

A REVIEW ON THE EFFECTIVENESS OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN REDUCING CARDIOVASCULAR MORBIDITY AND MORTALITY RISKS

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Contribution

MN conceived the idea and designed the review. Data collection and manuscript writing was done by MN, AS, SGB, and QB. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Angiotensin converting enzyme inhibitors (ACEIs) have long been preferred as a therapeutic choice for cardiovascular disease due to its safe supremacy to overcome the deleterious effects of Angiotensin II, which is a strong vasoconstrictor and increases the levels of different growth factors and adhesion molecules. It produces an oxidative stress that accounts for its apoptotic properties. The cardiac myocyte undergoes necrosis induced by angiotensin II and it also activates neurohumoral system in post infarction left ventricular dysfunction patients. ACE inhibitors reduce the production of angiotensin II by endothelial cells. It also simultaneously diminishes the deprivation of bradykinin that results in vasodilation to overcome the effects of angiotensin II by exerting its anti-apoptotic actions. Clinical trials such as SAVE, SOLVD, AIRE and TRACE indicated that the life expectancy can be increase by ACE inhibitors in patients having left ventricular dysfunction. EUROPA study suggested that in all patients of coronary heart diseases, perindopril is a treatment of choice along with other preventive therapies. Evidence of clinical researches support the usage of ACE inhibitors and showed improve clinical results in patients with primary hypertension, stable coronary artery diseases, stable ischemic diseases with preserved ventricular function or reduced ventricular function, and myocardial infarction. FDA has approved ACE inhibitors as adjunctive therapy in systolic heart failure, and in patients with a history of myocardial infarction and those having reduced ejection fraction to prevent HF. Perindopril is also approved by FDA for cases of stable coronary artery diseases and it is helpful to reduce the risk of mortality with Myocardial infarction.

Keywords: Angiotensin II, Cardiac Dysfunction, Coronary artery disease, Heart Failure, Hypertension

INTRODUCTION

There is a positive association between the increasing threats to morbidity and mortality with chronic condition of Hypertension.¹ Angiotensin Converting Enzyme (ACE) inhibitors are a preferred class of drug to be chosen for the treatment of majority of the cases of elevated blood pressure. It is also a First-line therapy for management of hypertension in patients ageing less than 55 years. Other high-risk patients who are indicated for use of ACE inhibitor includes those suffering from Diabetes, Heart failure, myocardial infarction, recurrent stroke and left ventricular dysfunction.^{2,3} Most commonly use medicines included in this class are enalapril, captopril, lisinopril, ramipril and quinapril.⁴

Pharmacological Aspects of ACE Inhibitors:

ACE produces its action by acting on Renin-angiotensin aldosterone (RAAS) system and aids in the conversion of angiotensin I to angiotensin II. Renin is an enzyme responsible for regulating the pressure in circulatory system. It is responsible for converting angiotensinogen to angiotensin I, that is later converted into angiotensin II. Angiotensin II is a powerful vasoconstrictor.⁵

Angiotensin converting enzyme inhibitors have dual mode effect on ACE releasing tissues which results in twin effects on the endothelium. The production of ACE by endothelium is also minimized by ACE inhibitors thus protect the endothelium from vasoconstriction resulting from angiotensin II. As the level of angiotensin II is declined various growth factors and adhesion molecules are also affected and their level are diminished. The protective role of ACE inhibitors is further enhanced by their ability to reduce oxidative stress and preventing apoptosis. The degradation of bradykinin which is responsible for physiological antiapoptotic mechanism and produce the actions opposite to angiotensin II is also prevented by ACE inhibitors. The release of nitric oxide and other mediators of vasodilation by endothelial cell is also stimulated by bradykinin.⁶

The oxidative stress produced by Angiotensin regulated cascade of events results in Inflammation initiation and causes progression of atherosclerosis, nephropathy, and cardiomyopathy. The initiation and preservation of inflammatory diseases is also related

to this mechanism. Consequently, ACE inhibitors by suppressing the influence of angiotensin II will reduce the cardiovascular risks associated with inflammation.

Primary hypertension and ACE inhibitors:

If a person have his systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg and there exist no secondary cause of elevation of pressure, the person is said to have primary hypertension.

