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COMPARATIVE STUDIES OF EFFICACY AND EFFECT ON OXIDATIVE STRESS OF ENALAPRIL AND RAMIPRIL IN THE HYPERTENSIVE PATIENTS OF NORTH EAST INDIA

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Abstract:

Over production of oxygen free radical which is mediated by super oxide, occurs in human hypertension. There are several important enzymatic sources of super oxide production including NADPH oxidase, xanthine oxidase uncoupled nitric oxide synthase. The major vascular reactive oxygen species (ROS) is superoxide which inactivates NO thus impairing vascular relaxation. Ramipril and Enalapril are Angiotensin converting enzyme inhibitors (ACEI) which are frequently prescribed for hypertensive patients. An attempt was made to compare the efficacy of these two ACEIs in the hypertensive patients of this region and to investigate the effect of such agents on different blood parameters, antioxidant status, SGOT and SGPT levels. Study consisted of three groups. One group was healthy volunteers [N=20] and rest two groups of hypertensive patients. Each patient group comprises of 20 hypertensives (N=20) patients both male and female in age group of 25-70 years with normal blood sugar level. The study population included newly detected mild to moderate essential hypertensive patients without suffering from any other diseases. Patients were subjected to blood pressure measurement, estimation of blood parameters (fasting blood sugar level, lipid profiles, SGPT and SGOT). Weight, age, health status was checked up before entering in the study. The patients were following up after a period of 4 weeks and 8weeks after initiation of monotherapy either Ramipril or Enalapril. Subsequently antioxidant status enzymatic & non-enzymatic were estimated before treatment and during antihypertensive treatment. The present study reveals that there is a significant reduction of blood pressure during antihypertensive therapy by both the drugs. Ramipril and Enalapril also have significant reduction of oxidative stress; they increase the levels of glutathione [GTH], total antioxidant [TAS], and superoxide dismutase [SOD] and reduce the malondialdehyde [MDA] during antihypertensive treatment.

Key words: Hypertensive status, Oxidative stress, Ramipril, SEM.

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Introduction

Hypertension is a long term medical condition in which blood pressure in the arteries is persistently elevated and usually defined as systolic readings greater than or equal to 140 mm of Hg and diastolic readings greater than or equal to 90 mm of Hg (≥ 140/90) (Chobanian et al, 2003). Hypertension is the leading cause of cardiovascular diseases worldwide. Cardiovascular diseases account for a large proportion of deaths and disability all over the world (Gupta RM 1996). It has been predicted that by the year 2020, there will be an increased by 75% in the global cardiovascular disease burden (Kearney et al, 2005) Hypertension is a common disorder if not effectively treated results in a greatly increased probability of coronary thrombosis, renal failure, and stroke (Lawes et al, 2003). Hypertension is an independent risk factor for both coronary heart disease and stroke. High blood pressure is an important public health problem in India. In India heart disease occurs 10-15 years earlier than in the west (Simon 2004). High level of superoxide anion the consequent accumulation of hydrogen peroxide and diminished NO bioavailability play a critical role in the modulation of vascular remodeling (Mulvany 2002). The reaction product between super oxide and NO, peroxynitrite, constitutes a strong oxidant molecule which is able to oxidize protein, lipids and nucleic acid, causing cell damage. These pathological processes are associated with hypertension because of narrowing arterial lumen.

Renin release from the kidney cortex is stimulated by reduced renal arterial pressure. Renin acts upon angiotensinogen to split off the inactive decapeptide angiotensin-I which is then converted to angiotensin-II by endothelial angiotensin converting enzyme [ACE]. Angiotensin-II is a vasoconstrictor and has sodium retention activity. So, peripheral resistance is increased. The ACE inhibitor blocks the ACE enzyme therefore reduced peripheral resistance.

Enalapril maleate was the second ACE inhibitor approved in the United State. It is a pro drug not highly active and hydrolyzes by esterases in the liver to active parent dicarboxylic acid, enalaprilate. Enalapril is rapidly absorbed orally. Oral bioavailability is 60%. Peak plasma concentration is achieved within an hour. An enaprilate peak concentration is achieved only after 3-4 hours. Plasma half life is about 11 hours. It is eliminated by the kidney either as intact enalapril or enaprilate (Sotoskar et al, 2001). Ramipril is also a pro drug comparatively long-acting member of ACE inhibitor. Following oral administration peak plasma concentration of ramipril is reached within one hour. The extent of absorption is at least 50-60%, not influenced by the presence of food in the GIT (Tripathi, 2006).

