Role of ACE inhibitors in primary and secondary prevention of heart disease

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Abstract

The renin-angiotensin-aldosterone system (RAAS) is a complex system that regulates arterial blood pressure, extracellular fluid volume and electrolyte balance, and thus acts as one of the key regulators in maintaining homeostasis in human body. Overwhelming data exists which implicates excessive RAAS activity in promoting endothelial dysfunction and important in pathogenesis of various cardiovascular diseases like hypertension, acute myocardial infarction (AMI), chronic systolic heart failure, stroke and also renal disorders, particularly diabetic nephropathy (DN). Debatable yet, yet supportive data is emerging for RAAS inhibition as a treatment option for the primary and secondary prevention of atrial fibrillation. Improvement of the patient's cardiovascular risk by blockade of the renin-angiotensin system is, therefore, not unexpected and blockade of RAAS cascade by ACE inhibitors has shown to be beneficial in terms of both morbidity and mortality. This article focuses on the latest published data regarding ACE-inhibition and discusses the possible mechanisms and the evidence that has been generated regarding the additive prevention of cardiovascular events by ACE blockage and explores newer aspects of the renin-angiotensin system that continue to emerge as targets for novel therapeutic strategies.

Key Words

- Renin-angiotensin aldosterone system
- Hypertension
- Angiotensin II
- Renin
- ACE inhibitors
- Atherosclerosis
- Endothelial dysfunction

Introduction

The renin-angiotensin-aldosterone system (RAAS) is a complex system that plays an important role in maintaining hemodynamic stability in the human body through regulation of arterial blood pressure, water and electrolyte balance. Blockade of RAAS has been shown to be beneficial in patients with hypertension, acute myocardial infarction (AMI), chronic systolic heart failure, stroke and diabetic nephropathy (DN). ACE inhibitors (ACEIs) by virtue of different actions like promoting vasodilatation, limiting neurohormonal activation and vasoconstriction, improving endothelial function by reducing oxidative stress, modifying fibrinolytic balance, inhibiting platelet activation and reversing negative vascular remodeling, slowing down the development of atherosclerosis have played a remarkable role in primary and secondary prevention of cardiovascular disorders. This article focuses on the latest published data regarding ACE-inhibition and discusses the possible mechanisms and the evidence that has been generated regarding the additive prevention of cardiovascular events by ACE blockage.

Historical perspective

Discovery of RAAS occurred more than a century ago when in 1898, Tigerstedt and Bergmann demonstrated the existence of a substance (subsequently named renin) in crude extracts of rabbit renal cortex that caused a sustained increase in arterial pressure. Further understanding of RAAS pathway was brought forth by discovery of ANG-I and II by Skegg's and colleagues in 1950s. Finally, cortical
hormone Aldosterone was discovered whose release was mediated via Ang-II and there by establishing the role of RAAS system in the regulation of blood pressure, fluid and electrolyte balance in the body.

- Components of the RAAS

The renin-angiotensin-aldosterone hormonal cascade begins with the biosynthesis of renin by the juxtaglomerular cells (JG) that line the afferent (and occasionally efferent) arterioles of the renal glomerulus. Renin regulates the initial and rate-limiting step of the RAAS cascade, i.e., converting angiotensinogen, formed constitutively in liver to Ang-I. The Ang-I is hydrolyzed by angiotensin-converting enzyme (ACE) to Ang-II, a biologically active, potent vasoconstrictor, ACE, an exopeptidase, and is localized on the plasma membranes of various tissues including vascular endothelial cells. ACE metabolizes a number of other peptides, including the vasodilator peptides bradykinin and kallikrein, to inactive metabolites.

Alternative pathways exist that convert angiotensinogen directly to Ang-II, such as tissue plasminogen activator, cathepsin G, and tomin, whereas Ang-I is also catalyzed to Ang-II by chymase and cathepsin G part of which forms the basis of “Ang-II escape.” Ang-II once formed acts on the adrenal cortex and causes the release of aldosterone. The net effects include vasoconstriction, sodium and water retention, increased arterial blood pressure and increased myocardial contractility, which in combination increase the effective circulating volume. Apart from the classical physiologic role of tissue RAAS is complementary to the paracrine or autocrine manner (Paul et al., 2006). The involvement of RAAS system in the regulation of blood pressure, fluid and electrolyte balance in the body.

