental effect on diabetes & risk of its development
AVOID Trial (Aliskerin in the Evaluation of Proteinuria in Diabetes)	599 patients with Type 2 diabetes and nephropathy	dual blockade: adding Aliskerin to maximal dose of Losartan vs placebo	Primary end point: reduction albumin- creatinine ratio- 20% in Aliskerin group vs 12.5% in placebo despite a small difference in BP	Aliskerin may have renoprotective effects independent of BP lowering
ONTARGET trial (The Ongoing Telmisartan alone and in combination with Ramipril Global Endpoint Trial),	25,620 patients with vascular disease or diabetes	ACE inhibitor Ramipril vs ARB Telmisartan vs combination	Primary renal outcome: composite of dialysis, doubling of serum creatinine & death: similar for Ramipril and Temlisartan but was increased with combination therapy Although combination therapy reduced proteinuria more than either single therapy, overall it worsened major renal outcomes	
Meta-analysis by Casas	Thirteen trials 37,089 subjects		Drugs which inhibit RAAS provide only marginal benefit for nondiabetic kidney disease & no benefit in diabetic renal disease When analysis was limited to studies with no BP difference, no benefit was identified	

ABCD trial (Appropriate Blood Pressure Control Trial)	Patients with microalbuminuria & mean baseline GFR 84 ml/min	Comparison of ACEI & CCB	No difference in renal outcome when BP lowered < 130/80 mmHg	

Table 2. B. Summary of Trials in patients with renal disease and renal outcomes (Renal Trials). DIABETIC

4. Cardiovascular trials

While it has been suggested that ACEI/ARBs are beneficial in individuals with cardiovascular disease, it is the achieved blood pressure rather than the specific drug that may be responsible for the benefits. Also, while the JNC 7 recommends a target blood pressure of less than 140/90, the data cited below also suggest that as in CKD (chronic kidney disease), a blood pressure target of less than 130/80 may be appropriate.

In the **HOPE Trial (Heart Outcomes Prevention Evaluation)** (57,58) patients with high cardiovascular risk (without acute MI, LV dysfunction or heart failure) were randomly assigned to Ramipril 5-10 mg/day or placebo. The trial was terminated prematurely after 4.5 years because of significant benefits in the Ramipril arm with only14% reaching the primary end point (any cardiovascular event: CVA, MI, Cardiovascular death) versus 17.8 percent in the placebo group. A reduction was also seen in stroke events despite a mean BP of 135/76, which was only 3.3/1.4 mm Hg less than placebo (59). However, although the benefits were thought to be independent of BP control, an analysis of a subset of 38 patients who underwent ambulatory blood pressure monitoring showed a significant drop in night time blood pressure.

The **EUROPA Trial (European Trial on Reduction of cardiac Events with Perindopril in Stable Coronary Artery Disease)** was similar to the HOPE but patients in this trial had lower cardiovascular risk as evidenced by lower prevalence of hypertension, diabetes or peripheral vascular disease as well as lower cardiovascular mortality in the placebo group. The mean blood pressure at entry was 137/82 mm Hg. In this study patients were given Perindopril (8 mg once a day) or placebo and were followed for a mean of 4.2 years with primary end point of MI, cardiac arrest or cardiovascular death. A significant reduction in primary end point was noted in favour of the Perindopril group vs. Placebo (8 versus 10). However Perindopril therapy was associated with a blood pressure that was 5/2 mm Hg lower than placebo (60). Hence from both of these trials it can be concluded that the benefits of ACEI may be due to lowering of blood pressure and not to intrinsic property of the ACEI.

The two trials comparing ACEIs and CCBs were the VALUE and CAMELOT Trials.

