Original Article

A comparative, prospective, randomized, open label study between enalapril and perindopril in patients of mild to moderate hypertension

Santosh C Gursale[1*], Mohankrishna Ghanta[2], Sudheer Kumar[3], Narayan P Burte[4], Vandana M Thorat[5]

[1]Professor and HOD, Department of Pharmacology, B.K.L.Walawalkar, Rural Medical College, Sawarde, Dist- Ratnagiri, Maharashtra, INDIA.
[2]PHD Research scholar Sree Ramchandra University, Chennai, Tamil Nadu, INDIA.
[3]Drug Safety Assistant, Ventiv Health Clinical Hyderabad, Andhra Pradesh, INDIA.
[4]Professor and HOD, Department of Pharmacology, M.N.R. Medical College, Sangareddy, Andhra Pradesh, INDIA.
[5]Professor, Department of Pharmacology, K.I.M.S. Karad, Maharashtra, INDIA.
Email: drsantoshgursale@gmail.com

Abstract

Introduction: Hypertension is one of the major contributors to premature death globally. In India, hypertension is responsible for 57% of stroke related mortality and 24% related to coronary heart disease. A small decrease in blood pressure levels can prevent stroke and coronary heart disease related deaths. ACE inhibitors are commonly prescribed antihypertensives. So this study was promptedto have maximum data on their efficacy and adverse reactions. **Aims and Objective**: To observe and compare the anti-hypertensive efficacy as well as incidence of adverse drug reactions between enalapril and perindopril. **Materials and Methods**: This prospective, comparative, randomized, open-label study included 80 patients suffering from stage I / II essential hypertension. **Observation and Result:** We observed that enalapril, perindopril are effective agents in reducing both systolic and diastolic BP throughout the study period when measured at the 15thday, 30thday, 45thday and 90th day. We found that these two drugs were equally effective in reducing the systolic and diastolic blood pressure. A total of 25% of the patients reported some sort of adverse-effects like cough (10%), nausea(7.5%), musculoskeletal pain(2.5%), headache (5%) and dizziness (0%) in theenalapril treated group A and 20% in the perindopril treated group B, with noted adverse-effects like cough(10%), headache (5%), dizziness (2.5%), nausea (2.5%) and musculoskeletal pain(0%). **Conclusion:** The antihypertensive effect of these two drugs included in the study was statistically significant. These two drugs were equally effective in reducing the systolic and diastolic blood pressure. The incidence of nausea and musculoskeletal pain was more in enalapril treated group than perindopril group and incidence of dizziness was more in perindopril group than enalapril group. However, these differences in the frequency of adverse-effects between the two groups were not statistically significant ($P > 0.05$). Adverse effects were tolerated by both the study groups and hence effective antihypertensive drugs in management of essential hypertension.
Keywords: ACE inhibitors, enalapril, hypertension, perindopril.

[*]**Address for Correspondence:**
Dr. Santosh C. Gursale, Professor and HOD, Department of Pharmacology, B.K.L.Walawalkar, Rural Medical College, Sawarde, Dist-Ratnagiri, Maharashtra, INDIA.
Email: drsantoshgursale@gmail.com
Received Date: 14/11/2015 Revised Date: 18/12/2015 Accepted Date: 18/01/2016

Access this article online

Quick Response Code:

Website: www.statperson.com

DOI: 20 June 2016

INTRODUCTION

High blood pressure is a major public health problem in India and elsewhere[1-4]. It is a major cardiovascular risk factor[5-7] and contributes significantly to cardiovascular mortality[8,9]. Hypertension is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value. However, increasing evidence indicates that the cardiovascular risk associated with elevation of blood pressure above approximately 115 / 75 mm Hg increases in a log-linear fashion.[10-14] Hypertension is one of the major contributors

How to site this article: Santosh C Gursale, Mohankrishna Ghanta, Sudheer Kumar, Narayan P Burte, Vandana M Thorat. A comparative, prospective, randomized, open label study between enalapril and perindopril in patients of mild to moderate hypertension. *International Journal of Recent Trends in Science and Technology* June 2016; 19(2): 282-288. http://www.statperson.com (accessed 23 June 2016).