Role of RAAS Activation

RAAS has been shown to be associated with both primary and secondary hypertension. Certain forms of secondary hypertension, including renin secreting neoplasms, renovascular hypertension (e.g., renal artery stenosis), malignant hypertension, phochromocytoma, and primary hyperaldosteronism are supposed to be a direct consequence of increased RAAS activity. In patients with primary (essential) hypertension, the plasma renin activity (PRA) can be high, normal, or low. Activation of local RAAS has been implicated in “Low-renin” hypertension which is commonly seen in the elderly, diabetics and those with chronic renal parenchymal disease.

- Atherosclerosis and endothelial dysfunction

The endothelium maintains vascular homeostasis through a network of complex interactions with vessel wall cells and plays a key role in the regulation of vascular tone, platelet adhesion and aggregation, inflammation and cell proliferation. The endothelial dysfunction that results from presence of multiple cardiovascular risk factors up-regulates Ang-II levels which triggers responses in vascular smooth muscle cells that lead to proliferation, migration and a phenotypic modulation, resulting in production of growth factors and extracellular matrix, all contributing to neointima formation and development of atherosclerotic process. These effects are mediated by the reactive release of vasoactive substances (Thromboxane A2, free radicals, endothelin, prostacyclin). Ang II, elaborated by activated endothelial ACE, impairs nitric oxide bioactivity, by increasing production of superoxide radicals (O2−) that scavenge nitric oxide and reduce both endothelium-dependent vasodilation and migration of smooth muscle cells into tissue. The accumulation of angiotensin and metalloproteinase in the shoulder region of the vulnerable plaque may contribute to increased local circumferential stress and plaque instability, and hence may be implicated in acute complications by promoting plaque rupture and a hyperthrombotic state. ACEIs reduce CV risk through cardioprotective and vasoprotective effects (Figure 2) by blocking both the circulating & tissue RAAS, inhibiting the formation of Ang-II as well as preventing the degradation of bradykinin, thereby enhancing release of NO by the endothelium.

- Pathophysiological cross-talk between metabolic and vascular tissues: Role of RAAS in development of diabetes and its complications

Metabolic syndrome, a disorder characterized primarily by insulin resistance has emerged as a major risk factor for cardiovascular disease. Research has highlighted cross talk between angiotensin II (Ang-II) and insulin signaling that contributes to the pathophysiology of the metabolic syndrome.

Studies have delineated the complex cellular interactions of the RAAS and insulin signaling including the shared signal transduction pathways (Phosphatidylinositol kinase and Mitogen Activated Protein kinase pathways). The activation of phosphatidylinositol kinase pathway (PI3K), enhances nitric oxide production and insulin-induced vasodilatory response whereas the mitogen-activated protein kinase pathway (MAPK) promotes vascular smooth muscle cell proliferation and migration induced by insulin, thrombin, and platelet-derived growth factors. A key feature of insulin resistance is that it is characterized by specific impairment in PI 3-kinase– dependent signaling pathways, whereas other insulin-signaling branches, including RAAS/MAP-kinase-dependent pathways, are unaffected and this intracellular cross-talk between Ang-II and insulin signaling may be of pathophysiologic significance in the insulin resistance associated with hypertension and accelerated atherosclerosis.

- RAAS as therapeutic target

The effects of angiotensins are exerted through specific heptahedral G-protein coupled receptors. The four subtypes of angiotensin receptors are AT1, AT2, AT3, and AT4. Most of the biological effects of Ang-II are mediated by AT1 receptors whose gene contains a polymorphism that may be associated with hypertension, hypertrophic cardiomyopathy, coronary artery vasoconstriction and aortic stiffness. Functional roles of AT2 receptors which are widely distributed in fetal tissues than adults are poorly defined. They may exert antiproliferative, prosklerotic, vasodilatory and antihypertensive & ECM modification effects.

