

## A REVIEW ON IMPORTANCE OF ACE INHIBITORS IN CLINICAL PRACTICE

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### Abstract

Angiotensin converting enzyme inhibitors not only have become the cornerstone of the treatment of heart failure, but increasingly also play a major role in hypertension and in cardiovascular protection. The role of renin-angiotensin-aldosterone system in cardiovascular pathology, with excess activities of angiotensin II and of aldosterone contributing to major adverse maladaptive roles. Angiotensin converting enzyme inhibitors act on crucial enzyme that generate angiotensin II and mediates the breakdown of bradykinin. Angiotensin converting enzyme inhibitors give both primary and secondary protection from cardiovascular diseases.

**Keywords:** Angiotensin converting enzyme inhibitors, heart failure, hypertension, cardiovascular protection and renin-angiotensin-aldosterone system.

### Introduction

ACE inhibitors play a vital role in both primary and secondary cardiovascular diseases. Major indications of ACE inhibitors in clinical settings based on trials were in heart failure-all stages, hypertension- especially in high risk patients and in diabetes, AMI-early phase for high risk patients, postinfarct LV dysfunction, nephropathy- non diabetic and diabetic, lessens new microalbuminuria and LV hypertrophy.

Beneficial neurohumoral effects: ACE inhibitors consistently increase the release of plasma renin and decrease in angiotensin II levels and aldosterone with a fall in norepinephrine and in vasopressin release.

### Renin-Angiotensin-Aldosterone System:

The major factors stimulating renin release from the juxtaglomerular cells of the kidney and results in angiotensin activation are 1. A low arterial blood pressure; 2. Decreased sodium reabsorption in distal tubular, as when dietary sodium is low or during diuretic therapy; 3. Decreased blood volume; and 4. increased sympathetic activity. ACE inhibitors are associated with reduction in aldosterone and has potential indirect natriuretic and potassium-retaining effects.

### Angiotensin II effects:

ACE inhibitors have indirect permissive antiadrenergic effects. Angiotensin II

promotes the release of norepinephrine from adrenergic terminal neuron, and enhances adrenergic tone by central activation and by facilitation of ganglionic transmission. Thus, angiotensin II leads to increased activity of vasoconstrictory norepinephrine. The combined antiadrenergic and vagomimetic mechanism could contribute to antiarrhythmic effects of ACE inhibitors and reduction of sudden death in several trials in congestive heart failure, especially post MI.<sup>1</sup> Occupation of angiotensin II receptor stimulates the phosphodiesterase (phospholipase C) that leads to a series of signals that activate a specialized enzyme, protein kinase C, that in turn evokes the activity growth pathways that stimulates ventricular remodeling.<sup>2</sup> Phospholipase C also activates the inositol triphosphosphate (IP3) signaling pathway in blood vessels to liberate calcium from the intracellular sarcoplasmic reticulum to promote vasoconstriction as well as cardiac and vascular structural alterations.

#### **Bradykinin:**

Apart from decreased formation of angiotensin II, increased bradykinin is another alternate site of action of ACE inhibitors. Action of bradykinin in Gut: slow contraction, vascular endothelium: vasodilation; antiplatelet aggregation and endothelial protection, respiratory tract: cough; angioedema, heart myocardium: protects against repeat ischemia. Bradykinin acts on its receptors in vascular endothelium to promote the release of two vasodilators: nitric oxide and vasodilatory prostaglandins such as prostacyclin and prostaglandin E2.

#### **Clinical benefits of ACE inhibitors in clinical practice:**

##### **ACE inhibitors for heart failure**

CONSENSUS<sup>4</sup> trial conducted on 253 patients with severe heart failure showed that enalapril cause 40% mortality reduction. SOLVD<sup>5</sup> treatment trial conducted on 2369 patients with mild – moderate heart failure showed that enalapril cause 18% reduction.

SOLVD<sup>3</sup> prevention trial conducted on 4228 patients with asymptomatic LV dysfunction showed that enalapril cause 37% reduction in risk of CHF; mortality unchanged.

X-SOLVD<sup>6</sup>, follow up of both SOLVD arms shows 10% death risk fall in both SOLVD arms.

V-HeFT-II<sup>7</sup> trial conducted on 804 patients with chronic heart failure showed that enalapril cause 18% reduction death versus nitrate-hydralazine.

SAVE<sup>8</sup> trial conducted on 2231 patients with postinfarct LV dysfunction showed that captopril cause 37% reduction in risk of CHF and 19% reduction in mortality.

TRACE<sup>9</sup> trial conducted on 1749 patients with postinfarct LV dysfunction showed thattrandolapril cause 22% reduction in mortality.

AIRE<sup>10</sup> trial conducted on 1986 patients with postinfarct clinical heart failure showed that ramipril cause 27% reduction in mortality.