to premature death globally. In India, hypertension is responsible for 57% of stroke related mortality and 24% related to coronary heart disease. A small decrease in blood pressure levels can prevent stroke and coronary heart disease related deaths. Hypertension is a "life time" condition and, if left untreated, leads to lethal complications. The renin-angiotensin system plays an important role in the regulation of normal blood pressure (BP) and also in the pathogenesis and maintenance of essential hypertension. Angiotensin II acts on AT1 Receptors and causes vasoconstriction, 40 times more than Noradrenaline and also secretes Aldosterone leading to Na+ and H2O retention which ultimately causes rise in blood pressure.[15] Angiotensin converting enzyme inhibitors (ACEIs) have a well-established role in the management of essential hypertension. They are structurally classified as sulfhydryl containing ACEIs, for example, captopril, fentiapril, zofenopril, and so on; di-carboxyl containing ACEIs namely enalapril, lisinopril, perindopril, quinapril, moexipril, and so on; and phosphonate containing ACEIs namely fosinopril, on the basis of their binding with the angiotensin converting enzyme (ACE).[16] The most obvious potential benefit of ACE inhibitors is their effect on the renin–angiotensin–aldosterone system by reducing the levels of Ang. II. Clinical studies have demonstrated that ACE inhibitors significantly reduce the incidence of patients with myocardial infarction, ischemic events in patients with coronary artery disease.[17] Clinical studies have demonstrated that ACE inhibitors significantly reduce the morbidity and mortality of patients with myocardial infarction or heart failure.[18]. This study was prompted by the fact that a large number of people suffer from essential hypertension and ACEIs certainly are among the most widely prescribed agents in its treatment. It is therefore imperative that we should have maximum data on their pattern of utilization and the adverse drug reactions. The purpose of the present study was to observe the anti-hypertensive efficacy, incidence and severity of adverse drug reactions between the di-carboxyl group containing ACE inhibitors namely enalapril and perindopril.

MATERIALS AND METHODS

Eighty patients suffering from stage I / II essential hypertension, according to JNC-VII guidelines,[19] without any underlying comorbid conditions or complications, aged between 20 and 60 years, were enrolled in the study after obtaining informed consent and due approval of the ethics committee.

Study Design

It was a prospective, parallel, open-label, comparative trial, and the patients were randomized into two groups of 40 each.

- **GROUP A:** Includes subjects receiving enalapril
- **GROUP B:** Includes subjects receiving perindopril

Each group received enalapril (5mg), perindopril (4mg) respectively once daily. The investigational drugs were prescribed by the Cardiologist to the study subjects and purchased from the hospital pharmacy. The individual dose was subsequently titrated in case of inadequate blood pressure control, which was predefined for blood pressure levels of < 140 / 90 mmHg. Standardized technique was used to measure blood pressure. Mercury sphygmomanometer was used for measuring blood pressure. Every subject was followed up for four months, which included eight follow-ups at an interval of 15 days. During every follow-up, the blood pressure in the left arm (sitting position) was recorded after allowing 10 minutes of rest, the compliance with therapy and use of concomitant medicines was documented;

Inclusion Criteria

Patients with Moderate Hypertension without complications Patients with age group between 20-50years. Equal male and females

Exclusion Criteria

Patients with Cardiovascular abnormalities like Myocardial Infarction, Angina Pectoris Patients with Bronchial Asthma Patients with Renal Failure Patients with Cerebrovascular accidents Any additional anti-hypertensive medication precluded the subject from continuing in the study. Hematological and biochemical examinations were performed at baseline and end of the study. Haematological and biochemical examinations included Complete blood picture Serum creatinine Serum electrolytes Plasma lipid profile

- Blood sugars Other investigations included
- Chest X-ray
- Electrocardiogram

Complete history of the patients was documented, regarding their lifestyle, diet, family etc. Height and weight of the patients were documented to calculate the body mass index and grade and relate the physical status of them. Adverse Events (AEs) if any were documented during the follow-up visit and their causality was assessed using the Naranjo ADR probability scale [20]. Cough was further evaluated on the basis of its interference in routine activities and sleep disturbances in the subject. To propose a hypothesis, after comparing the incidence of ADRs between the two drugs, namely enalapril and perindopril, we employed the statistical hypothesis test of Student's t-test and Anova, to calculate the P-value in terms of significance. Graphpad Instat®ver. 3.10, 32 bit

for Windows was used for statistical analysis. Student's t-test was used to compare the blood pressures between 0 day, 15th, 30th, 45th and 90th day of group A and group B. This comparison was done for each group and for each parameter (SBP, DBP) separately. Anova was used to compare the antihypertensive efficacy between the two groups.