The **VALUE Trial (Valsartan Antihypertensive Long–term use evaluation)** evaluated Valsartan versus Amlodipine in 15,000 hypertensive patients with mean blood pressure 155/88 mm Hg. Initial findings noted fewer Myocardial Infarctions and strokes within the Amlodipine arm, however further analysis showed significant differences in blood pressure in favour of Amlodipine group. The structure of the trial was so designed to gradually introduce diuretics in the Valsartan arm over several months. Until this was achieved, a higher blood pressure in the Valsartan group produced higher event rates that subsequently disappeared as blood pressure control improved. A post hoc attempt to control for this difference with matched blood pressure pairings of Amlodipine and Valsartan groups showed no difference in cardiac events, MI, stroke or mortality (61).

This study once again suggested that the main determinant of cardiovascular event was blood pressure response.

The **CAMELOT Trial (**Comparison of Enalapril vs. Amlodipine to Limit Occurrences of Thrombosis) compared Amlodipine (10 mg per day) and Enalapril (20 mg per day) versus placebo in reducing cardiovascular endpoints in patients with known coronary disease (62). The main outcomes were non-fatal MI, cardiac arrest and other cardiovascular events, which occurred at a rate of 23 % in placebo, 16.6% in Amlodipine and 20.2 % in the Enalapril group. Blood pressure increased by 0.7/0.6 mm Hg in placebo group and decreased by 4.8/2.5 mm Hg and 4.9/2.4 mm Hg in the Amlodipine and Enalapril groups respectively. Though there were equivalent hard endpoint events (all-cause mortality, non fatal MI, stroke) in both Amlodipine and Enalaprilarms, the soft endpoint events such as angina pectoris were significantly reduced by Amlodipine, hence reducing the total in favour of Amlodipine. While Amlodipine is known to have anti-anginal effect it is not the case with Enalapril. Also there were differences in pharmacodynamics of the drugs as Enalapril once a day has a half life of 11 hours while that of Amlodipine is 50 hours. Hence, since Enalapril was taken in the mornings, the blood pressure readings during the day will have severely underestimated the rise in night time BP in the Enalapril arm compared to Amlodipine.

The role of CCBs in patients with high cardiovascular risk was further evaluated in the four trials outlined below. The INSIGHT Trial **(Intervention as a Goal in Hypertension Treatment)** of 6000 high risk patients defined as having Hypertension plus at least one additional cardiovascular risk factor, compared CCB (Nifedipine) to Hydrochlorothiazide plus Amiloride (63). In this study total cardiovascular outcome (cardiovascular death, myocardial infarction, congestive heart failure, stroke) were the same in both groups, however the Nifedipine arm showed higher risk of fatal myocardial infarction and non fatal heart failure.

The **INVEST Trial** (The International verapamil-Trandolapril Study Hypertensive patients with known coronary artery disease compared Verapamil (maximum dose 180 mg twice daily) and Atenolol (maximum dose 50 mg twice daily) in reducing cardiovascular mortality and morbidity. Trandanopril and/or Thiazides were added for additional blood pressure control as needed. There was no difference in primary outcomes of death, non fatal myocardial infarction or nonfatal stroke (64). Hence, while DHP-CCBs (Nifedipine) were shown to increase cardiovascular mortality, non DHP-CCBs (Verapamil) have not shown such adverse outcomes. It has been shown that the peak and trough concentrations and variability in blood pressure with short acting Nifedipineare likely responsible factors for the increased cardiovascular mortality. This was further evaluated by the **ACTION Trial** (A Coronary Disease Trial Investigating Outcomes with Nifedipine GITS) comparing long acting Nifedipine (60 mg once a day) to placebo in patients with chronic stable angina (65). Most patients were treated with other anti-anginal therapy including Beta-blockers, aspirin and lipid lowering drugs and had a mean BP of 137/80.The primary end point was survival free of major cardiovascular events. At a follow up of 4.9 years, the mean blood pressure was significantly lower in the long acting Nifedipine group however despite this, it did not reduce primary end points or all cause mortality. The lack of benefit despite lowering of blood pressure may be due to lower cardiovascular risk of the patient population studied.