The function of AT1 receptor is unknown. However, AT2 receptor may be involved in modulation of endothelial function.

- Pharmacokinetic profile of ACE inhibitors (Table 1)

ACEIs can be classified according to the group that binds the zinc atom of the ACE molecule into those containing a sulphydryl, a carbonyl or a phosphoryl group as zinc ligand.  

1. Sulphydryl containing ACEIs (structurally related to Captopril, e.g., Fentiapril, Pivalopril, Zefenopril, Alacepril.
2. Carboxyl-containing ACEIs, e.g., Enalapril, Lisinopril, Benazepril, Quinapril, Moexipril, Ramipril, Sprinapril, Perindopril, Pentopril, Cilazapril, Trandopril.
3. Phosphorous containing ACE inhibitors, e.g., Fosinopril.

Many of these drugs are available as oral as well as parenteral forms. Majority of them are prodrugs (except captopril and lisinopril), which get activated in the body after administration. These prodrugs are 100–1000 times less potent than the active metabolites, but have a much better oral bioavailability than the active molecules. ACEIs are primarily cleared by kidneys and hence dose must be reduced in patients with renal dysfunction.
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- Dysregulation of the RAAS in cardiovascular disorders

Cardiovascular disorders have been postulated as a continuum that starts with presence of risk factors in an individual and produce endothelial dysfunction and atherosclerosis. Once established both lead to various cardiovascular events ultimately leading to MI, stroke, atherosclerosis. Once established both lead to various individual and produce endothelial dysfunction and vasculature.

- Pathophysiological cross-talk between metabolic and vascular tissues: Role of RAAS in development of diabetes and its complications

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ACE inhibitors in primary prevention

Renin-angiotensin system and arterial hypertension

Anti-hypertensive therapy has been shown to reduce the risk of stroke (35–40%), myocardial infarction (20–25%) and heart failure (> 50%). Despite the negative result of the Captopril Prevention Project,17 Hansson et al., 1999), subsequent large trials involving other ACEIs (e.g., ramipril, perindopril, lisinopril, enalapril) like STOP-2 showed that anti-hypertensive treatment with ACEI have reduced mortality by 21% and No difference in major CV events despite producing similar blood pressure reduction, ACEI and CCB combination produced a 23% reduction in new onset stroke without any mortality benefit. Data support the use of ACEIs only for high-risk patients with diabetes or uncontrolled cholesterol levels and do not offer added benefit to low-risk patients already on aspirin, beta blockers, and statins.

Prevention of atrial fibrillation

Atrial fibrillation (AF) heightens the risk of cardiovascular events. Two large trials involving other ACEIs (e.g., ramipril, perindopril, lisinopril, enalapril) showed that anti-hypertensive treatment with ACEI have improved clinical outcomes. In the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA),18 patients with hypertension were randomized to either amlodipine plus perindopril (if needed) or atenolol plus bendroflumethiazide (β-blocker with thiazide diuretic). The trial was stopped prematurely due to a significant difference in the secondary endpoint of all-cause mortality favoring CCB PLUS ACE-inhibitor therapy (24% less mortality, fewer CV events and stroke).

The average systolic blood pressure difference between the two groups was only 2.7 mm Hg, which suggested that the clinical benefits of the amlodipine plus perindopril regimen may have been due to reasons other than hemodynamic changes.

Following ASCOT-BPLA, the ACCOMPLISH trial using either benazepril plus amlodipine or benazepril plus hydrochlorothiazide (HCTZ) to treat patients with hypertension and those at high risk for cardiovascular events. Despite producing similar blood pressure reduction, ACEI and CCB combination produced statistically significant reduction in primary endpoint of death from cardiovascular causes, MI, low-risk stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, or coronary revascularization.