Elena and coworkers reported that atenolol and captopril enhanced glutathione dependent antioxidant defences (Elena M, 2000).

Baykal and co-authors reported that oxygen free radicals and insufficiency of antioxidant enzymes implicated in pathogenesis of hypertension. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have notable effects on oxidative stress and are essential steps in managing essential hypertension by the way of improvement of endothelial dysfunction (Baykal Y et al, 2003).

Meta-analysis of 13 clinical trials report suggested that there was a difference in blood pressure response to ACE-Inhibitor monotherapy between black and white adult with arterial hypertension (Robert N et. al, 2013).

According to Cheng et al (2014), angiotensin-converting enzyme inhibitors reduced all-cause mortality, CV mortality, and major CV events in patients with DM, whereas ARBs had no benefits on these outcomes. Thus, ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in the population.

Study suggested that genetic and environmental factors play a significant role in the development of hypertension and associated cardiovascular and metabolic disease (Zanchetti, 2016). A prospective, comparative study was conducted in 370 diabetes patients suffering from mild to moderate hypertension suggested that ACEI as monotherapy or combination therapy reduced BP effectively (Beulah et al, 2012).

The objectives of the present study were to compare the efficacy parameters like blood pressure [B.P], fasting blood sugar levels [FBS], lipid profile, SGOT and SGPT in Ramipril as well as Enalapril treated group. Also to compare enzymatic and non-enzymatic antioxidants superoxide dismutase [SOD], total antioxidant status [TAS], glutathione [GTH] and lipid peroxidation [MDA] levels in normal healthy subjects as well as hypertensive patients

Study Design

Prospective randomized controlled studies of two ACEIs, Ramipril and Enalapril.

Population: This study population included male and female hypertensive patients in the age group of 25-70 years from the OPD of Assam Medical College & Hospital, Dibrugarh, Assam. Patients with hypertension without any other diseases were included in this study. The patients were subjected to the investigations before entering in the study, like Blood pressure, fasting blood sugar (FBS), lipid profile, SGOT and SGPT. The study was conducted after getting the approval by the Institutional Ethics Committee. The following data was obtained for each participant.

1. Demographic data (weight, height, age, ethnicity), 2. Taking history of patient, 3. Pre-existing medical conditions (history of hypertension, diabetes, or other chronic conditions), 4. Social History (smoking, alcohol consumption, food habit, occupation).

The present study comprised of three groups. One group was healthy subject and other two groups were hypertensive patient groups. This study included 60 subjects. Out of 60 subjects, 20 were normal human healthy volunteers (NHV) without history of smoking, alcoholism any other diseases taken as control and 40 subjects were untreated hypertensive patients without any other diseases. Out of the 40 (Male 26 and Female 14) subjects, 20 subjects were treated with Ramipril 5 mg/day and rest 20 subjects were treated with Enalapril 5 mg/day (both drugs were manufactured by same company). The blood pressure was measured in lying down or sitting position at ease and then 5 ml blood was collected with prior consent from the patient. The samples were analyzed for estimation of serum level of lipid profile, SGOT, SGPT and antioxidant status. Patients were again checked up after 8 weeks/14weeks during antihypertensive therapy and above tests were repeated.

Materials and Method

Assessment of blood pressure: Blood pressure was recorded by auscultatory method by using sphygmomanometer in left arm.

Collection of blood: Venous blood was collected from the subjects under aseptic condition by venipuncture using 5 ml sterile disposable syringe and needle. About 3-4 mL of blood was collected. Serum was separated by centrifugation at 3000 rpm for 10 min at room temperature. The samples were stored at 4°C before analysis and all the samples were analyzed on the same day of collection (Neidu et al, 2007).

All the methods were standardized first and standard graphs were obtained. Serum glutathione, total antioxidant status, lipid peroxidase, superoxide dismutase, fasting blood sugar, SGOT and SGPT were measured by using standard methods.

