Indo American Journal of Pharmacy
An International Peer Review Journal

Original Article

A Randomised Clinical Active Control Study to Assess the Safety and Efficacy of Nifedipine Besilate Comparated with Telmestran in Patients Suffering with Essential Hypertension

M.Swapna [1], A Thanga Thirupathi [1,*], KNV Rao [1], K Rajeshwar Dutt [1], Karunasri Alli [1], Srujana Perumalla [2]

[1] Nalanda college of pharmacy, Nalgonda, Telangana, India
[2] Syncorp Clincare Technologies, Hyderabad, India

Article Info - Received: 26-12-2016 Accepted: 18-01-2017

High blood pressure usually does not cause symptoms. Long term high blood pressure, however, is a important risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease. The intention of this study is to study the safety and efficacy of the Nifedipine besylate in essential hypertension. To measure the antihypertensive result and to tolerate of Nifedipine besylate with Telmesartan in essential hypertension.Principal objective of this study is to assess the well being of long-term administration of Nifedipinebesylate in patients with necessary hypertension. To assess the effects of the investigational drug X and the reference drug on standing blood pressure, sitting pulse and standing pulse[2]. The principal objective was to show that telmisartan/ amlodipine union therapy is superior to atenolol/amlodipine union therapy with respect to mean decrease in SBP and DBP at the end of therapy from baseline the primary comparison with a power of 80% at 5% level of significance. The treatment groups were equated for homogeneity at baseline using tests like Student's t test, Mann–Whitney U test for ongoing variables and chi-square test or Fisher's exact test for categorical variables[3]. The results of our study confirmed that the combination therapy with Nifedipine besylate is superior to Telmesartan therapy in patients with mild-to-average essential hypertension. The ability and well being was studied on the finished population. In conclusion, the study has shown that once daily medication with Nifedipine besylate offers superior antihypertensive efficacy over Telmesartan therapy in patients with mild-to-moderate essential hypertension.

Key Words: *Hypertenson,* Nifedipine besylate, Telmesartan.

Correspondence Address:
A Thanga Thirupathi, Nalanda College of Pharmacy, India

1. INTRODUCTION

The Hypertension is called the ***"silent killer"*** since it is often asymptomatic. It is also known as high blood pressure. The pressure of blood against the wall of arteries is known as blood pressure. High BP can lead to many heart diseases and it also increases the risk of coronary failure and strokes[4].**Systolic pressure**: It is peak pressure in the arteries, which occurs near the margin of the cardiac cycle when the ventricles are contracting[5].**Diastolic pressure**: Diastolic pressure is least pressure in the arteries, which happens near the starting of the cardiac cycle when the ventricles are filled with blood[6].

Juvenile diabetic patients should be deemed hypertensive if there is a constant increase of BP more than the 95th percentile for age.

DRUG PROFILE:

Nifedipine has been constructed as both a long- and short-acting 1,4-dihydropyridine calcium channel blocker. It acts principally on internal smooth muscle

cells by balancing voltage-gated L-type calcium channels in their inactive validation by obstructing the rush of calcium in smooth muscle cells, nifedipine stops calcium-dependent myocyte shrinkage and decrease in diameter of blood vessels. A second proposed mechanism for the drug's vasodilatory effects includes pH-dependent obstruction of calcium influx via obstruction of smooth muscle carbonic anhydrase. Nifedipine is used to treat hypertension and chronic stable angina. Designated for the management of vasospastic angina, chronic stable angina, hypertension, and Raynaud's event. May be used as a first line agent for left ventricular hypertrophy and isolated systolic hypertension[7].

Nifedipine decreases arterial smooth muscle contractility and subsequent vasoconstriction by obstructing the influx of calcium ions through L-type calcium channels. Calcium ions penetrating the cell through these channels bind to calmodulin. Calcium-bound calmodulin then binds to and initiates myosin light chain kinase (MLCK). initiated MLCK catalyzes the phosphorylation of the regulatory light chain subunit of myosin, a key step in muscle contraction. Quickly and entirely absorbed following oral administration. Protien binding is 92-98%. Hepatic metabolism via cytochrome P450 system. Predominantly metabolized by CYP3A4, but also by CYP1A2 and CYP2A6 isozymes. Nifedipine is significantly metabolized to highly water-soluble, inactive metabolites considering for 60 to 80% of the dose excreted in the urine. The remainder is eliminated in the feces in metabolized form, most likely as a result of biliary excretion. Half life 2 hours[8]