Renin-angiotensin system and atherosclerosis

Decades of research have implicated various factors in the pathogenesis of endothelial dysfunction and atherosclerosis, where activation of the renin-angiotensin system, and Ang-II binding to AT1 receptors play a central role. Landling support to this hypothesis was the TRENDS study,19 where ACE inhibitor quinapril had beneficial effect on impaired endothelial function in hypertensive patients.

Table 1: Pharmacokinetic profile of ACE-inhibitors

<table>
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<tr>
<th>Agent</th>
<th>Oral absorption</th>
<th>Protein binding</th>
<th>Biotransformation</th>
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<tbody>
<tr>
<td>Captopril</td>
<td>75%</td>
<td>25–30%</td>
<td>Hepatic</td>
<td>Less than 3 hrs</td>
<td>15–60 min</td>
<td>30–90 min</td>
<td>Renal</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>25%</td>
<td>Minimal</td>
<td>Hepatic</td>
<td>12 hrs</td>
<td>1 hr</td>
<td>7 hr</td>
<td>Renal</td>
</tr>
<tr>
<td>Enalapril</td>
<td>60%</td>
<td>50–60%</td>
<td>Hepatic</td>
<td>1.3 hrs</td>
<td>1 hr</td>
<td>1 hr</td>
<td>Renal, Fecal</td>
</tr>
<tr>
<td>Ramipril</td>
<td>50-60%</td>
<td>73%</td>
<td>Hepatic</td>
<td>5.1 hrs</td>
<td>Within 1–2 hr</td>
<td>Within 1 hr</td>
<td>Renal, Fecal</td>
</tr>
<tr>
<td>Benazepril</td>
<td>37%</td>
<td>95.5%</td>
<td>Hepatic</td>
<td>0.6 hrs</td>
<td>Within 1 hr</td>
<td>0.5–1 hr</td>
<td>Predominantly renal non renal (bilary) 11–12%</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>36%</td>
<td>97–98%</td>
<td>Hepatic</td>
<td>-</td>
<td>Within 1 hr</td>
<td>3–4 hrs</td>
<td>Renal, Fecal</td>
</tr>
<tr>
<td>Perindopril</td>
<td>65–75%</td>
<td>60%</td>
<td>Hepatic</td>
<td>Approximately 0.8 hrs</td>
<td>Within 1–2 hr</td>
<td>1 hr</td>
<td>Renal, Fecal</td>
</tr>
<tr>
<td>Moexapril</td>
<td>13%</td>
<td>50%</td>
<td>Hepatic</td>
<td>1.3 hrs</td>
<td>1 hr</td>
<td>1.5 hr</td>
<td>Renal, Fecal</td>
</tr>
<tr>
<td>Quinapril</td>
<td>60%</td>
<td>10–20%</td>
<td>Hepatic</td>
<td>Approximately 1–2 hrs</td>
<td>Within 1 hr</td>
<td>Within 1 hr</td>
<td>Renal, Fecal</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>10%</td>
<td>80%</td>
<td>Hepatic</td>
<td>6 hrs</td>
<td>2 hrs</td>
<td>1 hr</td>
<td>Renal, Fecal</td>
</tr>
</tbody>
</table>

Table 2: Clinical outcomes with ACEI in hypertensive subjects

<table>
<thead>
<tr>
<th>Trial</th>
<th>ACEI/Study meds</th>
<th>Patient group</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPP</td>
<td>Captopril vs diuretics or β-blockers</td>
<td>Hypertension</td>
<td>No difference in major CV events</td>
</tr>
<tr>
<td>Stop 2</td>
<td>β-blockers or diuretics or ACEI or CCB</td>
<td>HTN</td>
<td>No difference in major CV events</td>
</tr>
<tr>
<td>HYVET-Pilot</td>
<td>Diuretic vs ACEI vs no treatment</td>
<td>HTN</td>
<td>ACEI reduced stroke by 53% and stroke mortality by 43%</td>
</tr>
<tr>
<td>HYVET</td>
<td>Indapamide +/- Perindopril vs placebo</td>
<td>HTN</td>
<td>ACEI reduced mortality by 21% and CHF by 64%</td>
</tr>
<tr>
<td>ACCOMPLISH</td>
<td>Benazepril + Amlodipine vs Benazepril + HCTZ</td>
<td>HTN</td>
<td>Benazepril + amlodipine showed a 20% reduction in event rates</td>
</tr>
</tbody>
</table>