The **ASCOT Trial (The Anglo-Scandinavian Cardiac Outcomes Trial)** was designed to compare the incidence of adverse cardiovascular outcomes with Amlodipine 5 mg versus

Atenolol 50 mg in patients with hypertension and at least three other risk factors for Coronary Heart Disease. The combined primary outcome was fatal coronary events and nonfatal MI. Surprisingly, the trial was stopped prematurely due to worse outcomes in the Atenolol treated group (66, 67). Possible reasons for the difference in outcomes include lower blood pressure in Amlodipine group as well as once daily usage of Atenolol despite pharmokinetics favouring twice daily use as in the INVEST trial. It was estimated that the difference in blood pressure accounts for at least half the variance in outcomes. Therefore in summary, the ASCOT trial which included patients with no active cardiovascular disease, there was a difference in outcomes between Amlodipine and Atenolol partially attributed to BP differences between the two groups. In INVEST trial no such **difference was observed though it was in a different population.**

In the NAVIGATOR Trial (Valsartan in Impaired Glucose Tolerance Outcomes Research) in patients with Impaired Glucose Tolerance, over 9300 patients who had or were at risk of cardiovascular disease were randomly assigned to Valsartan (up to 160 mg/day) or placebo (68). The mean baseline BP was 140/83 mm Hg in both arms. At a median of 6.5 years there was no difference in the rate of cardiovascular events, despite significant lower blood pressure with Valsartan (132/78 mm HG, 2.8/1.4 mm Hg lower than placebo).

In the **ACCORD BP Trial (Action to Control Cardiovascular Risk in Diabetes)** of Goal Systolic Pressure less than 120 mm Hg in Type 2 Diabetes, 4733 patients were randomly assigned to a goal systolic blood pressure of less than 120 or less than 140 mm Hg (69). The mean baseline BP was 139/76 mm Hg at year one and thereafter, the average systolic pressures were 119 and 134 mm Hg in the two groups. At a mean follow up of 4.7 years, there was no significant difference between the groups in the primary outcome of cardiovascular death or non-fatal MI or stroke (1.9 versus 2.1 percent). The annual rate of all cause mortality was non-significantly higher with intensive therapy (1.28 versus 1.19 percent). Serious adverse events occurred in a higher proportion (3.3 versus 1.3 percent) in the intensive therapy arm. However, a prespecified secondary outcome, the annual rate of stroke, was significantly lower with intensive therapy (0.32 versus 0.53 percent). The conclusion of the ACCORD Trial, for those who meet the entry criteria (type 2 Diabetes Mellitus plus either cardiovascular disease or at least two additional risk factors for cardiovascular disease), the authors and reviewers of this topic suggest that the risks and burdens of aiming for a systolic pressure of less than 120 mm Hg plus the lack of experience of almost all physicians in attaining such a goal may be too great a burden to achieve the small reduction in stroke that may be attained (absolute benefit 1 in 89 patients at five years).

The **ONTARGET Trial** randomly assigned over 25,000 patients with atherosclerotic disease to Ramipril, Temlisartan, or both (54). There was a progressive reduction in stroke risk at attained systolic pressures of 121 compared to 130 mmHg or higher; in contrast, there was an increase in myocardial infarction risk at attained systolic pressures below 126 mmHg and cardiovascular mortality was unchanged or increased at attained systolic pressures below 130 mmHg expand.

The **PROGRESS Trial (Preventing Strokes by Lowering Blood Pressure in patients with Cerebral Ischemia)** compared Perindopril with or without adding Indapamide (a thiazide diuretic) to placebo in patients with a prior stroke (70). There was a progressive trend toward lower rates of recurrent stroke at lower systolic pressures down to below 120 mmHg in Perindopril group as compared to placebo. However as this was a placebo controlled trial the benefits of a particular anti hypertensive group of drugs were not studied.