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan attach to the angiotensin II type 1 (AT1) receptors with high similarity, attaining obstruction of the activity of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Latest studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could probably confer helpful metabolic effects. Designated forUsed single or in conjection with other classes of antihypertensives for the therapy of hypertension. Also used in the therapy of diabetic nephropathy in hypertensive patients with type 2 diabetes mellitus, as well as the therapy of congestive heart failure (only in patients who cannot tolerate ACE inhibitors)[9].

Telmisartan interferes with the combination of angiotensin II to the angiotensin II AT_1-receptor by combiningexchange rate and especially to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also initiates the synthesis and delivers aldosterone, stoppage of its effects results in lowering in systemic vascular resistance[10].

Absolute bioavailability depends on dosage. Food slightly lowering the bioavailability (a decrease of about 6% is seen when the 40-mg dose is administered with food). Highly bound to plasma proteins (>99.5%), mainly albumin and a1-acid glycoprotein. Binding is not dose-dependent.

2. MATERIALS AND METHODS:

This randomized, relative, multiple centre, 12 week, outpatient study assessed antihypertensive effectiveness ofamlodipine besylate combination in compared with olmesartan single drug.Patients were divided into two groups.Fixed Dose Combination of Nifedipine besylate(2.5mg). Fixed Dose Combination of Telmesartan(20 mg). The study drugs were given orally one time daily in morning.

Patients (either untreated or pre-treated with anti hypertensive agents) of both sex, aged 18 years and more than 18, diagnosed of essential hypertension as per JNC 7 criteria. Were involved in the study.

Patients with DBP >109 mmHg were not involved in the study. Patients with secondary hypertension, known history of hypersensitivity to study medication, patients with severe hypertension, notable medical illness , patients with electrolyte imbalance, abnormal hepatic, and renal functions were not included in the trial. Pregnant and lactating women or females of childbearing potential not practicing contraception were not included in the study.

The study was accepted by independent ethics committee of each centre. All patients were given an

oral explanation about the type of the study and regarding study drugs by the investigator at each centre. An information sheet was given in a language understood by the patient, and written informed consent was acquired from each participant before any study related procedure. The performance and observation of the study was done in follwing with the demandss of good clinical practice.

Efficiency of the treatment in treated population was assessed by BP measurement a teach study visit throughout study period. Blood pressure was studied by auscultator method. Quantifications were conducted after 10 minutes rest in identical separated by 2 minutes and then average was taken. If the first 2 readings of DBP differed by more than 5 mmHg, additional results was observed and average o f 2 closest reading was taken. The study investigator at each site conducted all the BP measurements throughout the study period**.** The similar method was followed at all study sites for B P measurement. Patients were designated as responder if their BP was controlled (SBP, 140 mmHg and DBP < 90 mmHg).

All enrolled patients were evaluable to tolerate assessment. Well-being evaluation was based on adverse events (AEs) reported at the time of the study. AEs were categorized by the investigator depending on their stength as mild, moderate, or severe and the relationship to the study drug as none, probably not, possible, probable or definite. At every visit during the entire study period, the reported AEs, clinical state of patients and details of related medications, if any were recorded. Blood samples were acquired at baseline and at the end of 3 months treatment or at last follow-up visit for early termination/withdrawal cases to perform hematology and biochemistry tests including complete blood count urine routine, electrocardiogram, serum electrolytes (Na+2,Cl+,K), fasting blood glucose.

Expressive statistics, involving mean, SD , frequency counts and percentage for categorical variables were used to check the difference of the treatment groups at baseline with respect to demographic characteristics. The treatment groups were compared for homogeneity at baseline using tests like Student's t test, Mann–Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables. The 2 treatment groups were similar with respect to demographic characteristics. None escalated patients included patients who received the baseline therapy up to 1 month and remained controlled on the same therapy to the end of study. While escalated patients include patients continued on the baseline therapy up to 1 month but escalate d to respective step-up therapies due to poor or no response to the baseline therapies. Both the treatment groups were compared after 1 month and the end of the study using Student's t test, Mann – Whitney U test as appropriate. All statistical tests we resided and the level of significance were set at 0.05. Statistic al analysis was performed using statistical software Graph Pad Prism Z6.01.