RESULTS

The prospective, comparative, open-label randomized study included 80 patients suffering from stage I / II essential hypertension. It was evident that the number of males in each study group was more than the females. Their mean (± S.D.) age was 48.816(±7.17955) years; baseline blood pressure (systolic / diastolic) mm Hg164.5(±8.149)/106.25(±4.9)mm Hg for enalapril group, 169.5(±1.3373)/104.75±5.05 mm Hg for Perindopril group; and body mass index27.6 kg/m ^{2}. The target blood pressure of ≤ 140/ 90 mm Hg was achieved in all subjects by appropriate individualized dose titration. The mean (±SD) blood pressure at end of the study was observed as 122.5(±6.69)/80.15(±1.05), mm Hg, 121.25(±6.07)/80.15(±1.05) mm Hg in group A, group B respectively. The study drugs were tolerated by the majority. It is evident that a majority (45%) of the subjects were in the age range of 41-50 years, whereas, only 25% of the population was in the age group of 51-60 years. During the study, three patients discontinued and it was compensated by inclusion of newly diagnosed patients basing on the inclusion and exclusion criteria. Baseline clinical characteristics of patients receiving enalapril and perindoprilwere compared. The groups were similar and comparable as regards systolic BP, diastolic BP and heart rate before treatment. There were no significant ECG changes in the study subjects before and during the study.

In The Enalapril-Treated- Group A

The mean systolic blood pressure prior to treatment was 164.5mmHg. After treatment, the systolic BP reduced to 136.75 mmHg, 134.25mmHg, 120.5 mmHg and 122.5mmHg at 15thday,30thday,45thday and 90th day respectively. The reduction in systolic BP was found to be statistically significant ($P < 0.001$) at 15thday, 30thday, 45thday and 90th day of therapy when compared with the baseline readings. The mean diastolic BP before enalapril treatment was 106.25mmHg. After treatment, the diastolic BP reduced to 85.25mmHg, 83.75mmHg, 80 mmHg and 80 mmHg at 15thday, 30thday, 45thday and90th day respectively. The reduction in diastolic BP was found to be statistically significant ($P < 0.001$) at 15thday,30thday,45thday and 90th day of therapy when compared with the baseline readings.

In The Perindopril-Treated- Group B

The mean systolic BP prior to treatment was 169.5mmHg. After treatment, the systolic BP reduced to137.5 mmHg, 133mmHg, 120mmHg and 121.25 mmHg at 15thday, 30thday, 45thday and 90th day respectively. The reduction in systolic BP was found to be statistically significant ($P < 0.001$) at 15thday, 30thday, 45thday and 90th day of therapy when compared with the baseline readings. The mean diastolic BP before perindopril treatment was104.75 mmHg. After treatment, the diastolic BP reduced to 86.5mmHg, 85.75mmHg, 80mmHg and 80 mmHg at 15thday, 30thday, 45thday and 90th day respectively. The reduction in diastolic BP was found to be statistically significant ($P < 0.001$) at 15thday, 30thday, 45thday and 90th day of therapy when compared with the baseline readings.

Intergroup comparison was done considering Group A as standard group.

Taking enalapril treated group A as standard group, intergroup comparison was done. The 90th day blood pressures were compared between the groups. The mean systolic blood pressure on 90thdayof enalapril treated group A was122.5mm Hg and mean diastolic blood pressure was 80mm Hg. The mean systolic blood pressure on 90thday of perindopril treated group B was 121.25mm Hg and mean diastolic blood pressure was 80mm Hg. The intergroup comparison was done using student's t-Test – Two sample and Analysis of variance. Comparison of group A 90thday blood pressures [SBP/DBP] with group B 90thday blood pressures [SBP/DBP] using t-Test, The obtained p-value was P>0.05 which is not significant. Using analysis of variance the two groups were compared column wise and the resultant p-value was P>0.05 which is insignificant.