Angiotensin converting enzyme (ACE) inhibitors as an effective choice for primary hypertension:

A study accessed fourteen different ACE Inhibitors for their effect on blood pressure. Their dose related effects were analyzed. It included Ninety-two trials with 12,954 participants. The baseline BP of participants were 157/101 mm Hg. When given a dose 50% to that of the original recommended daily dose by manufacturer, the resulting outcome in terms of having the maximum effect on BP lowering was 90%. Which suggest the satisfactory efficacy of ACE inhibitors in lowering BP. There are so many ACE inhibitors available in the market that doctors are uncertain, which is the most effective and should be chosen first.⁷

The study data suggested that different drug of this class do not differ significantly in their blood pressure lowering effects.⁴

Better approach: ACE Inhibitors or ARB'S?

Both drugs are used widely in primary hypertension, but a greater number of high-quality research data supports the use of ACE inhibitors in cardiac dysfunction and stroke to prevent death as compare to angiotensin receptor blockers usage.⁸

Comparison of ACE and ARB'S for Primary Hypertension:

A randomized control trial study was conducted with 11,007 patients. The criteria of inclusion were the presence of primary hypertension irrespective of its

severity whether it is controlled or not and associated with other risk factors or not. The goal of study was to obtain data about cardiovascular disease occurrence and death ratio associated with it.

Data obtained from study suggested that Angiotensin receptor blockers have better tolerability but when compared on the ground of efficacy to reduce mortality risk, ACE inhibitor is superior to angiotensin receptor blocker.⁸

Use of Antihypertensive in cardiovascular comorbidity

The major reason accounting for death globally now a days is related to cardiovascular disorders and almost 30% of overall deaths in world are due to it.⁹ The underlying cause of cardiovascular disease along with some other serious conditions like stroke has long been related to hypertension positively and independently in various prospective cohort studies.^{10,11} These co-morbid conditions including diabetes and cardiovascular disorders need careful selection of medication for ensuring the safety of patient.

Synergistic use of beta blockers and ACE inhibitors:

Perindopril has an adjuvant protective effects on cardiovascular system with beta blockers

The beta blockers and ACE inhibitor combination may provide various benefits such as by using it the weak heart is made active by movement of curve to up and left in Frank-Starling phenomenon. It is achieved by physiological improvement in contractility of heart muscles by positive inotropic effect of beta blocker along with reduction of hypertrophic muscle mass by ACE inhibitors.¹²

Individual data of few trials including EUROPA, ADVANCE and PROGRESS trial was merged for analysis in a cohort study and resulted in overall population of 24,463 high risk cardiovascular patients. The aim of the study was to have a comparison of betablocker with perindopril. Addition of perindopril to beta blocker therapy may reduce the primary endpoint of stroke, non-fatal and fatal myocardial infarction by 20%. A significant decrease

in overall secondary endpoint of cardiovascular death by 27%, overall death by 22% and cases of non-fatal MI by 23% was observed in comparison to placebo. Which further support the use of Perindopril with beta blocker for additional protective benefits for myocardial disease conditions.¹³

The Food and Drug administration of United states has now given the approval for perindopril to be used in stable coronary artery disease due to its risk lowering effects in cardiovascular problems irrespective of revascularization procedures already been applied or not. Various combination use for adjuvant therapy may include lipid lowering agents, antihypertensive medications and platelet lowering therapies.⁶

Significant role of an ACE inhibitor Trandolapril in lowering incidences of mortality after Acute Myocardial Infarction in patients with reduced left ventricular function.

TRACE Study:

In a randomized study, 1749 patients with echocardiographic signs of left ventricular dysfunction were included. They were assigned to oral trandolapril (876 patients) or placebo (873 patients) starting from days three to seven following the infarction with an average follow-up of 27 months.

It is concluded that long-term treatment with trandolapril significantly reduced total mortality in patients with reduced left ventricular function shortly after myocardial infarction.¹⁴

TRACE study also proved an influence of long-term once daily administration of Trandolapril on significant reduction of total and cardiovascular mortality, reduction of sudden death, reduction of severe and resistant congestive heart failure and reduction or relay of reinfarction. A good risk to benefit ratio has been found.¹⁵

Influence of ACE inhibitors on Cardiac myocyte necrosis induced by angiotensin II.