Estimation of Superoxide dismutase: The enzyme SOD level was measured in erythrocytes using photo-oxidation method (Misra and Friwicch, 1997; Arutla et al, 1998).

Extraction: 3 ml packed blood cells were lysed by the addition of equal volume of cold demonized water. Hemoglobin was precipitated by the addition of chloroform: ethanol (1:5). This was diluted with 500 µl water, centrifuge at 3000 rpm for 15 m. The supernatant containing SOD was used for measurement of its activity.

Assay procedure: 0.88 ml of riboflavin solution (1.3x10-5 M of 0.01M potassium phosphate buffer pH 7.5 was added to 66 µl of O-dianisidine and 100 µl of supernatant, optical density was measured at 460 nm. Then above cuvette containing reaction mixture was transferred to illuminating box for 4 min. The optical density was re measured. The change in optical density was determined. The SOD content was calculated from standard graph.

Glutathione in blood: 0.5 ml of 5% TCA solution was added to 0.5 ml of citrated blood to precipitate the proteins and centrifuged at 3000 rpm for 20 min. To 0.1 ml of supernatant, 1 ml of sodium phosphate buffer (pH 8) and 0.5 ml of DTNB (39.6 mg in 100 ml of 1% sodium citrate solution to give a concentration of 1 mM were added. The absorbance of the yellow color developed was measured at 412 nm (Beutler et al, 1963)

Total anti-oxidant status: Total anti-oxidant status in serum was determined by the method of (Blois,1968) using a stable, free radical, α, α-diphenyl-β-picrylhydrazyl (DPPH) at a concentration of 0.2 mM in methanol.

Lipid peroxides: The amount of lipid peroxidation products present in the serum samples were estimated by the thiobarbituric acid reactive substances (TBARS) method, which measures the malondialdehide (MDA) reactive products by using spectrophotometer method (Moore & Robert, 1998))

SGOT and SGPT: Both SGOT and SGPT in human serum or plasma are usually assayed by Reitman and Frankel (Reitman and Frankel, 1957) colorimetric method.

Statistical Analysis:

All the values were expressed as Mean ± SEM. The data were analyzed using student ANOVA, Newman Koel method. In tests, the criteria for statistical significance were $P<0.05$*, $P< 0.01$** and $P<0.001$***

Results

Demographic data and clinical characteristics of Ramipril and Enalapril pretreatment groups were shown in Table 1. Systolic blood pressure [SBP] and diastolic blood pressure [DBP] levels, age, weight, height, fasting blood sugar levels, lipid profile, SGOT and SGPT were not significantly different between Ramipril group and Enalapril group.

SBP was significantly reduced in first ($P<0.01$) and second follow up ($P<0.001$) as compared to pretreatment groups. Ramipril reduced SBP more effectively in first ($P<0.01$) and second follow up ($P<0.001$) as compared to Enalapril group. SBP significantly reduced in Ramipril group in first ($P<0.01$) and second follow ups ($P<0.001$) as compared to pretreatment values. P-value for Enalapril group were first follow up ($P<0.05$) and second follow up ($P<0.01$) (Table 2).

Blood sugar levels were not significantly reduced during treatment in case of both Ramipril and Enalapril (Table 2).

Serum levels of total cholesterol, triglyceride and LDL were not significantly reduced after treatment both the drugs, Significant change was not observed in HDL level during treatment Ramipril and Enalapril.

SGPT levels showed significant difference for Ramipril treated group ($P<0.01$) in the second follow ups But such trend was not observed in Enalapril group. For both groups changes of SGOT levels were insignificant (Table 3).

Table 4 shows that the SOD levels were significantly increased in first ($P<0.01$) and second follow ups ($P<0.001$) during ramipril treatment as compared to pretreatment values. Significant difference was observed in case of Enalapril. SOD levels in first ($P<0.05$) and second follow ups ($P<0.01$) as compared to pretreatment values. SOD levels were more significantly increased during Ramipril treatment as compared to enalapril group.

Total antioxidant levels were significantly increased in first and second follow ups ($P<0.001$) with ramipril treatment as compared to pretreatment values. Ramipril was more effective in increasing total antioxidant levels in first ($P<0.01$) and second ($P<0.001$) follow ups as compared to Enalapril group.