Table 1: Effects of the study drugs: group A Enalapril and group B Perindoprilon systolic blood pressure (mm Hg): intra-group analysis

Treatment groups		At different time points			P-value	Test used
		Baseline	15th day	90th day		
Group A	mean	164.5	136.75	122.5	***P < 0.0001	Paired T-Test
	SD	8.14	4.740	6.69		
Group B	mean	169.5	137.5	121.25	*** P< 0.0001	Paired T-Test
	SD	8.45	4.38	6.07		

SD- standard deviation, *** - extremely significant, ** - very significant, * - significant, ns- not significant.

Table 2: Effects of the study drugs: group A Enalapril, group B Perindopril on systolic blood pressure (mm Hg): intergroup analysis

Time Points	Treatment groups		P-value	Test used
	Group A [mean] mmHg	Group B [mean] mmHg		
Baseline	164.5	169.5	ns P>0.05	T- test
15th day	136.75	137.5	ns P>0.05	T- test
30th day	134.25	133	ns P>0.05	T- test
45th day	120.5	120.15	ns P>0.05	T- test
90th day	122.5	121.25	ns P>0.05	T- test

*** - extremely significant, ** - very significant, * - significant, ns- not significant

Table 3: Effects of the study drugs: group A Enalapril, group B Perindopril on diastolic blood pressure (mm Hg): intra-group analysis

Treatment groups		At different time points			P-value	Test used
		Baseline	15th day	90th day		
Group A	mean	106.25	85.25	80.15	***P < 0.0001	Paired T-Test
	SD	4.9	5.05	1.05		
Group B	mean	104.75	86.5	80.15	*** P< 0.0001	Paired T-Test
	SD	5.05	4.83	1.05		

SD- standard deviation, *** - extremely significant, ** - very significant, * - significant, ns- not significant

Table 4: Effects of the study drugs: group A Enalapril, group B Perindopril on diastolic blood pressure (mm Hg): intergroup analysis

Time Points	Treatment groups		P-value	Test used
	Group A [mean] mm Hg	Group B [mean] mm Hg		
Baseline	106.25	104.75	ns P>0.05	T- test
15TH DAY	85.25	86.5	ns P>0.05	T- test
30TH DAY	83.75	85.75	ns P>0.05	T- test
45TH DAY	80.15	80.15	ns P>0.05	T- test
90TH DAY	80.15	80.15	ns P>0.05	T- test

*** - extremely significant, ** - very significant, * - significant, ns- not significant

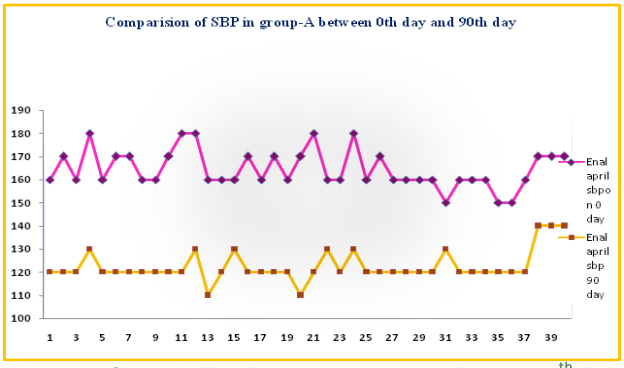

Figure 1: Comparision of systolic blood pressure in group a between 0th day and 90th day

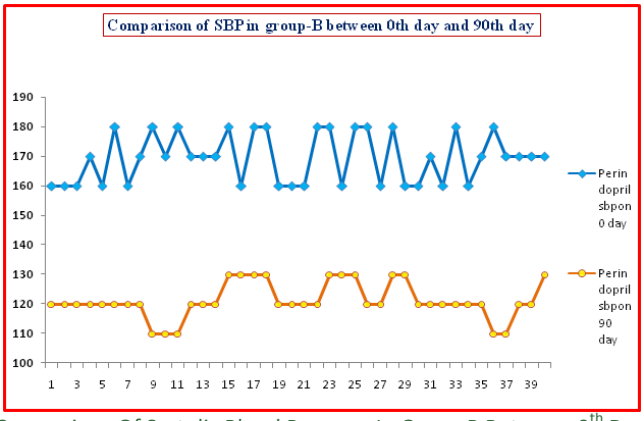

Figure 2: Comparison Of Systolic Blood Pressure In Group B Between 0th Day And 90th