Trials	Population Studied	Intervention	Outcome	Comments
HOPE Trial (Heart Outcomes Prevention Evaluation)	Patients with high cardiovascular risk (without acute MI, LV dysfunction or heart failure)	Randomly assigned to Ramipril 5-10 mg/day or placebo	Terminated prematurely because of significant benefits in Ramipril arm only14% reaching primary end point (any cardiovascular event: CVA, MI, Cardiovascular death) vs17.8% in placebo A reduction in stroke was also seen with Ramipril	Although benefits were thought to be independent of BP control, an analysis of subset who underwent ABPM showed a significant drop in night time BP
EUROPA Trial (European Trial on Reduction of cardiac Events with Perindopril in Stable Coronary Artery Disease)	Similar to HOPE but patients with lower cardiovascular risk	Perindopril (8 mg once a day) vs placebo	Primary end point: MI, cardiac arrest or cardiovascular death- significant reduction in favour of Perindopril Perindopril associated with (5/2 mmHg) lower BP	Benefits of ACEI may be due to BP lowering and not to intrinsic property of the ACEI
VALUE Trial (Valsartan Antihypertensive Long –term use evaluation)	15,000 hypertensive patients	Valsartan vs Amlodipine	Initial findings fewer Myocardial Infarctions and strokes in Amlodipine arm, however there were significant differences in BP in favour of Amlodipine A post hoc attempt to control for this difference with matched BP pairings of Amlodipine and Valsartan groups showed no difference in cardiac events, MI, stroke or mortality	Suggests that main Determinant of cardiovascular event is BP response
CAMELOT Trial (Comparison of Enalapril vs. Amlodipine to Limit Occurrences of Thrombosis)	Patients with known coronary disease	Compared Amlodipine (10 mg per day) and Enalapril (20 mg per day) vs placebo in reducing cardiovascular endpoints	Equivalent hard endpoint events (all-cause mortality, non fatal MI, stroke) in both Amlodipine and Enalapril arms Soft endpoint events such as angina pectoris were significantly reduced by Amlodipine, hence reducing the total in favour of Amlodipine	Amlodipine has anti-anginal properties Differences exist in pharmacodynamics of the drugs (Enalapril half life shorter than Amlodipine 11 vs 50 hrs)
The INSIGHT Trial **(Intervention as a Goal in**	6000 high risk patients defined as having	CCB (Nifedipine) to Hydrochlorothiazide plus Amiloride	Cardiovascular outcome (cardiovascular death, myocardial infarction, congestive heart failure,	

Hypertension Treatment)	Hypertension plus at least one additional cardiovascular risk factor		stroke) were same However Nifedipine arm showed higher risk of fatal myocardial infarction & non fatal heart failure	
The INVEST Trial (The International verapamil-Trandolapril Study)	Hypertensive patients with known coronary artery disease	Compared Verapamil and Atenolol in reducing cardiovascular mortality & morbidity Trandanopril and/or Thiazides added for BP control as needed	No difference in primary outcomes of death, non fatal myocardial infarction or nonfatal stroke	In contrast to outcomes with Nifedipine suggesting that peak / trough concentrations and variability in BP with short acting Nifedipine might be responsible for increased cardiovascular mortality
ACTION Trial (A Coronary Disease Trial Investigating Outcomes with Nifedipine GITS)	Patients with chronic stable angina	long acting Nifedipine (60 mg once a day) vs placebo	Primary end point: survival free of major cardiovascular events Mean BP significantly lower in long acting Nifedipine group however despite this, it did not reduce primary end points or all cause mortality	May be due to lower cardiovascular risk of the patients
ASCOT Trial (The Anglo-Scandinavian Cardiac Outcomes Trial)	Patients with hypertension and at least three other risk factors for Coronary Heart Disease	Amlodipine 5 mg vs Atenolol 50 mg	Primary outcome: fatal coronary events and nonfatal MI Stopped prematurely due to worse outcomes in Atenolol group	Reasons for difference in outcomes include lower BP in Amlodipine group and once daily usage of Atenolol despite pharmokinetics favouring twice daily use
NAVIGATOR Trial (Valsartan in Impaired Glucose Tolerance Outcomes Research	Over 9300 patients with Impaired Glucose Tolerance at risk of cardiovascular disease	Randomly assigned to Valsartan or placebo	No difference in rate of cardiovascular events, despite significant lower BP with Valsartan	
ACCORD BP Trial (Action to Control Cardiovascular Risk in Diabetes)	4733 patients type 2 Diabetes Mellitus plus either cardiovascular	Randomly assigned to goal systolic BP < 120 vs <140 mm Hg	No significant difference in primary outcome of cardiovascular death or non-fatal MI or stroke	