##### **ACE inhibitors for hypertension:**

ACE inhibitors are effective antihypertensive in mild to moderate hypertension. It lowers BP by multiple mechanisms. Major effects are on peripheral arterioles, causing vasodilation and fall in systemic vascular resistance. Indirect inhibition of adrenergic activity also promotes arteriolar dilation several ancillary mechanisms including renal and indirect adrenal effects as well as possible central inhibition. Parasympathetic activity may also be stimulated. ACE inhibitors are more effective in white patients that are why ALLHAT<sup>11</sup> trial shows less effectiveness than diuretic due to high proportion of black patients in trial. CAPP<sup>12</sup> and STOP-2<sup>13</sup> trials shows less new diabetes, as ACE inhibitors does not alter glucose tolerance or blood uric acid or cholesterol levels, with few side effects apart from cough, their use in hypertension has rapidly increased. In DREAM<sup>14</sup> study, ramipril reduce fasting blood glucose but not new diabetes but the study was only 3 years in duration. Used in

coronary prevention trials (HOPE, EUROPA, PEACE) showed better results.

#### **ACE inhibitors for early-phase acute MI**

Within 24 hours of onset of acute MI, nearly 19,000 patients in GISSI-3<sup>15</sup>, lisinopril reduced mortality at 6 weeks and it is also beneficial in non-diabetic patients with high risk. The meta analysis of three major ACE inhibitor prevention trials, HOPE, EUROPA and PEACE, found an 18% reduction in odds ratio for the combined outcomes of cardiovascular death, nonfatal MI, or stroke and reduced the intima-to-media ratio of carotid arteries in patients at high risk for cardiovascular events.<sup>16,29</sup> In MICRO-HOPE<sup>17</sup> trial, ramipril cause reduction in both overt nephropathy and all-cause mortality by 24%. The REIN<sup>18</sup> (ramipril efficacy in nephropathy) trial shows impressive results in slowing the progression of proteinuria. There is good evidence from meta analysis on 1594 patients showing ACE inhibitors beneficially alter the course of end-stage renal failure, although BP reduction could also contribute to the results<sup>19</sup>. PROGRESS<sup>20</sup> trial results showed less repeat stroke with perindopril only if with diuretic.

Several clinical studies have examined the effects of ACE inhibition in the CABG patient.<sup>37</sup> In the Effects of Quinapril on Vascular Angiotensin-Converting Enzyme and Determinants of Ischemia (QUOVADIS) trial, patients were randomized 27 days before CABG to receive either quinapril (40 mg/d) or placebo for 1 year after surgery. Quinapril-treated patients had an 80% reduction in ischemic events (myocardial infarction, stroke, transient ischemic attacks, or recurrence of angina). Quinapril was well tolerated and was not associated with any untoward perioperative hemodynamic events. The Angiotensin-Converting Enzyme Inhibition Post-Revascularization Study (APRES) examined the effects of ramipril in 159 revascularized (130 CABG, 29 percutaneous coronary

intervention) normotensive patients with moderately depressed (30% to 50%) ejection fractions. Ramipril-treated patients had a 58% risk reduction in the composite end point of cardiac death, myocardial infarction, and congestive heart failure. Ramipril also significantly reduced echo-derived end-diastolic and end-systolic volume indexes. These beneficial effects were consistent in all patient groups, regardless of whether CABG or percutaneous transluminal coronary angiography was performed. In the Heart Outcomes Prevention Evaluation (HOPE) trial, patients with low to moderate risk for future cardiovascular events were randomized to ramipril (10 mg) or placebo for 5 years and 26% of patients had already received a CABG. Ramipril therapy significantly decreased the combined incidence of MI, stroke, and cardiovascular death by 22%. The beneficial effects of ACE inhibition were evident in multiple subgroups, including men and women, patients of all ages, and those with and without evidence of cardiovascular disease, hypertension, or cerebrovascular disease.

The collaborative study group reported positive results of ACE inhibitors on progression of diabetic nephropathy.<sup>21,25</sup> In non-diabetic renal disease ACE inhibitors have brought undoubtedly effective antihypertensive agents and data suggest that they may have a beneficial role in the prevention of progression of renal disease.<sup>22</sup> A role for ACE inhibitors in hypertension complicated by vascular disease, particularly in the management of cerebrovascular disease, where ACE inhibitors seem capable of preserving auto regulation of flow. ACE inhibitors do not seem to worsen symptoms in most hypertensive patients with angina, but their antianginal effect is modest at best.<sup>23</sup> There are no evident reasons for undue reluctance about their early introduction in essential hypertension.<sup>24</sup> A pooled analysis of 20 cardiovascular morbidity–mortality trials results showed

that in patients with hypertension, treatment with an ACE inhibitor results in a significant further reduction in all-cause mortality. Because of the high prevalence of hypertension, the widespread use of ACE inhibitors may result in an important gain in lives saved.<sup>40</sup>