GSH levels were significantly increased in first and second follow ups ($P<0.001$) treatment with Ramipril as compared to pretreatment values. GSH levels were increased in first ($P<0.05$) and second follow ups ($P<0.01$) in enalapril group as compared to pretreatment values. Ramipril was comparatively more effective in increasing GSH levels as compared to Enalapril group.

MDA levels were decreased in second follow ups ($P<0.05$) treatment with Ramipril as compared to pretreatment values. MDA levels were also significantly decreased with Enalapril (Table 4).

Table 1: Demographic data: Clinical characteristics of pretreatment groups of Ramipril and Enalapril.

Demographic data	NHV	Ramipril	Enalapril
Age (years)	42.3±.1.93	49.3 ±2.45	49.65 ±2.01
Height (cm)	151.4±1.45	147.9±1.63	152.15±1.43
Weight (kg)	57.20±2.79	53.05±2.87	56.15±2.48

Table 2: Effect of Ramipril and Enalapril on the systolic blood pressure, diastolic blood pressure and blood glucose levels of hypertensive subjects.

	NHS	Ramipril		Enalapril	
Parameter		Pre	after	Pre	after
SBP (mmHg)	121.0±0.42	166.5 ± 3.71	136.6 ± 2.60***	168.4 ± 4.81	146.8± 3.44**
DBP (mmHg)	80.55±0.41	95.15 ± 1.87	82.9 5± 2.66**	99.55 ± 3.28	87.90 ±1.42**
FBS (mg/dl)	86.55±2.18	95.45 ± 2.13	91.0 ± 1.36	99.55 ±1.86	91.9 ±1.75

Table 3: Effect of Ramipril and Enalapril on the total cholesterol, Triglycerides, HDL, LDL, SGOT and SGPT of hypertensive subjects.

	NHS	Ramipril		Enalapril	
Parameter		Pre	after	Pre	After
TC (mg/dl)	145.9±2.34	160.25± 2.22	157.05±1.61	158.25±2.32	155.95 ±1.97
Trig (mg/dl)	149.6±1.87	150.65 ±3.17	151.6 ±2.68	153.95 ±3.76	154.45±3.41
HDL(mg/dl)	37.55±0.52	36.25 ± 0.79	38.70±0.45	38.4 ± 0.48	39.45 ±0.38
LDL (mg/dl)	78.44±2.07	93.34 ±1.94	86.09 ± 1.62	86.95 ± 2.63	85.11 ± 1.73
SGOT(IU/L)	25.35±1.08	32..35 ±1.56	27.50± 1.17	31.45± 2.00	27.9 ±1.761
SGPT(IU/L)	26.75±1.42	33.25 ± 1.481	25.20± 1.15*	31.35 ± 2.08	27.65 ±1.46

Table 4: Effect of Ramipril and Enalapril the Super oxide dismutase, TAS, GTH and MDA levels of hypertensive subjects.

Parameter		Ramipril		Enalapril	
	NHS	Before	After	before	after
SOD (IU/ml)	69.38±2.47	16.15 ±1.80	33.12±2.66* +++	21.39± 2.19	34.63 ±2.405 ++
TAS (nM/ml)	92.96±3.78	24.07 ±2.02	46.53±2.132**+++	26.683±1.47	38.42 ±1.54++
GSH (nM/ml)	636.65±63.51	232.89±12.992	572.49±24.825** ++	242.18±15.78	428.83±18.19+++
MDA(nM/ml/hr)	3.36± 0.22	6.94 ±1.07	3.72±0.71** + +	8.342± 1.06	4.78±0.78 + + +

In all tables, the values are expressed as Mean ± SEM of 20 subjects. The criteria for statistical significance were $P<0.05$, $P< 0.01$ and $P<0.001$.
Values are expressed as mean ± SEM of 20 subjects
*$P < 0.05$ Ramipril vs Enalapril
**$P < 0.01$ Ramipril vs Enalapril
++$P < 0.01$ Pretreatment vs follow up with drug
+++$P < 0.001$ Pretreatment vs follow up with drug

Discussions

High blood pressure is one of the important public health problems in India and worldwide (Gupta et al 1996). If remain untreated, sustained hypertension is a risk factor for the development of cardiovascular diseases. Oxidative stress mediated by reactive oxygen species [ROS] and reactive nitrogen species [RNS]. They are the primary or secondary cause of many chronic diseases (Touzy, 2000 ; Ferrira et al, 2005).The serious complications are not only the consequences of increased blood pressure but also related to the arterial endothelial dysfunction thereby accelerates the process of hypertension.

