Review Article

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Pleiotropic benefits and utility of angiotensin converting enzyme inhibitors in current practice

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ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) is responsible for maintaining hemodynamic stability and thereby impacts multiple organ systems, such as the central nervous system, heart, and kidneys. Angiotensin II (ang II) is the main effector of the RAAS. However, overactivity of the RAAS can give rise to cardiovascular disorders, stroke, and nephrosclerosis. Unfavorable effects on cardiovascular system are attributed to ang II. RAAS activation also results in release and increased activity of several hormonal and inflammatory mediators, trigger formation of a number of secondary messengers and/or activate pathways, which negatively affects blood vessels and tissue. RAAS inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers can protect various organs from damage by blocking the protean manifestation of RAAS activity, either in its circulating or its locally tissue-active form. This review explains on the pleiotropic effects and benefits that go beyond mere blood pressure control. ACEIs in terms of mortality reduction, long-term survival benefits, cardioprotective and vasculo-protective effects as well as improve fibrinolytic balance. Ramipril has been clinically proven to reduce rates of mortality, myocardial infarction, and stroke. ACEIs and ARBs were associated with lesser risks of COVID-19 infection.

Keywords: ACE inhibitors, Renin-angiotensin system, Pleiotropic benefits, COVID-19

INTRODUCTION

Overview of the RAAS system

The RAAS plays a major role in maintaining hemodynamic stability by regulating extracellular fluid volume, sodium balance, and exerting cardiac and vascular trophic effects. Studies have pointed out that the RAAS exerts its effects on multiple organ systems, including the central nervous system, heart, and the kidneys. ²

However, overactivity of the RAAS can lead to atherosclerosis, hypertension, left ventricular hypertrophy, and cardiovascular events, such as

myocardial infarction, stroke, congestive heart failure, and nephrosclerosis.¹ Pathophysiologic effects on cardiovascular system is attributed to angiotensin II (ang II), the main effector of the RAAS, which can cause vasoconstriction, thrombogenicity, increased production of reactive oxygen species (ROS), vascular smooth muscle growth, myocyte hypertrophy, fibrosis, and maladaptive remodeling of tissues. In addition, reninangiotensin-aldosterone system activation initiates release and increased activity of a number of hormonal and inflammatory mediators, and cytokines. Primary reninangiotensin-aldosterone system activation will also trigger formation of a number of secondary messengers and/or activate pathways, which contribute to its untoward vascular/tissue effects.³

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Clinical trials have demonstrated that renin-angiotensinaldosterone system inhibition by suppression of angiotensin converting enzyme (ACE), angiotensin type 1 (AT1) receptor blockade or aldosterone receptor blockade can mitigate cardiovascular diseases. Thus, blockade of RAAS is now an evidence-based strategy with a view to protect cardiovascular, cerebrovascular, and renal systems.

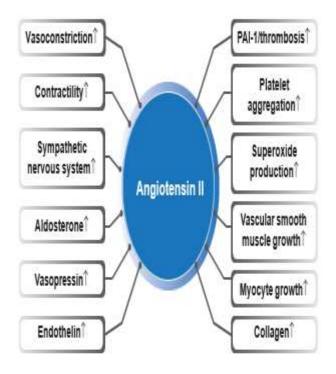


Figure 1: Pathophysiological effects of angiotensin II via angiotensin II type 1 (AT1)-receptor stimulation.²³

FOCUS ON THE PLEIOTROPIC EFFECTS OF RAAS INHIBITORS

Plausible benefits to patients over and beyond blood pressure control

While optimum blood pressure (BP) for preventing cardiovascular (CV) events is currently under discussion, the ability of certain antihypertensive medications to provide a CV and/or renal benefit independent of their BP-lowering effects, appearing as pleiotropic effect, is an area gathering interest.³ Evidence from small studies and preclinical data have pointed out the possibility of specific benefits that go beyond mere blood pressure control with drug classes such as ACE inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers.³