It is reported that myocyte injury might be a process involved in the pathogenesis and progression of the failing heart which is driven by Angiotensin II. A study assessed this possibility by giving non-acute hypertensive doses of Angiotensin II. The cardio toxic effects were examined in 90 rats. Angiotensin II resulted to injure myocytes. Later, the influence of an ACE inhibitor Captopril on the myocyte injury was investigated and it occurred that this injury is prevented with captopril (65 mg/day p.o.).¹⁶

Effectiveness of Zofenopril in reducing Anterior Myocardial Infarction related risk of mortality and morbidity

Acute anterior myocardial infarction may lead to stimulation of some neuroendocrine functions and may also cause dilatation of left ventricles and finally results in heart failure. Interventions which can prevent the stimulation of neurohormonal system can prevent the prognosis towards heart failure.¹⁷

Treatment with ACE inhibitors for long period of time can prevent these destructing mechanisms which are responsible for necrosis of myocardial cell.

Various studies have been conducted to evaluate short term and long-term benefits obtained from ACE inhibitors. A double blind study which included about 1556 Patient who have recently undergone acute anterior myocardial infarction within the last 24 hours period was conducted. Placebo and Zofenopril were randomly assigned to 784 and 772 patients respectively for six weeks. Reinvestigation to evaluate year survival was performed and any occurrence of congestive heart failure and death was also recorded.

After six weeks of treatment, less incidences of death and heart failure were found in zofenopril group on contrary to placebo group. The overall risk of mortality and severe congestive heart failure was decreased by 34 percent with 46 percent reduction in occurrence of congestive heart failure and 25 percent reduction in manifestation of death. After one year there was a significant lessening of about 29 people in the risk of mortality in patients treated with zofenopril and resulted in both short- and long-term benefits.

The effectiveness of ACE inhibitor is not only associated with remodeling of ventricles but also from its primary protective effect on cardiac cells

along with its ability to inhibit the activation of neurohormonal mechanisms.

In patient who are at high risk and are suffering from large anterior infarction of myocardium, the prompt administration of ACE inhibitors is well thought-out as a sensible approach.¹⁸

The era of early 90 was revolutionary in terms of cardiovascular therapy as the efficacy and safety of ACE inhibitors was established via various randomized controlled trial especially in case of heart failure with left ventricular systolic dysfunction.¹⁹ Clinical trials such as SAVE, SOLVD, AIRE and TRACE indicated that ACE inhibitors increases life expectancy in those suffering from left ventricular dysfunction and hence ACE-inhibitors soon became the keystone of treatment for left ventricular dysfunction.²⁰⁻²³

Several trials assessed substantial and unpredicted benefit of fewer myocardial infarction incidences in patients' group receiving the treatment with ACE-inhibitors.²⁴⁻²⁵

Clearly, the next logical step was to assess the efficiency of ACE-inhibitors in vascular disease patients, but with no history of left ventricular dysfunction and heart failure. There exists good evidence that suggest that ACE inhibitors can be used effectively in stable ischemic heart disease with ventricular function preserved.²⁶

The success of treatment with Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers in adults was assessed in a systematic review. Which comprised the focus on standard medication and treatment to patients who have preserved ventricular function with stable Ischemic heart disease. The queries evaluated in such patients included:

1. Evaluation of positive and negative aspects resulting from addition of ACE inhibitors or Angiotensin receptor blocker to standard medical therapy such as β -blockers, statins, and aspirin compared with standard medication therapy alone
2. Advantages and disadvantages obtained with combination therapy of ACE inhibitors and Angiotensin receptor blockers in contrast to monotherapy of any of these two.

41 studies with moderate to high-strength evidence were included. Results obtained from these data lead the researchers to conclude the supremacy of ACE inhibitors in fading the overall chances of

mortality and cardiac dysfunction. The addition of ACE inhibitors to standard therapy also enhanced the clinical outcome while the monotherapy with ACE inhibitors was associated with reduced risks and harms as compared to the combination therapy of ACE inhibitors and Angiotensin receptor blockers. Evidence about effects of ARBs alone was limited.²⁷

EUROPA study to illuminate the role of Perindopril in plummeting the cardiovascular problems associated with stable coronary artery disease

In a placebo controlled trial with randomized double blinds approach, a total of 12,218 patients were selected for study and Perindopril in a once daily dose of 8 mg was given to 6110 patients and other 6108 patients were given placebo. Where cardiovascular death and myocardial infarction considered as primary endpoint.

According to results there was a 20% reduction in risk of primary endpoint with perindopril as compared to placebo improving the clinical consequences and endorsing that ACE inhibitors are well tolerated.