	disease or at least two additional risk factors		All cause mortality was non-significantly higher with intensive therapy Higher rate of serious adverse events in intensive therapy arm but secondary outcome: annual stroke rate was significantly lower	
ONTARGET Trial	Over 25,000 patients with atherosclerotic disease	Randomly assigned to Ramipril, Temlisartan, or both	Reduction in stroke risk at systolic BP 121 vs 130 mmHg or higher An increase in myocardial infarction risk at systolic BP < 126 mmHg Cardiovascular mortality unchanged or increased at systolic BP < 130 mmHg	
PROGRESS Trial (Preventing Strokes by Lowering Blood Pressure in patients with Cerebral Ischemia)	Patients with a prior stroke	Perindopril with or without Indapamide (thiazide diuretic) vs placebo	Trend toward lower rates of recurrent stroke at lower systolic BP (down to < 120 mmHg) in Perindopril group	As this was placebo controlled trial, benefits of a particular anti hypertensive group of drugs were not studied

Table 3. Summary of Cardiovascular Trials

"Reconciling the evidence"

Some controversies still exist in hypertension trials. For example, though it is established unequivocally that hypertension is a risk factor for chronic kidney disease and cardiovascular disease, the superiority of individual drug classes over others, with regards to these outcomes remains unclear. Landmark trials, such as the ALLHAT (Antihypertensive and Lipid Lowering to Prevent Heart Attack Trial) (6) lie at the heart of this controversy. Their finding of no superiority for Angiotensin converting enzyme inhibitors (ACEI) with respect to ESRD outcome is in clear contradiction to the multitude of outcome trials in CKD patients where the role of ACEI has been established.

Further confusion in comparing outcomes from various trials arises because of variability in their design, patient demographics, underlying cardiovascular risk factors as well as the studied primary outcomes. This leads to tremendous variability in studies addressing the supremacy or lack of, for a specific drug class. For instance, the LIFE trial (Lorsartan Intervention for End Points) (71) demonstrated lower CV outcomes for patients with LVH treated with Losartan versus Atenolol despite equivalent blood pressure (BP) control. Conversely, in VALUE (Valsartan Antihypertensive Long Term Use Evaluation)(72) Valsartan did not show benefit in cardiovascular mortality as compared to Amlodipine for the same level of blood pressure control. However, there was significant difference in the blood pressure between the two groups favouring the Amlodipine arm. These studies show

how the conduct of different trials can lead to contrasting findings with respect to superiority of one drug over the other and the care needed to evaluate them.

Controversies further arise when trials designed to study cardiac outcomes are used to evaluate renal outcomes. One example is the ALLHAT trial (6), which showed that diuretics were superior to ACEI with regards to renal outcomes, even though it was primarily designed to study cardiac and not renal outcomes. This is in contrast to most studies with primary renal outcomes which showed that administration of ACEI or Angiotensin receptor blockers (ARBs) was associated with lower urine protein excretion, slower doubling of serum creatinine and lower rate of decline of GFR and hence progression to End Stage Renal Disease (ESRD). However these renal outcome trials were not designed or powered to evaluate cardiovascular events. Therefore it is important to carefully scrutinize trials to identify the primary outcome they were intended to and thus are powered to assess.