Adverse drug reactions

The safety analysis was performed on all patients who completed the study. The various adverse drug reactions observed in the study subjects were dizziness, cough, musculoskeletal pain, fatigue, headache, nausea [Table 5]. A total of 25% of the patients reported some sort of adverse-effects like cough (10%), nausea(7.5%), musculoskeletal pain(2.5%), headache (5%) and dizziness (0%) in the group A and 20% in the perindopril treated group B, with noted adverse-effects like cough(10%), headache (5%), dizziness (2.5%), nausea (2.5%) and musculoskeletal pain(0%). However, this difference in the frequency of adverse-effects between the groups was not statistically significant ($P > 0.05$).

Table 5: Summary of Incidence Of All Adverse Drug Reactions Observed In The Study Subjects (N = 80)

Adverse Drug Reaction Observed	Enalapril [n=40]	Perindopril [n=40]
Cough	4	4
Nausea	3	1
Headache	2	2
Musculoskeletal pain	1	0
Dizziness	0	1

Cough

Four subjects on enalapril (10%; 95%CI) and four subjects on perindopril (10%; 95%CI),. Details regarding the intensity of the cough and other related features are tabulated in [Table 6]. Cough was seen in both male and female in two groups. In enalapril treated group A and perindopril treated group B male were more affected than female. Cough was seen in all the age groups. Subjects receiving enalapril and perindopril developed dry cough after one to one and half month of therapy. In all these subjects, the cough was mild in nature and there were no specific aggravating or relieving factors. It did not warrant discontinuation of therapy.

Nausea

3 subjects on enalapril (7.5%incidence; 95%C.I.) and One subject on perindopril (2.5%; 95%C.I.) presented with nausea. The nausea was mild-to-moderate in intensity. The time of onset was 60-90 minutes after consuming the drug and it lasted for another two to three hours in all the subjects. There were no associated episodes of vomiting. Nausea did not warrant discontinuation of therapy. Details of nausea are tabulated in [Table 7]. Musculoskeletal pain was seen in younger age groups between 30-40 years.

Table 6: Cough seen in study subjects of group a, group b (n =8).

Characteristic Features of Cough	ENALAPRIL	PERINDOPRIL
No. of cases	4	4
Sex distribution	3M+1F	3M+1F
Onset	1month	45 days
Nature	mild	mild
Discontinuation from therapy	No	No
Sleep disturbances	No	No

Table 7: Nausea Observed In Study Subjects of Group A and Group B (N =4)

Characteristic Features of Nausea	ENALAPRIL	PERINDOPRIL
No. Of cases	3	1
Sex distribution	2M+1F	1M+0F
Intensity	mild	mild
Time of onset	1hour	1hour
Duration	2-5	2-5

DISCUSSION

The ability to reduce levels of angiotensin II with orally effective inhibitors of angiotensin converting enzyme represents an important advance in the treatment of hypertension. Captopril, enalapril, lisinopril, quinapril , ramipril, benazepril, moexipril, fosinopril, trandolapril, and perindopril have proven to be very useful for the treatment of hypertension because of their efficacy and their very favorable profile of adverse effects[15], which enhances patient adherence. There are several cautions in the use of ACE inhibitors. Angioedema is a rare but potentially fatal adverse effect of the ACE inhibitors. Patients starting treatment with these drugs should beexplicitly warned to discontinue their use with the advent of any signs of angioedema. Due to the risk of severe fetal adverse effects, ACE inhibitors are contraindicated during pregnancy, a fact that must be communicated to women of childbearing age. Our study was designed to monitor the Efficacy and various adverse drug reactions seen with the ACEIs containing the dicarboxyl group namely enalapril and perindopril with the aim to observe the efficacy, incidence of adverse drug reactions between the two groups. The two groups were comparable to each other in terms of age, weight and baseline characteristics such as sex ratio, smoking and alcohol habits. The observed age distribution of subjects receiving ACEIs in each study group is expressed in. It is evident that a majority (45%) of the subjects were in the age range of 41-50 years, whereas, only 25% of the population was in the age group of 51-60 years. In the present study, we have observed that Enalapril and Perindopril are effective agents in reducing both systolic and diastolic BP throughout the study period when measured at the 15thday, 30thday, 45thday and 90th day. When efficacy was compared, we found that these two drugs were equally effective in reducing the systolic and diastolic blood pressure. The mean(± S.D.) age was 48.816(±7.17955) years. Baseline blood pressure (systolic / diastolic) mm Hg was, 164.5(±8.149) mm Hg for Enalapril group, 169.5(±1.3373) mm Hg for Perindopril group; and body mass index 27.6 kg/m^2. The target blood pressure of ≤ 140/ 90 mm Hg was achieved in all subjects by appropriate individualized dose titration. The mean (±SD) blood pressure at end of the study was observed as