It was suggested that perindopril can be considered as a preferred choice in coronary heart problems along with other preventive medications. In addition, ACE inhibitor is also effective in stable coronary diseases where symptoms of heart failures are minimal.²⁸ Figure 1 illustrate the outcome of ACE inhibitors on cardiovascular events.

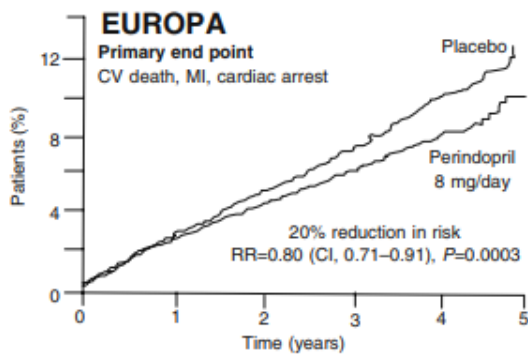


Figure I Europa study

Significance of ramipril in high risk patients having lowered ejection fraction to reduce the chances of

stroke, mortality and myocardial infarction

Left ventricular dysfunction can thought to be improved by angiotensin converting enzyme inhibitor for so long irrespective of heart failure. To further assess the efficacy of angiotensin converting enzyme inhibitors in high risk patient but having their ventricular functions preserved, a study conducted on high risk elderly patients having age 55 or greater. Total of 9297 patients selected based on the criteria of inclusion that was the presence of diabetes or vascular disease along with other condition that may pose risk to cardiovascular functions but having the normal ejection fraction.

10 mg once daily dose of test drug and placebo was given for a period of five years. Myocardial infarction related death and stroke were set as a prime endpoint of study. The results show a reduction in death rate in ramipril treated group.²⁹ The reduction rate for death in indifferent condition was as follows; see Table 1 and Figure II.

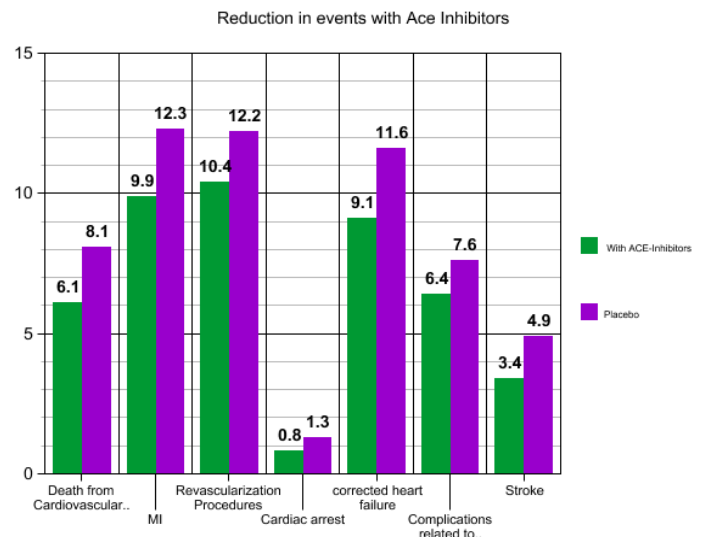


Figure II

Table 1: Adverse events

Condition	Ramipril Group %	Placebo Group %
Cardiovascular problem	6.1	8.1
Myocardial Infarction	9.9	12.3
Stroke	3.4	4.9
Revascularization methods	16.3	18.8
Cardiac arrest	0.8	1.3
Corrected Heart Failure	9.1	11.6
Complications related to diabetes	6.4	7.6
Other cause	10.4	12.2

Zofenopril efficacy in patients having ischemia related to myocardial condition post infarction but having proper functioning of left ventricle

Long-term Evaluation (SMILE)-ISCHEMIA study:

The study was designed to evaluate the effects of Zofenopril which is an angiotensin converting enzyme inhibitor in the survival and protection of cardiac functions in patients who have previously experienced infarction but their left ventricles have preserved function.

For the purpose double blind randomized study was designed with 49 patient who previously had myocardial infarction however the ejection fraction of left ventricles was greater than 40%. The patients were divided into two groups having 177 patients in test group (given zofenopril 30-60 mg) and 172 patients in control group (given placebo).