Blood pressure (BP): Systolic BP is controlled by the stroke volume of the heart and the stiffness of the arterial vessels. BP varies from moment to moment with respiration, exercise, meals, alcohol, tobacco, bladder distension, temperature and pain. It is also influenced by circadian rhythm, age and race. Systolic blood pressure is a best predictor of CV risk than DBP, especially after the age of 55 years (JNC). In the overall population mean SBP increases progressively throughout adult life in men and women. The third National Health and Nutrition Examination Survey (NHANES III) found that mean SBP is higher in men than women during early adulthood but the subsequent rate of rise in BP is steeper for women than men (Pimenta, 2012).

The present study SBP levels were significantly higher in hypertensive patients without antihypertensive treatment compared with healthy subjects. Ramipril significantly reduced SBP than Enalapril treated subjects due to its antioxidant property and dual mode of action by release of NO. The first and second follow up with Enalapril has also shown significant decrease in SBP but it is less effective than Ramipril in reducing SBP.

DBP levels were significantly higher in hypertensive patients without antihypertensive treatment compared with healthy subjects. Ramipril treated hypertensive patients have shown more significant results in reducing DBP than Enalapril treated subjects.

Blood sugar: Glucose is oxidized by glucose oxidase to gluconic acid and hydrogen peroxide in a subsequent peroxidase catalyzed reaction. Glucose is the major carbohydrate present in blood and is the main source of energy for the body. Increased levels of glucose are found in diabetes mellitus , hyperparathyroidism, pancreatitis and renal failure. Decreased levels are found in insulinoma, hypothyroidism, hypopitutarism and extensive liver disease.

In the present study blood sugar levels were not significantly changed during treatment by both the drugs.

Super Oxide Dismutase (SOD): Superoxide dismutase is one of the important free radical scavenging enzymes present in our body. The enzyme superoxide dismutase, catalyses the dismutation of superoxide radicals to O2 and H2O2. In the present study it

was observed that the enzyme activity was decreased indicating that the enzyme SOD was nearly completely utilized to scavenge the superoxide radicals. Prevention of tissue damage due to intracellular superoxide requires elevation of intracellular SOD. ACE inhibitor increases antioxidant enzyme activity (Sebekova and Hcidland, 2003; Verbcelam et al, 1998).

In the present study the SOD levels were reduced significantly in all hypertensive patients without antihypertensive treatment. SOD levels have been significantly increased with clinical improvement during treatment with Ramipril after second follow ups($P<0.001$) as compared to enalapril ($P<0.01$) treatment due its antioxidant property. Ramipril treatment may be resulted in a normalization of the NADPH oxidase activity in membrane fractions from the heart. The study indicates that Ramipril can correct effectively on the restoration of NO bioavailability and endothelial function.

Total Anti-Oxidant Status (TAS): Antioxidants decrease the incidence of diseases however more human studies are required to establish the efficacy and safety of these agents in various chronic or acute oxidative stress-related diseases (Rees et al, 2004) e.g. cardiovascular diseases. The role of antioxidants in CVDs is based on the premise that free radicals can injure arteries; also induce atherosclerosis by inducing fatty streaks resulting in atheroma. By oxidation of LDL can injure myocardium during reperfusion in MI. Hypertension occur due to deregulating of nitric oxide production. The antioxidants can prevent most of these above processes. Several factors such as low food intake, nutrients malabsorption and inadequate nutrient release from the liver, acute phase response , infection and an inadequate availability of carrier molecules may influence circulating antioxidant concentrations (Solzback et al, 1997). Ramipril protects the vascular endothelium against free radical induced functional injury (Gillis et al, 1992).

In present study the total antioxidant levels were found to be significantly reduced in all hypertensive patients without antihypertensive treatment compared with healthy subjects. Total antioxidant levels have been significantly increased with clinical improvement during treatment with Ramipril after second follow ups ($P<0.01$) as compared to Enalapril ($P<0.01$) treatment due to its antioxidant property.