A Prospective observational study showed that apart from control on blood pressure, the initiation of ACE inhibitor therapy can reduce CRP levels and result in anti-inflammatory actions in the vascular wall, inducing the reduction of reactive oxygen species, inflammatory cytokines, and adhesion molecules.<sup>30</sup> The cardiac antifibrotic effect of ACE inhibitors is a result of the inhibition of N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) hydrolysis, resulting in a decrease in cardiac cell proliferation (probably fibroblasts), inflammatory cell infiltration, TGF-expression, Smad2 activation, and collagen deposition.<sup>34</sup>

ACE inhibitors are undoubtedly the 'better' class of drug for the treatment of heart failure and for the prevention of serious cardiovascular events. A systemic review results supported the use of ACE inhibitors early in the treatment of acute MI, either to a wide range of patients or selectively in patients with anterior MI and in those at increased risk of death.<sup>26</sup> Contemporary guidelines on hypertension management recommend the use of ACE inhibitors for those patients in whom hypertension is associated with heart failure, left ventricular dysfunction or post myocardial infarction. They are also preferred therapy for Type 1 diabetes with proteinuria and hypertension.<sup>27,28,31</sup> Using the Saskatchewan health databases, a case cohort study proved that the use of ACE inhibitors was associated with a significant reduction in all-cause and cardiovascular-related mortality in a broad spectrum of patients with type 2 diabetes and no cardiovascular disease.<sup>32</sup> A systemic literature showed that ACEIs or ARBs may decrease patients' odds of

developing new-onset type 2 diabetes but does not reduce the odds of mortality, cardiovascular, or cerebrovascular outcomes over the study follow-up periods among patients with hypertension.<sup>33</sup>

ACE inhibitors have long been the cornerstone of therapy for systolic HF irrespective of aetiology. Recent trials have now shown that treatment with beta-blockers, aldosterone antagonists and angiotensin receptor blockers also leads to substantial improvements in outcome.<sup>35</sup> Newer ACE inhibitors with pharmacological profiles differing from those of older agents have added to the ease of application and relative safety of these drugs both for reduction of symptoms and for improvement of outcomes. ACE inhibitors remain unique in the range of their proven benefits, justifying their central role in the armamentarium of the CV specialist.<sup>36,38</sup>

The EUROASPIRE III survey results showed the use of cardioprotective medication was: antiplatelets 91%;  $\beta$ -blockers 80%; angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers 71%; calcium channel blockers 25% and statins 78%.<sup>39</sup> A triple therapy combination consisting of diuretics with angiotensin converting enzyme inhibitors or angiotensin receptor blockers and NSAIDs was associated with an increased risk of acute kidney injury. The risk was greatest at the start of treatment. Although antihypertensive drugs have cardiovascular benefits, vigilance may be warranted when they are used concurrently with NSAIDs.<sup>41</sup> A Observational case-control study concluded that Cognitive scores may improve in the first 6 months after centrally acting ACE inhibitors (CACE-Is) treatment and use of CACE-Is is associated with a reduced rate of cognitive decline in patients with dementia.<sup>42</sup>

### Conclusion:

ACE inhibitors play a vital role in clinical practice. It both decreases angiotensin II and

increase protective bradykinin. Reduction of end points, such as mortality, hospitalization, and prevention of disease progression. ACE inhibitors cause less adverse effects. Precaution to be taken to avoid hyperkalemia. If cough and angioedema occur, alternative choice is angiotensin receptor AT-1 blocker. ACE inhibitors are as effective as monotherapy in BP reduction in most patients group except black, in whom higher doses may be needed. It prevents the development of overt CHF, as shown in two trials, SAVE and SOLVD. Two large-scale prevention trials on patients at high risk of cardiovascular events, HOPE and EUROPA, found reduction in end points, such as MI, stroke and all-cause mortality. ACE inhibitors also cause less new diabetes compared with  $\beta$ -blockers or diuretics. The cardioprotective effects and role of centrally acting ACE inhibitors in patients with dementia had warranted its wide use in clinical settings.

#### **Conflict Of Interest:**

The Authors has no conflict of interest.

#### **Authors' contributions:**

Authors equally contributed to the development of the concept and manuscript, critically read and approved the final manuscript.

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#### List of Abbreviations:

- ACE: angiotensin converting enzyme.  
 AMI: acute myocardial infraction.  
 LDL: low density lipoprotein.  
 PAI-1: plasminogen activator inhibitor-1.  
 SOLVD: studies of left ventricular dysfunction.  
 CONSENSUS: cooperative north scandinavian enalapril survival study.  
 X-SOLVD: extended studies of left ventricular dysfunction.  
 V-HeFT-II: veterans' administration cooperative vasodilator heart failure trial.

SAVE: survival and ventricular enlargement.

TRACE:trandopril cardiac evaluation.  
AIRE: acute infraction ramipril efficacy

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