Various criteria were defined for the evaluation of primary end point which included any changes in normal pattern of electrocardiogram or a variation in ST-T in ambulatory electrocardiogram, reoccurrence of myocardial infarction, failed exercise test and requirement of revascularization for angina. SMILE-ISCHEMIA study was helpful to pronounce the cardioprotective role of zofenopril in post MI patients with preserved ventricular functions which was shown by relatively greater occurrence of primary endpoint events in placebo group (~20.3%) as compared to zofenopril group (~35.9%) with $P=0.001$ and there was no alteration observed in function of left ventricle, blood pressure and associated therapies. It was found that there is a decreased rate of progression towards congestive heart diseases and an over all reduction in cardiac events with the use of ACE inhibitor zofenopril.³⁰

Time of Initiation of Therapy:

A systematic overview was performed evaluating questions related to initiation time, the time in which effects become evident, and assessing risk to benefit ratios of therapy in patients. Extensive data of 1000 patients were pooled for overviewing the individual data obtained from randomized trials conducted on MI patients. In all these patients the treatment with ACE inhibitors was initiated ed

acutely within 0 hours to 36 hours and was sustained for almost 4-6 weeks. After comparing the result of 4 trials in which around 98946 patients were included overall, it was concluded that ACE inhibitors are a preferred choice in early management of myocardial infarction in majority of patients. It is also beneficial in those patients who are at increased risk of death due to myocardial abnormality.

Beneficial effects of ACE inhibitors are usually achieved during the early first week of initiation of therapy and can prevent death in 5 people out of each thousand.³¹

Diabetes Mellitus, Cardiovascular Events and Efficacy of ACE-Inhibitors:

The prevalence of Diabetes mellitus (DM) is increasing worldwide. It is estimated that around 6.6% population of adults is affected by this disease globally.

It is predicted that by the year 2030, the worldwide population of people affected by diabetes mellitus will reach to 350 million.^{32,33}

A significant major risk of cardiovascular disease onset is Type 2 Diabetes mellitus. A huge number of around 70% of diabetic patients are hypertensive and the primary reason of death in patients suffering from diabetes mellitus is associated with cardiac problems which makes it necessary to control the blood pressure of diabetic hypertensive patients to a target point of less than 130/80 mm of Hg

Diabetes mellitus is itself a leading risk factor contributing to the worsening of various cardiovascular condition and giving rise to macrovascular hitches and complications. The severity of the disease can be further estimated by 6.8% global percentage of mortality in adults having diabetes mellitus with concomitant heart problem or stroke. So, it is considered as one of the major factors causing premature deaths.³⁴

It increases the death rate resulting from cardiac abnormalities 2- to 4-fold higher in comparison to the patients who do not have diabetes.^{35,36}

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are recommended to be included in all the treatment regimens of diabetic

hypertensive patients as suggested by the American Diabetic Association.³⁷

Angiotensin converting enzyme inhibitors limits the risks of mortality and morbidity in diabetic population. A number of trials were considered essential for the study which included 13 trial conducted on 23,867 patients focused on comparison of angiotensin receptor blocker with absence of therapy and 23 trials conducted on 32,827 patients for the comparison of Angiotensin Converting Enzyme with placebo or active drugs

An overall risk reduction in cardiac mortality along with all-cause mortality and decrease in occurrence of cardiac events in diabetic patients was observed in patients treated with Angiotensin converting Enzyme inhibitors while none of such benefits was observed in patients who were given angiotensin receptor blocker. Which further illuminate the significance of ACE inhibitors as a first line agents in reducing the mortality and morbidity risk in such patients.³⁸ Risk of cardiovascular complications may increase abruptly in aged population. It is suggested in recent guidelines that aggressive therapies must be considered for reducing cardiovascular risk in elderly population.³⁹

Another trial named Heart Outcomes Prevention Evaluation (HOPE) investigated ramipril which is an ACE inhibitor having high affinity for tissues. It was a randomized trial of 9297 patients who had diabetes along with stable coronary disease or they are in high risk group. The result of trial showed reduced number of cardiovascular events in such patients.

A post-hoc analysis on long term Effect of ACE-inhibitor in elderly patient with vascular complications

HOPE study conducted on elderly patients includes patients having age 70 or above with diabetes or vascular problems along with any other cardiovascular issue whereas there was no history of lowered ejection fraction or cardiac failure. Effect of Ramipril was investigated on this subgroup by the help of post hoc trial. 2755 patients were selected for the study and were administered 10 mg of placebo or ramipril. After a well-tolerated treatment, it was found that ramipril group showed lesser complication related to vessel as compared to placebo group.