These drugs have the capacity to block the protean manifestation of RAAS activity, either in its circulating or its locally tissue-active form.³ This leads to blocking pathologic effects of the renin-angiotensin-aldosterone system at several points reducing target-organ damage of

the cardiovascular, cerebrovascular, and the renal systems.¹

Pleiotropic effects of ace inhibitors

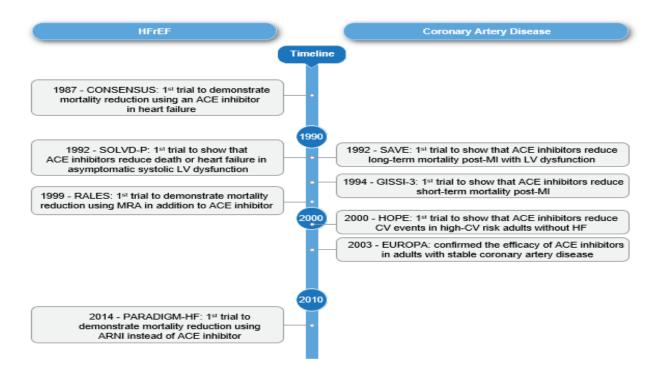
ACEIs in post-MI heart failure

Angiotensin-converting enzyme inhibitors must be administered to patients with impaired ejection fractions (≤40%) or those who have experienced heart failure (HF) in the early phase of myocardial infarction (MI). Medical therapy for HF after MI includes early (within 24 h) initiation of ACE inhibitors. A systematic overview of 4 trials studying early initiation of ACEIs (0 to 36 h) in STEMI involving>98,000 patients, showed a 7% relative reduction in 30-day mortality vs. placebo. The absolute benefit was particularly greater in high-risk groups (such as Killip class II/III, heart rate >100 beats/min at entry) and anterior MI. More notable was that 40% of the survival benefit occurred on the first day of treatment. This study highlighted the importance of initiating ACEIs early, among patients having adequate blood pressure.4 The ACC/AHA guidelines recommend, based on evidence from post-infarction trials and randomized trials, as a class I, Level of Evidence: A, recommendation: "An ACE inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or EF < 0.40%, unless contraindicated."4

ARB MI paradox

There are contradictory results showing increased risk of MI with ARBs. Clinical evidences from various trials have pointed out that unlike ACEIs, angiotensin receptor blockers are either neutral or increase the rates of myocardial infarction despite their beneficial effects on reducing blood pressure.⁵ In the VALUE trial, valsartan produced a statistically significant 19% relative increase in the prespecified secondary end point of MI (fatal and non-fatal) compared with amlodipine. Similarly, the CHARM-alternative trial showed a significant 36% increase in MI with candesartan (versus placebo) despite a reduction in blood pressure.⁵ As opposed to these results. McDonald et al conducted systematic review of controlled trials of ARBs and pointed out that treatment with ARBs was not associated with significantly increased risk of myocardial infarction.⁶ A meta-analysis performed by Volpe et al showed that the risk of MI is comparable with use of angiotensin receptor blockers and other antihypertensive drugs in a wide range of clinical conditions such as hypertension, high cardiovascular risk, stroke, coronary disease, renal disease and the heart failure.7

These peculiar effects of ARBs on myocardial infarction are completely contradictory to those of ACEIs, which consistently produce a≥20% reduction in MI in patients with diabetes, hypertension, renal insufficiency, and atherosclerosis.⁵



RAAS: Renin-angiotensin-aldosterone system; ACE: Angiotensin converting enzyme; HFrEF: Heart failure with reduced ejection fraction; CAD: Coronary artery disease

Figure 2: Landmark trials involving RAAS/ACE inhibitors in HFrEF and CAD.

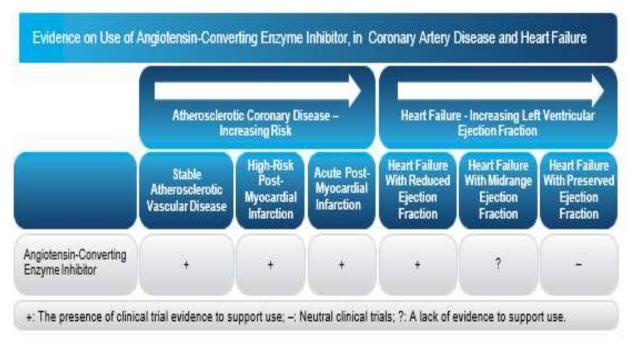


Figure 3: Evidence to support the use of ACE inhibitor in coronary artery disease and heart failure.²⁴