Table 3: Comparison of three large scale clinical trials examining the effect of ACE inhibition on cardiovascular events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Follow-up (years)</th>
<th>Composite primary endpoint*</th>
<th>Non-fatal myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE</td>
<td>High risk (n=9297)</td>
<td>5.0</td>
<td>14.0% vs 17.8%</td>
<td>22% (14 to 30)</td>
</tr>
<tr>
<td>PEACE</td>
<td>Low risk (n=2890)</td>
<td>4.8</td>
<td>21.9% vs 22.5%</td>
<td>4% (~5 to 12)</td>
</tr>
</tbody>
</table>

* Primary composite endpoints: HOPE: cardiovascular death, non-fatal myocardial infarction or stroke, EUROPA: cardiovascular death, non-fatal myocardial infarction or coronary revascularization; +95% CI in brackets.
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In the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA), patients with hypertension were randomized to either amlodipine plus perindopril (if needed) or atenolol plus bendroflumethiazide (β-blocker with thiazide diuretic). The trial was stopped prematurely due to a significant difference in the secondary endpoint of all-cause mortality favoring CCB PLUS ACE-inhibitor therapy (24% less cardiovascular mortality, fewer CV events and stroke).

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<tr>
<td>Step 2 (n=6614)</td>
<td>β-blockers or diuretics vs ACEI or CCB</td>
<td>No difference in major CV events</td>
<td></td>
</tr>
<tr>
<td>HYVET-Pilot (n=1283)</td>
<td>Diuretic vs ACEI vs no treatment</td>
<td>HTN</td>
<td>ACEI reduced stroke by 53% and stroke mortality by 43%</td>
</tr>
<tr>
<td>HYVET (n=3845)</td>
<td>Indapamide +/- Perindopril vs placebo</td>
<td>HTN</td>
<td>ACEI reduced mortality by 21% and CHF by 64%</td>
</tr>
<tr>
<td>ACCOMPLISH (n=11,508)</td>
<td>Benazepril + Amlodipine vs Benazepril + HCTZ</td>
<td>HTN</td>
<td>Benazepril + amlodipine showed a 20% reduction in CV events</td>
</tr>
</tbody>
</table>

Table 3: Comparison of three large scale clinical trials examining the effect of ACE inhibition on cardiovascular events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Baseline Parameters</th>
<th>Composite primary endpoint</th>
<th>Non-fatal myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOPE Ramipril – 10 mg</td>
<td></td>
<td>Frequency</td>
<td>Relative risk reduction*</td>
</tr>
<tr>
<td>EUROPA Perindopril – 8 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEACE Trandolapril – 4 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Follow-up (years)</td>
<td>Composite primary endpoint*</td>
<td>Non-fatal myocardial infarction</td>
</tr>
<tr>
<td>Low risk (n=8290)</td>
<td>28%</td>
<td>50%</td>
<td>58%</td>
</tr>
<tr>
<td>High risk (n=9297)</td>
<td>22%</td>
<td>9.9% vs 12.3%</td>
<td>20% (10 to 30)</td>
</tr>
<tr>
<td>EUROPA Perindopril – 8 mg</td>
<td>9.9% vs 12.3%</td>
<td>20% (10 to 30)</td>
<td>20% to 30%</td>
</tr>
<tr>
<td>PEACE Low risk (n=8290)</td>
<td>5.3% vs 5.3%</td>
<td>0% to 20%</td>
<td>22%</td>
</tr>
<tr>
<td>(stable coronary artery disease)</td>
<td>21.9% vs 22.5%</td>
<td>4% (−6 to 12)</td>
<td>4% (−6 to 12)</td>
</tr>
<tr>
<td>(stable coronary artery disease)</td>
<td>4.8% vs 6.2%</td>
<td>22%</td>
<td>22%</td>
</tr>
</tbody>
</table>