A treatment with given regimen for 4.5 years reduces major events related to cardiovascular health. Proportional reduction of 31% in stroke cases, 25% in events of myocardial infarction and vascular complications each, 25% in deaths of cardiac origin and 18% in all cause death was detected. Therefore, ACE inhibitors can also be used as a first line treatment in elderly for prevention of secondary complications.⁴⁰

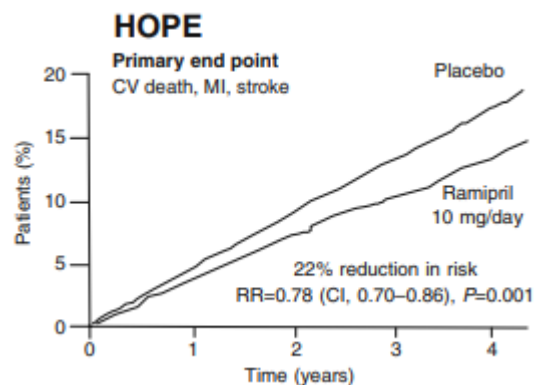


Figure III

FDA approved Indications of ACE inhibitors:

- Heart failure can be prevented by the use of Angiotensin Converting Enzyme inhibitors in patient who have previous history of myocardial infarction or those having their ejection fraction reduced. It is also a recommended choice for treating systolic heart failure as an adjuvant.
- Angiotensin Converting Enzyme inhibitors are also preferred in majority of the cases of hypertension whether as a monotherapy or a combination therapy with other medicine having antihypertensive action.
- Guidelines for Hypertension recommends ACE inhibitors for the management of HTN to decrease blood pressure (BP) in the subsequent patients including
 - a. To achieve the treatment goal of achieving systolic blood pressure lower than 140 mm Hg and diastolic blood pressure of 90 mm Hg in hypertensive patient who are younger than 60 years of age.
 - b. In Diabetic hypertensive patient who are 18 years old or elder than that to achieve the similar therapeutic goal as discussed above.
 - c. In Patients suffering from chronic kidney disease who are 18 years old or elder than that to achieve similar therapeutic goal.

- d. ACE inhibitors are considered as first line therapy for initiating the treatment and obtaining the beneficial outcomes on kidney regardless of the race and presence or absence of diabetes
- e. In patients having chronic stable angina and hypertension, Angiotensin Converting Enzyme inhibitors are considered as a part of regimen specifically if there is previous history of diabetes, left ventricular dysfunction and chronic kidney disease.
- f. ACE inhibitors are also preferred and should be use within 24 hours in myocardial infarction in which ST segment is not elevated when Electrocardiogram is recorded. In addition, Heart failure, acute myocardial infarction and low ventricular ejection fraction i.e. 40 % or less may also be treated by ACE inhibitors.⁴¹

METHOD:

Articles related to the influence of ACE inhibitors in reducing CV risks, morbidity and mortality were searched on Cochrane library, PubMed and Elsevier. The related articles which showed effectiveness of ACE inhibitors were included.

CONCLUSION:

Angiotensin-converting-enzyme inhibitors are known to expand the upshots in Primary Hypertension. The clinical evidences support the use of ACE inhibitors to diminish the risk of mortality and morbidity associated with cardiovascular dysfunctions and suggests that the treatment with Anti-Hypertensive medication reduces cardiovascular disease risk in hypertensive patients even when they fall in the normal ranges. The goal of treatment in the cardiovascular disease is to make the debilitating heart better and efficient. The cardiac hypertrophy significantly makes the heart weak which can be countered pharmacologically by using ACE Inhibitors. Evidence supports that the addition of an ACE inhibitor with beta blockers therapy may improve symptoms associated with cardiovascular diseases. Clinical study also proved an influence of long-term once daily administration of ACE inhibitors on significant reduction of total and cardiovascular mortality, decrease the risk of unexpected death, severe and resistant Congestive Heart disease and reduction or delay of reinfarction. Evidence also proposed that ACE inhibitors can be effectively used to treat the condition of stable ischemia and related heart problems specifically if the ventricular function is preserved. The beneficial effects are achieved by remodeling of ventricles along with other protective

functions performed by ACE inhibitors by blocking the stimulation of neurohormonal mediators and preventing its troublesome consequences and imposing the defensive role on heart.

High amount of qualitative as well as quantitative data supports the use of ACE inhibitors in cardiac ailments and stroke to prevent death. The practice of ACE inhibitors in patients with cardiovascular risks is supposedly the logical step to take.

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