ACEIs in post MI

Early ACE inhibitor therapy post MI offers mortality benefits. A systematic overview of individual data from 1,00,000 patients in randomized trials aimed to study effect of ACE-inhibitor therapy on cumulative mortality during days 0 to 30 in 4 trials combined. The results showed a 7% proportional reduction in mortality with ACE inhibitors within 30 days of acute MI. In addition, ACE Inhibitors provided average absolute benefit of nearly 5 lives saved per 1000 patients treated.⁸ De Kam et al reported that long term therapy had better survival benefit compared to short term therapy. Four studies

(Survival and ventricular enlargement [SAVE], acute infarction ramipril efficacy [AIRE], TRandolapril cardiac evaluation [TRACE] and survival of myocardial infarction long-term evaluation [SMILE]) included patients with LV dysfunction or anterior MI allocated to ACE-I or placebo, with a treatment duration of 1.5 to 48 months. These studies showed that, after MI, a yearly mortality reduction of about 5% was achieved by administration of ACEIs.⁹

Comparison of CV and all-cause mortality between ACEIs and ARBs

Choi et al performed data analysis from Korea acute myocardial infarction registry-national institutes of health registry which included patients with acute MI (AMI). The RAAS inhibitors, ACEIs and ARBs, were administered and patients were assessed at 12 months and followed up at 6, 12, 24 and 36 months. The CV mortality with ACEIs was 1.9% while it was 3.5% with ARBs. Similarly, all-cause mortality with ACEIs was 2.9% while with ARBs was 5.7%. It was observed that ACEI therapy was associated with lower hazard ratios for 1-year CV and total mortality rates, whereas ARB therapy was not. The authors concluded that ACEI therapy in patients with AMI was associated with better long-term survival benefits than ARB therapy.9 Lv et al reported that treatment with ACEI resulted in notably reduced while ARBs showed no decrease for all the 3 conditions. Hence, ACEIs are more preferred over ARBs for hypertensive patients with T2DM.¹⁰

ACEIs in reducing risk of atherosclerotic cardiovascular disease

Observations from studies indicate that ACE inhibitors reduce the risk associated with atherosclerotic cardiovascular disease probably by blocking both circulating and tissue renin-angiotensin systems. These can be classified into "cardioprotective" effects, which includes the benefits in overall cardiac hemodynamics, energetics, electrical stability, and the reduction in left ventricular mass, and "vasculoprotective" effects, which encompasses direct antiproliferative effects, possible antiatherogenic properties, favorable effects on thrombotic mechanisms and on arterial compliance and tone. 11

Cardioprotective effects of ACEIs

These effects include restoring the balance between myocardial oxygen supply and demand, reduction in LV preload and afterload, LV mass and in sympathetic stimulation. ¹² Cardioprotective effect is exerted through attenuation of LV dilatation and, in combination with the reduction of the preload and afterload, treatment with ACEIs results in a reduction in wall stress and in oxygen demand. In turn, oxygen supply increases due to vasodilatation caused by reduction of ang II levels. Other than the restoration of the balance between oxygen

supply and demand, ACEIs have consistently reduced LV mass in hypertensive patients, which is linked to the inhibition of both ang II and aldosterone. Also, ACEIs attenuate neurohormonal activation by inhibition of ang II and reduction of sympathetic activity. ACEIs also reduce ventricular remodeling and infarct size, reperfusion injury, reperfusion arrhythmias and other ventricular arrhythmias thereby contributing to cardioprotective effect.⁹

Vasculoprotective effects of ACE inhibitors

The vasculoprotective effects of ACEIs together prevent atherosclerosis from progressing. ACEIs improve endothelial dysfunction caused by ang II and increase the nitric oxide concentration also through a possible antioxidant effect. Several experimental studies indicate that these vasculoprotective properties of ACEIs may be explained by reduction of ang II levels and the breakdown of bradykinin, which induces vascular dilatation, inhibits attraction, adhesion and activation of leucocytes and growth of vascular smooth muscle cells and promotes thrombolysis.⁹