3. RESULTS

Patient distribution:

- A total of 190 eligible patients (TEST GROUP: 94 subjects; COMPARATOR: 96 subjects) satisfying inclusion/exclusion criteria were enrolled on the study.
- Nine patients from test group and six patients from reference group were lost to follow-up
- 1 patient from test group was withdrawn due to adverse event.
- A total of 174 patients completed the study (test group: 84; reference group: 90). The 2 treatment groups were similar with respect to demography and baseline disease characteristics (Table 1).

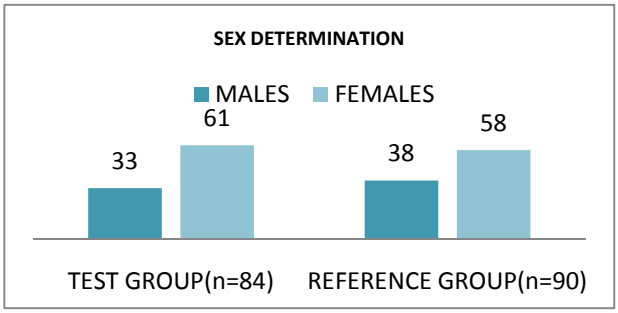

Fig 1: baseline demographic characteristic variables gender

Table 1: Baseline characteristics of patients

Parameters	Nifedipine besylate (test group) (n=84)	Telmesartan(n=90)	*P* value
Males (%)	33 (35.11)	38 (39.58)	0.524
Females (%)	61 (64.89)	58 (60.42)	-
Mean age (years) (range)	53.3 ±12.0 (25-80)	55.2±11.9(28-80)	0.274
Mean weight (kg) ±SD	61.1 ±10.8	59.8±10.7	0.395
Mean height (cm) ±SD	158.1 ±10.3	156.9±10.2	0.422
Heart rate (breaths/min) ±SD	79.62 ±7.54	79.46±6.86	0.880
Respiration rate (breaths/min) (mean± SD)	15.50± 2.96	15.49±2.53	0.979
Stage I essential hypertension	53	62	0.248
Stage II essential hypertension	41	34	-
Systolic blood pressure (mmHg) (mean±SD)	156.17 ±9,82	153.1±11.6	0.051
Diastolic blood pressure (mmHg) (mean±SD)	95.06± 5.79	94.07±5.54	0.230

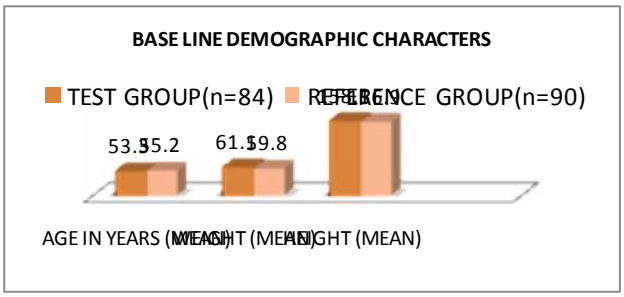

Fig 2: Base Line Demographic Variables Age,Height,Weight.

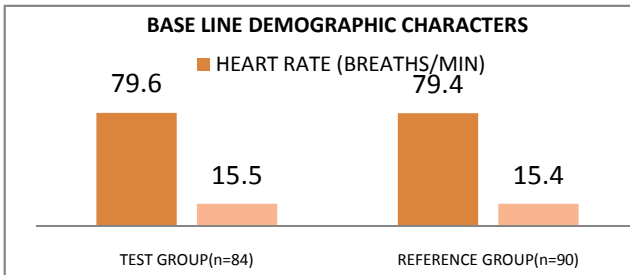

Fig 3: Base Line Demographic Characteristic Variables Heart Rate, Respiartory Rate.