Possible explanations for the adverse outcomes seen with ACEI in ALLHAT include the following:

The diuretic arm had better control of blood pressure. During The first two years there was a significantly better BP control of at least 4 mm Hg in the diuretic arm.

The ACEI may be handicapped by the unfavourable use of Beta-blockers as add- on therapy in a significant number of black patients.

In the ALLHAT trial Beta-blockers were used as a second line agent in all four groups. Specifically, only 18 percent of the ACEI group received a diuretic and mainly in the last year or two. This led to a 4-5 mm Hg higher blood pressure in the ACEI arm likely accounting for greater CV outcomes.

The ALLHAT trial hence concluded that diuretics are similar if not superior to ACEI and CCBs with regards to cardiovascular protection and mortality. However the increased incidence of diabetes mellitus noted with diuretic use is not without significant clinical consequences. Notably, the effect of diabetes on CV event rates is not apparent until a minimum of 6 years and becomes progressively more pronounced. It eventually results in increased cardiovascular event rate at 15 years, which is similar to that seen in pre-existing diabetes. This was shown in **SHEP trial** (Systolic Hypertension in Elderly Program) where new onset diabetes was associated with a high risk of CV events, similar to its incidence in patients with diabetes at the beginning of the study (73). Hence, because of the short observation period of ALLHAT of only 12.5 years, diuretic-linked new onset diabetes, would be expected to result in increased CV events had the follow- up been extended.

Possible explanations for the contrasting findings between the ALLHAT and ANBP2 trials include:

1. Different patient demographics, with a predominant white population as compared to high proportion of black patients in ALLHAT trial who were in fact older. As stated previously white patients have shown better response to ACEI's than diuretics.
2. The patient population were different, ALLHAT included patients with one additional cardiovascular risk factor.
3. In ANBP2 trial the antihypertensive agent (Lisinopril or Hydrochlorothiazide) and dose were chosen by the physician. The possible high dose use of Hydrochlorothiazide with its associated adverse cardiovascular side effects may have contributed to adverse outcomes.
4. Primary outcomes for ALLHAT and ANBP2 were different. While in ALLHAT the primary outcome was death from coronary causes or nonfatal myocardial infarction, in ANBP2 it was all fatal and nonfatal cardiovascular events. Once again this highlights how differences between ALLHAT and ANBP2 trials in design, demographics and outcomes can influence the results of the study.

Though, the **ALLHAT Trial** (24) of more than 44,000 hypertensive patients failed to show superiority of ACEI, DHP-CCBs and alpha blockers over a thiazide diuretic with respect to cardiovascular outcomes. In post hoc analysis, neither ACEI nor CCB was superior to thiazide diuretic with respect to renal outcomes. This trial was contradictory to other primary renal outcome trials that showed benefit of ACEI over other drug classes. Some of the factors responsible for this controversy will be explored. The ALLHAT did not select patients with renal disease as an inclusion criterion, since it was not mainly a renal outcome trial. Blood pressure was also lower in thiazide arm as compared to the other arms hence equivalency of blood pressure was not achieved. Furthermore, no urine tests were performed even though renal outcomes were studied thus failing to identify those who were at highest risk for progression and most likely to derive benefit from ACEI i.e. patients with proteinuric diabetic kidney disease. Hence, in the ALLHAT trial little or no attention was paid to kidney function, consequently the results of ALLHAT regarding renal outcomes remain unresolved.

In addition, the Casas meta-analysis was heavily weighted on the ALLHAT (non renal outcome trial) and little or no attention was paid to IDNT, RENAAL, AASK and REIN trials, the latter studies upon which our current guidelines are based. Hence, this analysis correctly concludes that these agents benefit non-diabetic renal disease and, mistakenly deduces that ACEI/A2RBs are non beneficial in diabetic proteinuric kidney disease. This partially flawed trial may result in physicians using less effective antihypertensive drugs in patients with kidney disease. Any attempt to reconcile the renal outcomes in ALLHAT, a cardiovascular outcomes trial, with those from IDNT, RENAAL, REIN, AASK and other renal trials fails because of different patient populations, designs and outcomes. Though less expensive antihypertensive drugs are desirable for BP control, they are less effective for renoprotection in chronic kidney disease and should therefore be used as adjuncts. Moreover, the average GFR of the studies selected was equivalent to Stage 2 CKD, and was much higher than in those studies that showed benefit of ACEI and ARBs.