ACE inhibition and fibrinolysis

Fibrinolytic activity is primarily governed by the balance between the levels of tissue plasminogen activator (t-PA) and plasminogen activator inhibitor type 1 (PAI-1). Impaired fibrinolytic function, characterized by increased PAI-1 level and decreased t-PA activity, has been found in patients with hypertension. The t-PA antigen concentration reflects both active t-PA and inactive t-PA complexed with PAI-1. The t-PA antigen concentration is determined in part by increased PAI-1 level. Free and unbound t-PA is physiologically active and leads to endogenous fibrinolysis. ¹²

Previous comparative studies have shown that ACEI and ARB differ in their effects on fibrinolysis. ACEI have generally been shown to improve the fibrinolytic balance by reducing plasma PAI-1 level, and ARB seem to be neutral in their effect (Figure 1). The positive effect of ACEI on the fibrinolytic system is related to: 1) a decrease in the release of angiotensin II-mediated PAI-1, 2) an increase in the release of bradykinin-induced t-PA and 3) improvement of insulin sensitivity.

Fogari et al compared the effects of 12-week treatment with the ACE-I imidapril and the ARB candesartan on plasma PAI-1 antigen and its activity, and on plasma t-PA activity in hypertensive patients with normal weight. In this study, despite similar blood pressure reduction, imidapril but not candesartan, improved the fibrinolytic balance, possibly through bradykinin-mediated effects on insulin sensitivity and endothelial function. It has been previously reported that intracoronary infusion of bradykinin stimulates the release of t-PA from the coronary vasculature in patients with hypertension, and this effect is potentiated by chronic ACE inhibition. Such

effects are not seen with ARB. In addition, chronic inhibition of ACE has been shown to increase endogenous coronary release of t-PA without affecting PAI-1 level in hypertensive patients. It has been suggested that ACE inhibition may have a more favorable effect on t-PA production beyond blood pressure-lowering effects. ¹³

UNRAVELLING THE UTILITY OF RAMIPRIL IN CURRENT ERA

Ramipril, an ACE inhibitor, is a prodrug which is rapidly hydrolyzed after absorption to the active metabolite ramiprilat. It acts upon the RAAS to decrease vasopressor activity, aldosterone secretion, and bradykinin degradation. It is generally well tolerated and effective in the treatment of patients aged \geq 55 years at high risk for the development of CV events, in whom the risk of MI, stroke, and CV death can be significantly reduced. I4

Excerpts from clinical trials with ramipril

The AIRE study investigated the effect of therapy with ramipril 2.5 mg/day up titrated to 5 mg/day in 1004 patients admitted to ICU with AMI while 982 patients received placebo for 10 days. They were followed up to 30 months. Primary outcome was all-cause mortality. Ramipril significantly reduced the risk of all-cause mortality by 27% in patients with clinical evidence of HF after acute MI. Risk reduction was apparent by 1 month. Mortality curves continued to diverge throughout the study. Also, consistent benefit was observed with ramipril over a wide range of subgroups. Subgroup analysis of prespecified secondary outcomes revealed a risk reduction of 19% for the first validated outcome (i.e., first event in an individual patient) namely, death, severe/resistant heart failure, myocardial infarction, or stroke (p=0.008). 15

The AIRE extension (AIREX) study assessed the longterm (5-year) robustness of the survival benefit observed with ramipril in the AIRE study. Follow-up was for a minimum of 42 months and a mean of 59 months. The average duration of treatment with masked trial medication was 13.4 months for placebo and 12.4 months for ramipril. The findings revealed that death from all causes had occurred in 38.9% of patients in placebo group and 27.5% patients randomly assigned ramipril, representing a relative risk reduction of 36% (p=0.002) and an absolute reduction in mortality of 11.4% (114 additional 5-year survivors per 1000 patients treated for an average of 12.4 months). The extension study provided robust evidence that administration of ramipril to patients with clinically defined heart failure after AMI results in a survival benefit that is not only large in magnitude, but also sustained over many years. 16