Efficacy after 4 weeks of therapy:

At the end of 4 weeks of therapy, 62 patients from test group and 50 patients from reference group responded to the therapy (SBP < 140 mmHg and DBP < 90 mmHg) (P = 0.012) (Table 2). Mean fall in SBP (-30 .0 ± 10.4 vs. -25.08 ± 9.05; P = 0.008) and DBP (-18 .10 ± 7.45 vs. -14.78 ± 7.48; P = 0.021) was notably higherin test drug therapy as equated with reference drug combination therapy at the end of 4 weeks. Mean SBP and mean DBP was significantly lower in test drug group as equated with reference group at the end of 4 weeks of therapy (P < 0.05) (Table 2). Responders from both the treatment groups rest controlled till the end of therapy (day 90). Figure 1 show s fall in mean SBP and DBP for responders on starting therapies.

Table 2: change in mean at base line and after 4 weeks.

Efficacy parameters	TEST GROUP (n=62)	REFERENCE GROUP (n=50)	*P* value
Mean SBP (mmHg)(at baseline) (mean ±SD)	154.77±9.29	152.68±8.37	0.213
Mean SBP(mmHg)P (at 4 weeks) (mean ±SD)	124.74±6.76	127.60±7.97	0.046
Mean DBP (mmHg) (at baseline) (mean ±SD)	95.35±5.90	94.64±5.02	0.49
Mean DBP (mmHg) (at 4 weeks) (mean ±SD)	77.26±5.59	79.86±5.66	0.017
Mean DBP (mmHg) (at 4 weeks) (mean ±SD)	-30.0±10.4	-25.08±9.05	0.008
Mean fall in DBP (mmHg) (mean ±SD)	-18.10±7.45	-14.78±7.48	0.021

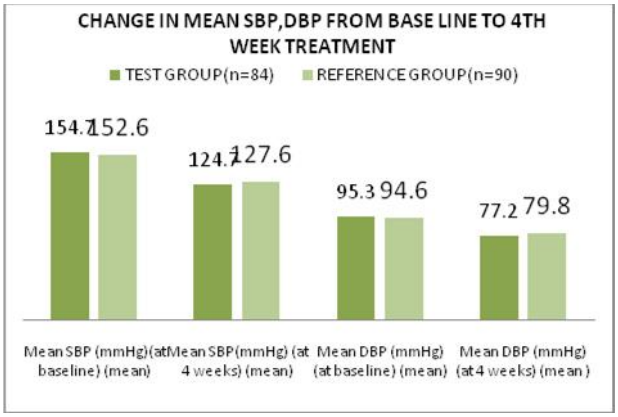

Fig 4: change in SBP and DBP at baseline and after 4 weeks.

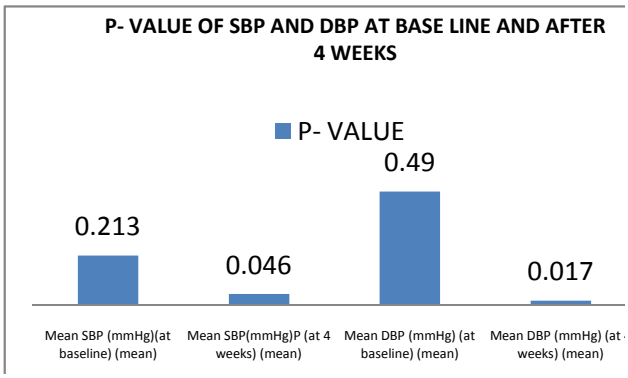

Fig 5: P Value Of Change In SBP and DBP At Baseline And After 4 Weeks

Efficacy after 12 weeks of therapy

- Sixty-two who not responded (Ne/Am combination therapy:22; At/Am combination therapy:40) were acelerated to respective step-up therapies to accept Nebivolol 5 mg/ Nifedipine 2.5mg for further 8 weeks. At the end of therapy, total 22 patients (test drug therapy: 12; Telmesartantherapy group: 10) shown response to the step-u p therapies (SBP < 140 mmHg and DBP < 90 mmHg). Step-up therapy of test group showed significantly better response rate as compared with step-up therapy of Telmesartan(P = 0.035) (Table 3).
- Both the step-up therapies were related with respect to mean fall in SBP and mean fall in DBP (P > 0.05) at the end of therapy. However, at the end of 12 weeks, mean SBP (127.82 ± 8.90 vs. 138.0 ± 14.4; P = 0.001) and mean DBP (81.73 ± 8.78 vs. 87.35 ± 5.50; P = 0.011) were significantly lower in test group as compared with those in reference group therapy (Table 3). Nonresponders at the end of treatment period (10: test group and 30: Telmesartan therapy group) were then treated approximately at the option of the investigator.
- At the end of therapy, notably more number of combination treated patients attained normalization of BP (SBP < 120 mm Hg and DB P < 80 mmHg) as compared with olmesartan therapy (33 vs. 19) (P = 0.009). In both the treatment groups, the fall in BP was maximum at the end of 4 weeks of therapy, and subsequently the fall was sustained till the end of therapy, that is, day 90 (Figure 2).