Clinical pearls

It can be concluded that ACEIs are the medication of choice in reducing microalbuminuria in diabetic hypertensive patients. Studies clearly show that blocking of the Renin Angiotensin Aldosterone System (RAAS) with ACEI or ARBs in patient with type II diabetes mellitus reduces the risk of progression of microalbuminuria to overt proteinuria and may even revert it back to normoalbuminuria, both in hypertensive and normotensive patients. It is also likely that Aliskerin may have additional renoprotective effects, independent of blood pressure lowering, in hypertensive patients with type2 diabetes and nephropathy who are already receiving the recommended therapy.

Recommendations on choice of antihypertensive agents

The choice of antihypertensive agents in diabetic patients is based upon their ability to prevent adverse cardiovascular events and to slow progression of renal disease, if present.

The two major studies which would influence the choice of therapy are the ALLHAT and ACCOMPLISH trials. To summarize again, in the ALLHAT trial, the benefits from diuretics compared to other classes, may have been related to the lower attained blood pressures. Another factor which was not addressed was the detrimental effects of thiazides on glucose metabolism. In the ACCOMPLISH trial, on the other hand, the combination of an ACE inhibitor and CCB provided better cardiovascular protection as compared to ACE inhibitor with thiazide.

While long acting ACEI or ARB would be the drug of choice in diabetic patients with hypertension and microalbuminuria, we would also recommend adding a long acting

dihydropyridine calcium channel blocker as combination therapy for uncontrolled hypertension, given the results of ACCOMPLISH trial. If a Beta-blocker is given, Carvedilol may be the drug of choice because of potential benefits on glycemic control and lower rate of development of microalbuminuria compared to Metoprolol. A loop diuretic is likely to be necessary in patients with renal disease or heart failure.

Recommendations on target/goal blood pressure

Based on the trials described above including ACCORD BP trial, we recommend, a goal blood pressure of less than 140/90 mmHg in patients with diabetes. A goal blood pressure of less than 130/80 mmHg is recommended for patients with diabetic nephropathy and proteinuria (defined as 500 mg/day or more). These recommendations differ from the pre-ACCORD era when a goal of less than 130/80 mmHg was recommended for all diabetic patients.

Goal BP recommendations

While the guidelines suggested by European Society of Hypertension/European Society of Cardiology and American Heart Association recommend a blood pressure less than 130/80 for patients with atherosclerotic cardiovascular disease, the recent ACCORD trial along with ONTARGET and PROGRESS raise some concerns with this target.

We recommend antihypertensive therapy to lower the blood pressure to less than 140/90 mmHg in all patients. An attempt to lower the systolic pressure below 130 to 135 mmHg should be undertaken, if it can be achieved without producing significant side effects, though this has not been well defined. The risks of aiming for a goal systolic pressure of less than 120 mmHg may be too great a burden to achieve the small reduction in stroke that may be attained (absolute benefit 1 in 89 patients at five years). However, such a goal may be considered in highly motivated patients who would accept more aggressive antihypertensive therapy to further reduce their risk of stroke.

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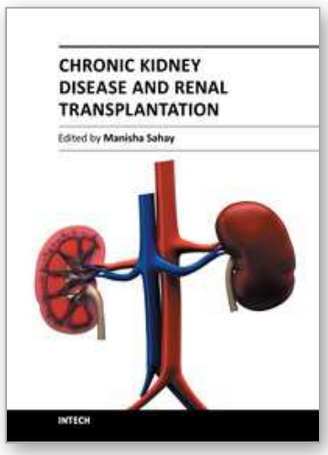

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