*Primary composite endpoints: HOPE: cardiovascular death, non-fatal myocardial infarction or stroke; EUROPA: cardiovascular death, non-fatal myocardial infarction or coronary revascularization; +95% CI in brackets.
Table 4: Summary of ACEI clinical trials

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<th>Trial</th>
<th>ACEI/Study meds</th>
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<tr>
<td>SOLVD, treatment arm</td>
<td>Enalapril vs placebo</td>
<td>NYHA II &amp; III, CHF</td>
<td>16% reduction in mortality and 26% reduction in death and hospitalization combined</td>
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<tr>
<td>V-HeFT II (n=5804)</td>
<td>Enalapril vs hydralazine-isosorbide</td>
<td>NYHA II &amp; III, CHF</td>
<td>28% reduction in 2-year mortality</td>
</tr>
<tr>
<td>SAVE (n=52231)</td>
<td>Captopril vs placebo</td>
<td>Recent MI with asymptomatic LVD</td>
<td>32% reduction in mortality</td>
</tr>
<tr>
<td>SOLVD, prevention arm (n=54228)</td>
<td>Enalapril vs placebo</td>
<td>Asymptomatic LVD</td>
<td>29% reduction in death and hospitalization due to CHF</td>
</tr>
<tr>
<td>AIRE (n=52006)</td>
<td>Ramipril vs placebo</td>
<td>Recent MI with overt CHF</td>
<td>30% reduction in sudden cardiac death and 23% reduction in CHF progression</td>
</tr>
<tr>
<td>ISIS-4 (n=58,050)</td>
<td>Captopril vs placebo</td>
<td>Acute MI</td>
<td>7% reduction in mortality</td>
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<td>GISSI-3 (n=519394)</td>
<td>Lisinopril vs open control</td>
<td>Acute MI</td>
<td>12% reduction in mortality in 6 wk and 6% in 6 mo</td>
</tr>
<tr>
<td>TRACE (n=51749)</td>
<td>Trandolapril vs placebo</td>
<td>Recent MI with LVD</td>
<td>25% reduction in mortality</td>
</tr>
<tr>
<td>SMILE (n=51556)</td>
<td>Zofenopril vs placebo</td>
<td>Acute MI</td>
<td>34% reduction in mortality in 6 wk and 29% in 1 year</td>
</tr>
<tr>
<td>PROGRESS (n=56105)</td>
<td>Perindopril +/- indapamide vs placebo</td>
<td>Stroke</td>
<td>28% reduction in stroke and 26% in CV events</td>
</tr>
</tbody>
</table>

ACE inhibitors in congestive heart failure

Enalapril in CONSENSUS, SOLVD treatment and prevention, and V-HeFT II (Table 4) demonstrated significant overall mortality reduction in patients with congestive heart failure. Compared with hydralazine and isosorbide dinitrate combination, enalapril was superior in patients with anterior AMI without thrombolysis, zofenopril reduced mortality and incidence of severe heart failure when the drug was started within 24 h after the onset of AMI. Meta-analysis of pooled data showed that use of ACEI was associated with a reduction in cardiovascular mortality (RR 0.83, 95% CI 0.72–0.96, P < 0.01), nonfatal myocardial infarction (MI) (RR 0.84, 95% CI 0.75–0.94, P = 0.003), all-cause mortality (RR 0.87, 95% CI 0.81–0.94, P = 0.003) and revascularization rates (RR 0.93, 95% CI 0.87–1.00, P = 0.44).

ACE inhibitors in secondary prevention

Recent MI with LVD

NYHA II & III, CHF 16% reduction in mortality and 26% reduction in death and hospitalization combined.

V-HeFT II (n=5804)

Enalapril vs hydralazine-isosorbide NYHA II & III, CHF 28% reduction in 2-year mortality.

SAVE (n=52231)

Captopril vs placebo Recent MI with asymptomatic LVD 32% reduction in mortality.

SOLVD, prevention arm (n=54228)

Enalapril vs placebo Asymptomatic LVD 29% reduction in death and hospitalization due to CHF.