Glutathione: Glutathione peroxidase appears to have a major role in the prevention of oxidative stress; it may also be an important antiatherogenic antioxidant. Glutathione (GSH) is a tripeptide comprised of glutamate, cysteine and glyceine. GSH is present in mast cells, where it functions as an antioxidant protecting cells from toxic effects of ROS (Arthur, 2000). Glutathione peroxidase deficiency has endothelial dysfunction combined with structural vascular abnormalities, such as increased periadventitial inflammation and collagen deposition surrounding the coronary arteries. Glutathione has been regulated by immune cell function. Glutathione peroxidase with 5-lipoxygenase might constitute a

protective function of the enzyme, in addition to its antioxidant activity (Sies, 1999). Enalapril and captropril enhance glutathione dependent antioxidant defenses (Elena M and Cavanagh, 2000).

In present study Glutathione levels were estimated in hypertensive patients. Glutathione levels were significantly low in all hypertensive patients, the decreased was more pronounced in untreated hypertensive. But the glutathione levels were significantly increased ($P<0.01$) after second follow up treatment with ramipril as compared to enalapril.

Lipid Peroxidation (MDA): Hypertension is a state of increased free-radical activity which oxidative stresses or injuries the endothelium conjugated dienes and lipid peroxides are by products of the lipid Peroxidation of cellular structures inducted by free radicals and can be conveniently measured as thiobarbituric acid reactive substances (TBARS). Lipid peroxidation is thought to be involved in a number of pathological processes. ROS have been implicated in the pathogenesis of various conditions including cardiovascular diseases, MDA is an end product of fatty acid oxidation, and is often used as an indicator of lipid peroxidation (Mollanau et al, 2005). In the present study the MDA levels were found to be higher in all hypertensive patients without antihypertensive treatment compared with healthy subjects. MDA levels have been decreased with ramipril treatment as compared to enalapril treatment. It may result in its beneficial effects on the restoration of NO bioavailability and endothelial function.

Total Cholesterol: Cholesterol is a fatty substance found in blood, bile and brain tissue. It is mainly found in esterifies form. It serves as a precursor of bile acids (Kojda et al, 1989), steroids and vitamin D. Cholesterol esters are hydrolyzed to produce cholesterol.

In the present study Cholesterol levels were not significantly reduced with both the drugs..

Triglycerides: Triglycerides are a family of lipids absorbed from the diet and produced endogenously. Measurement of triglycerides is important in the diagnosis and management of hyperlipidaemias (Giugliano et al, 1995).

Triglyceride level no significant difference was observed in subjects treated with ramipril and enalapril.

HDL Cholesterol: HDL is the smallest lipoproteins. HDL particles synthesize both from the liver and intestine. HDL transport cholesterol from the peripheral tissues to the liver for excretion. The measurements of HDL cholesterol provide valuable information for the assessment of coronary heart diseases. In case of HDL cholesterol second follow up with Ramipril ($P<0.001$) had shown significant result and Enalapril virtually ineffective.

LDL Cholesterol: LDL contains 50% cholesterol by weight and is with high cholesterol. They are synthesized in the liver and are responsible for transporting cholesterol from the liver to the peripheral tissues and increase the risk of arteriosclerotic, heart and peripheral vascular disease. Hence high levels of LDL are atherogenic. No significant changes were observed in both the groups.

SGOT: SGOT is an enzyme found in heart muscle, liver cells, skeletal muscle and kidneys. Injury to these tissues results in the release of the enzyme in blood. In our study no significant changes were observed in both the treated groups

SGPT: SGPT is found in a variety of tissues but is mainly found in liver, increased levels are found in hepatitis, cirrhosis obstructive jaundice and other hepatic diseases. In the present study SGPT level was significant decreased by Ramipril.

Conclusion

Ramipril and Enalapril lower the BP with beneficial effect on endothelial dysfunction. The present study have demonstrated that Ramipril improved total antioxidant status, glutathione levels by scavenging superoxide ions and there by increasing intracellular GSH levels. Enalapril also has similar effect but lesser activity. Finally, Ramipril and Enalapril are effective antihypertensive agents but Ramipril has comparatively better activity for reducing oxidative stress as comparison to Enalapril.

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