The heart outcomes prevention evaluation (HOPE) study was a multicenter, double-blind, randomized, placebo-

controlled trial. A total of 9297 high-risk patients (aged ≥55 years) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive ramipril (10 mg once daily orally) or matching placebo for a mean of 5 years. The primary outcome was a composite of MI, stroke, or death from cardiovascular causes. Treatment with ramipril reduced the rates of death from cardiovascular causes (6.1%, as compared with 8.1% in the placebo group; p<0.001), myocardial infarction (9.9% vs. 12.3%; p<0.001), stroke (3.4% vs. 4.9%; p<0.001), death from any cause (10.4% vs. 12.2%; p=0.005), revascularization procedures (16.0% vs. 18.3%; p=0.002), cardiac arrest (0.8% vs. 1.3%; p=0.03), heart failure (9.0% vs. 11.5%; p<0.001), and complications related to diabetes (6.4% vs. 7.6%; p=0.03). Thus, ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.¹⁷

A sub-study of the HOPE trial assessed the effects of ramipril on left ventricular mass (LVM) and function in vascular disease patients with controlled blood pressure (BP) and with preserved left ventricular ejection fraction (LVEF). The effects of two doses of ramipril (10 mg/day and 2.5 mg/day) versus placebo in 506 patients with vascular disease on echocardiographic measures of LVM and LV function were studied. Baseline BP and LVEF were similar, 131/76 mm Hg and 58%, in all treatment groups. After a period of 4 years, LVM index increased by $3.98\pm2.08 \text{ g/m}^2$ in the placebo and by $4.16\pm1.86 \text{ g/m}^2$ in the ramipril 2.5 mg/day groups and decreased by 2.02 ± 2.25 g/m² in the ramipril 10 mg/day group (p=0.02). The changes in LV end-diastolic and end-systolic volumes were 4.16±2.55 ml and 5.31±1.67 ml in the placebo, -0.43±2.75 ml and 2.90±1.45 ml in the ramipril 2.5 mg/day, and-5.90±2.93 ml and -1.90±1.55 ml in the ramipril 10 mg/day groups (p=0.02 and p=0.001). The changes in LVEF were -2.02±0.72%, -1.54±0.74%, and -0.17±0.72%, respectively (p=0.01). Thus, ramipril showed beneficial effects on LV structure and function in vascular patients with controlled BP and with preserved LVEF.18

Comparison of ramipril over ACEIs

Ramipril has been compared with other ACEIs for mortality, morbidity and survival rates among patients with MI. Wienbergen et al examined the impact of treatment with ramipril vs. ACE inhibitors on clinical outcome in unselected patients of the prospective multicenter registry maximal individual therapy of acute myocardial infarction PLUS registry (MITRA PLUS). Of 14,608 consecutive patients with ST-elevation acute MI, 4.7% received acute therapy with ramipril, 39.0% received other ACE inhibitor therapy, and 56.3% received no ACE inhibitor therapy. Observation included reduction of "in hospital" mortality. Compared with other

generic ACE inhibitors, ramipril therapy was independently associated with a significantly lower hospital mortality (odds ratio [OR] 0.54, 95% confidence interval [CI] 0.32 to 0.90) and a lower rate of nonfatal major adverse coronary and cerebrovascular events (OR 0.65, 95% CI 0.46 to 0.93). 19

Pilote et al reported that among patients aged ≥65 years who were admitted for an acute myocardial infarction, enalapril, fosinopril, captopril, quinapril, and lisinopril were associated with higher mortality than was ramipril. They concluded that survival benefits in the first year after acute MI in patients aged ≥65 years seem to differ according to the specific ACE inhibitor prescribed. Ramipril was associated with lower mortality than most other ACE inhibitors.²⁰