Table 3: Change In SBP And DBP After 12 Weeks Of Treatment

Efficacy parameters	TEST GROUP (n=84)	REFERENCE GROUP (n=90)	*P* value
Mean SBP (mmHg) (at 12 weeks)	**127.82 ±8.90**	**138.0 ±14.4**	**0.001**
Mean DBP (mmHg) (at 12 weeks)	**81.73 ±8.78**	**87.35 ±5.50**	**0.011**

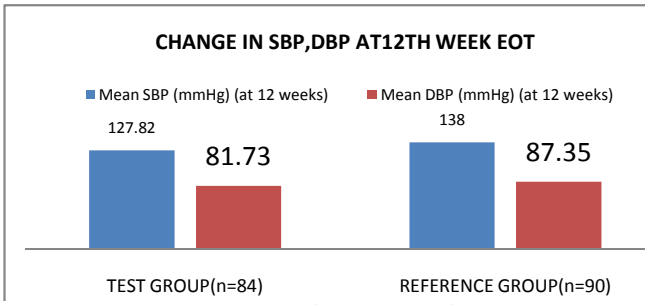

Fig 6: Change in SBP and DBP after 12 weeks of treatment

Table 4: laboratory parameters.

Laboratory parameters	Visit	TEST GROUP(n=84)	REFERENCE GROUP (n=90)	*P* value
Sodium (mEq/L)	Baseline	137.46 ±5.03	137.17 ±4.63	
	End	137.46 ±5.40	137.66 ±5.40	
	P value	1	0.441	0.619
Potassium (mEq/L)	Baseline	3.99± 0.68	4.03± 0.72	
	End	4.14 ±0.56	4.26 ±0.54	
	P value	0.129	0.025	0.6
Random blood glucose (mg/dL)	Baseline	113.93 ±47.54	102.24 ±23.59	
	End	103.66 ±48.99	105.03 ±29.51	
	P value	0.328	0.48	0.245

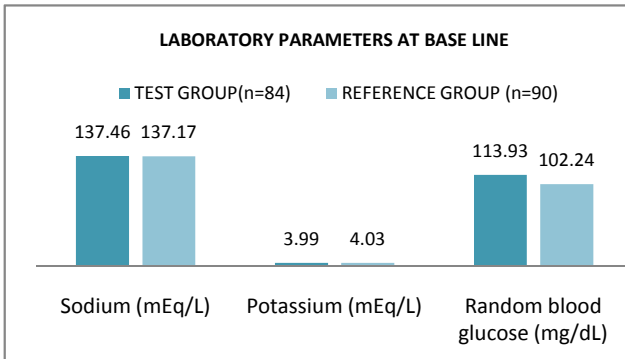

Fig 7: Laboratory Parameters

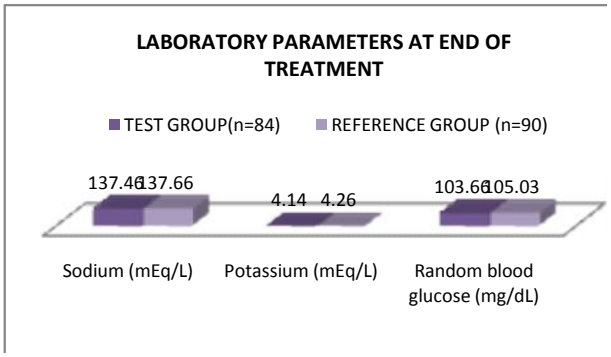

Fig 8: Laboratory Parameters at end of Treatment

Tolerability assessment:

- A total of 4 patients reported adverse events. Edema, gastritis, and abdominal pain were reported in patients treated;
- All reported adverse events were of mild-to - moderate in severity. None of the patients reported serious adverse event.
- The laboratory evaluations were done at baseline and at the end of therapy.
- Mean change s from baseline for various laboratory parameters were evaluated at the end of 3 months for all patients.
- There was non-significant reduction in heart rate at the end of therapy with either treatment.
- No significant changes from baseline were observed in haematology or biochemistry parameters
- Changes in blood glucose levels and lipid profile (high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol) were clinically unremarkable across the therapy groups.