122.5(±6.69)/80.15(±1.05), mm Hg, 121.25(±6.07)/80.15(±1.05) mm Hg, in group A and group B respectively. There were no significant ECG changes in the study subjects before and during the study. In our study, the incidence of cough withperindopril (10%; 95%CI) and enalapril (10%; 95%CI) was similar to that reported in literature. Subjects receiving enalapril and perindopril developed dry cough after one to one and half month of therapy. In all these subjects, the cough was mild in nature and there were no specific aggravating or relieving factors. It did not warrant discontinuation of therapy. In literature- Dry, brassy cough is commonly reported with the use of ACEIs and is estimated to be in the range of 5-10%.[21,22,23,24] The cough is usually persistent, paroxysmal, non-productive, worsening in the lying down position, and at times accompanied by a change in voice.[25] Studies have suggested the involvement of mediators such as, bradykinin, prostaglandins or substance P as mediators of the cough.[26,27] A literature survey suggests about a 6% incidence of cough with enalapril.[21,22,23] Some studies have suggested about 10% incidence of cough with perindopril[28]. Our findings indicated that the incidence of nausea was higher (7.5%) with enalapril and perindopril (2.5%). A literature survey suggests nausea with use of ACEIs is around 1-5%.[26,29] Some studies have suggested, incidence of nausea as 5-10%with enalapril and 0%with perindopril.[28,30] The incidence of nausea was less with perindopril. The causality needs to be confirmed by evaluating a larger number of subjects to make the study representative of the Indian population. Our findings indicated that the incidence of musculoskeletal pain was2.5% with enalapril, when compared to perindopril (0%). In another study, it was 3.3% with enalapril.[30] The incidence of dizziness in this study was 0% with enalapril and 2.5% with perindopril. In other comparative studies it was 6.6% with enalapril and 5% with perindopril.[28,30] The incidence of head ache in this study was enalapril (5%) and perindopril (5%). In other comparative studies, it was 6.6% with enalapril and 7.5% with perindopril.[28,30] The changes in laboratory parameters were minor and of no clinical relevance. As in previous studies change in plasma glucose and lipid values was slight with ACE inhibitors.[30] In consideration of cost, enalapril is the cheapest antihypertensive drug available in the market which is also well tolerated by the patients when compared to the other ACE inhibitors.

CONCLUSION

In the present study, the efficacy and incidence of adverse drug reactions between enalapril and perindopril in patients suffering from essential hypertension [StageI/II] was studied. The anti hypertensive effect of these two drugs included in the study was statistically significant. As a antihypertensive, there is no significant difference in the efficacy between enalapril and perindopril. Incidence of cough and headache are similar in both groups. Incidence of adverse effects like nausea, vomiting, musculoskeletal pain, are less in perindopril treated group B as compared to enalapril treated group A. Incidence of dizziness is more in perindopril treated group than enalapril treated group. However these differences in incidence of adverse effects between two groups were not statistically significant. Though both groups had adverse effects, they were tolerated by patients and hence effective antihypertensive drugs in management of essential hypertension.