Favorable effects of ramipril on fibrinolytic system

Wagner et al conducted a placebo-controlled, doubleblinded, randomized study to evaluate the effect of ramipril prior to thrombolysis on the course of PAI-1 plasma levels and on the frequency of post-infarct ischemic events in patients with acute MI. Patients were randomly assigned to receive either 2.5 mg ramipril (Tritace; Fa. Aventis) orally or placebo prior to thrombolysis. Patients received their second study medication (ramipril 2.5 mg or placebo) 12 hours after inclusion to the study protocol. On admission, PAI-1 plasma levels were similar in both groups (ramipril: 47.1 [4.8] ng/ml; placebo: 49.1 [4.8] ng/ml). The PAI-1AUC was 77.2 [6.7] ng/ml/h in the ramipril group and 95.4 [6.2] ng/ml/h in the placebo group (p value of=0.013). Significant differences between groups were observed at 4, 8 and 12 hours after thrombolysis (4 hours: 85.5 (11.3) versus 116 (12.3) ng/ml, p value of<0.01; 8 hours: 79.1 (11.2) versus 100.9 (9.3) ng/ml, p value of<0.01; 12 hours: 71.3 (9.5) versus 87.4 (7.7) ng/ml, p value of<0.05). The relative frequency of postinfarct ischemic events was significantly lower in the ramipril group (2.5% versus 7.1%, p value of=0.001). Additionally, a significant higher rate of TIMI grade 2 and 3 of the infarct-related artery in patients receiving oral ramipril compared to the placebo group (73% versus 54%; p value of=0.035) was observed. The study demonstrated a favorable effect of ramipril on the fibrinolytic system after thrombolysis associated with a lower rate of postinfarct ischemic events within the first days after myocardial infarction. Therefore, the application of ramipril prior to thrombolysis appears to be a reasonable concomitant treatment which may reduce early infarctrelated complications.²¹

UTILITY OF ACE INHIBITORS IN THE COVID PANDEMIC

The increased mortality and morbidity of COVID-19 in patients with hypertension is an association that has been noted in initial epidemiological studies outlining the characteristics of the COVID-19 epidemic in China. Wu

et al found hypertension to have a hazard ratio of 1.70 for death and 1.82 for acute respiratory distress syndrome in 201 patients with COVID-19. There has been a growing concern that this association with hypertension is confounded by treatment with specific antihypertensive medications, namely ACEIs and ARBs. The link with ACEIs and ARBs is due to the known association between angiotensin-converting enzyme 2 (ACE2) and SARS-CoV-2. ACE2 has been shown to be a co-receptor for viral entry for SARS-CoV-2 with increasing evidence that it has a protracted role in the pathogenesis of COVID-19.²²

The concern that ACEIs and ARBs affect the severity and mortality of COVID-19 is 2-fold. One suggestion is that ACEIs could directly inhibit ACE2; however, ACE2 functions as a carboxypeptidase and is not inhibited by clinically prescribed ACEIs. There is also another concern that the use of ACEIs and ARBs will increase expression of ACE2 and increase patient susceptibility to viral host cell entry and propagation. Despite the lack of evidence, there have been advocates for both the use and cessation of ACEIs, ARBs, or both during the treatment for COVID-19 in patients with hypertension.²²

In light of such uncertainties, Hippisley-Cox et al conducted a prospective cohort study using routinely collected data from 1205 general practices in England with 8.28 million participants aged 20-99 years. They assessed whether patients prescribed ACEIs and ARBs had altered risks of contracting severe COVID-19 disease and receiving associated intensive care unit (ICU) admission. The primary outcomes were: (a) COVID-19 RT-PCR diagnosed disease and (b) COVID-19 disease resulting in ICU care. Of the 19,486 patients who had COVID-19 disease, 1286 received ICU care. ACE inhibitors were associated with a significantly reduced risk of COVID-19 disease (adjusted HR 0.71, 95%CI 0.67 to 0.74) but no increased risk of ICU care (adjusted HR 0.89, 95%CI 0.75 to 1.06) after adjusting for a wide range of confounders. Adjusted HRs for ARBs were 0.63 (95% CI 0.59 to 0.67) for COVID-19 disease and 1.02 (95% CI 0.83 to 1.25) for ICU care. It was concluded that ACE inhibitors and ARBs are associated with reduced risks of COVID-19 disease after adjusting for a wide range of variables. Neither ACE inhibitors nor ARBs are associated with significantly increased risks of receiving ICU care.²³

CONCLUSION

RAAS inhibitors have the capacity to block the protean manifestation of RAAS activity, either in its circulating or its locally tissue-active form, thereby preventing pathologic effects of the RAAS at several points reducing target-organ damage of the cardiovascular, cerebrovascular, and renal systems. This contributes to their pleiotropic effects. ACEIs have demonstrated cardioprotective and vasculoprotective effects as well as reduction in risk of MI as well as occurrence of all-cause

mortality, CV death, and major CV events including stroke and HF. Ramipril provides survival benefit which is sustained for many years, reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure and associated with lower mortality than most other ACE inhibitors ACE inhibitors and ARBs were associated with reduced risks of COVID-19 disease and did not increase risk of receiving ICU care.

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