Safety Assessment-

Side effects found with olmesartan

- Tiredness -- in up to 26 percent of people
- Low blood pressure (hypotension) -- up to 25 percent
- Slow heart rate (bradycardia) -- up to 18 percent
- Dizziness -- up to 13 percent
- Cold hands or feet -- up to 12 percent
- Depression -- up to 12 percent Shortness of breath -- up to 6 percent
- Fatigue -- up to 6 percent.

Side effects found with Investigational Product

- Headache -- in up to 9 percent of people
- Fatigue -- up to 5 percent
- Dizziness -- up to 4 percent
- Diarrhea -- up to 3 percent
- Nausea -- up to 3 percent
- Insomnia -- up to 1 percent.

4. DISCUSSION

- The primary goal of treating hypertension is to reduce their blood pressure to target level, which eventually leads to a reduction in the long-term total risk of cardiovascular morbidity and mortality.
- In this regard, although some considerations are necessary before generalizing the results, the present study clearly demonstrated that test drug therapy is an effective method to achieve the target blood pressure without major safety issues.
- This randomized, comparative, multicentre, 12 week, outpatient study evaluated antihypertensive efficacy of Nifedipine besylate combination in comparison with Telmesartan alone.
- The results of this study showed that, Nifedipine besylate combination therapy with is superior to Telmesartan therapy with respect to mean fall in SBP, DBP, response rate, and normalization of BP.
- After 4 weeks of therapy with atenolol 25 mg , our study reported a fall of -20.6/ -10.34 in SBP/DBP which is com parable to that reported in

literature (-17.6/ -12.5). In our study, for responders after4 weeks of therapy, low-dose of INVESTIGATIONAL PRODUCT was found to be superior to low-dose reference drug therapy with respect to mean fall in SBP (P = 0.008), mean fall in DBP (P = 0.021) and response rate (P = 0.012).

- One reason for combining a calcium antagonist with a angiotensin receptor blockerin the treatment of mild to-moderate hypertension is that the latter should improve the patient tolerability of the former by preventing any initial reflex tachycardia which may, in it, because of some adverse effects.
- The results of our study confirmed that the combination therapy with Nifedipine besylate is superior to Telmesartan therapy in patients with mild-to-moderate essential hypertension.

5. CONCLUSION

The study was conducted in PRIME HOSPITALS, HYDERABAD for a period of 12 weeks. The efficacy and safety was studied on the finished population. In conclusion, our study has shown that comparition of Nifedipine and Telmesartan, Telmesertan shows superior efficacy when compared with Nifedipine alone, whereas once daily treatment with Nifedipine besylate combination offers superior antihypertensive efficacy over Telmesartan therapy in patients with mild-to-moderate essential hypertension.

6. REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217–223.
2. Centers for Disease Control and Prevention (CDC) Vital signs: prevalence, treatment, and control of hypertension – United States, 1999–2002 and 2005–2008. MMWR Morb Mortal Wkly Rep. 2011;60(4):103–108.
3. Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee Heart disease and stroke statistics – 2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2–e220.
4. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996;275(20):1557–1562.
5. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326(6):381–386.
6. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. 1996;334(1):13–18.
7. Morgan TO, Anderson AI, MacInnis RJ. ACE inhibitors, beta-blockers, calcium blockers, and diuretics for the control of systolic hypertension. Am J Hypertens. 2001;14(3):241–247.
8. Mancia G, Laurent S, Agabiti-Rosei E, et al. European Society of Hypertension Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27(11):2121–2158.
9. Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ. 2003;326(7404):1427.
10. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combinatory therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med. 2009;122(3):290–300.

Conflict of Interest: None
Source of Funding: Nil