REFERENCES

1. Kearney P, Whelton M, Reynolds K, Muntner P, Whelton PK,He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005; 365: 217-23.
2. Gupta R, Al-Odat NA, Gupta VP. Hypertension epidemiology in India: meta-analysis of 50 year prevalence rates and blood pressure trends. J Hum Hypertens 1996; 10: 465-72.
3. Gupta R. Trends in hypertension epidemiology in India J Hum Hypertens 2004; 18: 73-8.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global burden of disease study. Lancet 1997; 349: 1498-504.
5. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J 35. rd. Factors of risk in the development of coronary heart disease- six year follow-up experience. The Framingham Study. Ann Intern Med 1961; 55: 33-50.
6. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. Arch Intern Med 1993; 153: 598-615.
7. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannell WB, et al. Impact of high normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001; 345: 1291-7.
8. Rodgers A, Lawes C, MacMahon S. Reducing the global burden of blood pressure related cardiovascular disease. J Hypertens 2000; 18 (Suppl 1): S3-S6.
9. Gaziano T, Reddy KS, Paccaud F, Horton S, Chaturvedi V. Cardiovascular disease. In: Jamison DT, Breman JG, Measham AR, Alleyene G, Cleason M, Evans DB, Jha P, Mills A, Musgrove P, editors. Disease control priorities in developing world. Oxford: Oxford University Press; 2006. p. 645-62.
10. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA. 1996; 275:1571–1576.
11. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. 1996, 334:13–18.
12. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med. 2001, 345:1291–1297.7
13. Lewington S, Clarke R, Qizilbash N, et al; for the Prospective Studies Collaboration. Age-specific

relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002, 360:1903–1913.
14. Kikuya M, Hansen TW, Thijs L, et al; on behalf of the International Database on Ambulatory blood pressure monitoring in relation to cardiovascular Outcomes (IDACO) Investigators. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk.Circulation. 2007; 115:2145–2152.
15. Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J,Harrison's Principles of Internal Medicine, 18th Edition,Vol.1, 2012; McGraw Hill Medical, New York, Pg. no.2042.
16. Ondetti MA, Rubin B, Cushman DW. Design of specific inhibitors of Angiotensin converting enzyme: A new class of orally active hypertensive agents. Science 1977; 196:441-6.
17. T. Hayek, Cardiovascular Research, 1999, 44, (3), 579-587.
18. K. Arihara, Y. Nakashima, Meat Science, 2001, 57, 319-324.
19. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, NIH Publication No. 04-5230 August 2004
20. Naranjo et.al. Clin Pharmacol Ther. 1981 Aug; 30(2):239-45.
21. Arnolt MA, Damonte de Elia AR. Enalapril and cough. J Hypertension 1991; 4:28A.
22. Moyses C, Higgins TJ. Safety of long-term use of Lisinopril for congestive heart failure. Am J Cardiol 1992; 70:91C-7C. [PUBMED]
23. Williams B, Gosse P, Lowe L. The prospective, randomized investigation of safety and efficacy of telmisartan versus Ramipril using ambulatory blood pressure monitoring (PRISMA I). J Hypertens 2006; 24:193-200.
24. Bristol-Myers Squibb. Fosinopril prescribing information. Princeton (NJ). 1996.
25. Schreiner M, Berendes B, Verho M, Langley A, Cairns V. Anithypertensive efficacy, tolerance and safety of long term treatment with Ramipril. J Cardiovasc Pharmacol 1991; 18:S137-40. [PUBMED]
26. Ferner RE, Simpson JM, Rawlins MD. Effects of intradermal bradykinin after inhibition of angiotensin converting enzyme. BMJ 1987; 294:1119-20. [PUBMED] [FULLTEXT]
27. Clinical Acceptability of therapy in mild ace inhibitors to moderate hypertension, a comparison between perindopril and enalapril . Alcocer l., c. Campos, bahena jh, nacaud a., parra j carrillo., c. Calvo, c. Weber, g. Lerebours mickalonis l., Villahermosa cardiovasc drug ther mt 1995, 9:431-436.
28. Cooper WD, Sheldon D, Brown D, Kimber GR, Isitt VL, Currie WJ. Post marketing surveillance of Enalapril. 1987; 37:346-9. [PUBMED] [FULLTEXT]
29. Adverse drug reaction monitoring with angiotensin converting enzyme inhibitors: A prospective, randomized, open-label, comparative study, DOI: 10.4103/0253-7613.62408, PMID: 20606833

Source of Support: None Declared
Conflict of Interest: None Declared