AIRE (n=52006)

Ramipril vs placebo Recent MI with overt CHF 30% reduction in sudden cardiac death and 23% reduction in CHF progression.

ISIS-4 (n=58,050)

Captopril vs placebo Acute MI 7% reduction in mortality.

GISSI-3 (n=519394)

Lisinopril vs open control Acute MI 12% reduction in mortality in 6 wk and 6% in 6 mo.

TRACE (n=51749)

Trandolapril vs placebo Recent MI with LVD 25% reduction in mortality.

SMILE (n=51556)

Zofenopril vs placebo Acute MI 34% reduction in mortality in 6 wk and 29% in 1 year.

PROGRESS (n=56105)

Perindopril +/- indapamide vs placebo Stroke 28% reduction in stroke and 26% in CV events.

2. Those that required evidence of asymptomatic or symptomatic left ventricular dysfunction before randomization (SAVE, TRACE, AIRE, and SMILE).

Diuretics, beta-blockers, and calcium channel blockers. In patients with myocardial infarction and left ventricular dysfunction, captopril in the SA VE study and trandolapril in the TRACE study resulted in a 12% reduction in mortality and hospitalization combined.

ACE inhibitors in primary and secondary prevention of heart disease

Role of ACE inhibitors in primary and secondary prevention of heart disease

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Diabetic nephropathy

Albinurina is well known early sign of diabetic nephropathy. It represents a cardiovascular risk marker not only in diabetes, but also in hypertensives and general population.

Trials now indicate that reduction of albinurina is associated with better renal and cardiovascular outcome.

Blockade of the renin-angiotensin system prevents the overall risk of primary stroke was 25% reduction in mortality, respectively. This outcome was accomplished above and beyond thrombolytic therapy. The negative result shown by the CONSENSUS II study was thought to be secondary to significant hypotension caused by intravenous enalapril at given in the first 24 h after AMI. In patients with AMI and left ventricular systolic dysfunction, captopril in the SAVE study and trandolapril in the TRACE study resulted in 32% and 25% reduction in mortality, respectively, as compared with placebo. In patients with AMI and left ventricular systolic dysfunction, captopril in the SAVE study and trandolapril in the TRACE study resulted in a 28% reduction in stroke and a 26% in CV events.

Figure 3. Change of albumuric predicts occurrence of cardiovascular events and heart failure in patients with overt diabetic nephropathy.

In vitro studies have suggested that ACEIs may improve cardiac dispensability and cause regression of left ventricular hypertrophy with time. Theoretically it was expected that similar effects would be duplicated in clinical studies but the trials so far have suggested otherwise.

ACE inhibitors in stroke

The incidence and prevalence of stroke increases linearly with age and blood pressure and blood pressure control remains one of the most crucial factors in prevention. In a meta-analysis of four placebo-controlled trials of ACEIs in patients with coronary heart disease and/or diabetes mellitus, the overall risk of primary stroke was significantly reduced. In active-control comparisons in patients with hypertension, ACEIs have demonstrated reductions in primary stroke risk similar to reductions with diuretics, beta-blockers, and calcium channel blockers.

Two large trials with ACEI, PROGRESS and HOPE (Table 4), have been performed. In the PROGRESS study, subjects with a history of cerebrovascular disease were randomly assigned to receive perindopril with or without addition of indapamide or placebo. At 4-year follow-up, perindopril alone reduced the incidence of recurrent stroke by 28%, whereas the combination with indapamide reduced stroke risk by 43%. Treatment effects were consistent across different patient subgroups, including those with and without hypertension, and for both ischemic and hemorrhagic strokes. Similarly, in the HOPE study, ramipril reduced the RR of any stroke by 32% and the risk of fatal stroke by 61%. ACEIs seem to lower stroke risk by mechanisms other than lowering of blood pressure.

Renin-angiotensin system and type 2 diabetes

Cardiovascular mortality and morbidity in patients with type 2 diabetes is very high. In view of the worldwide rising cases of metabolic syndrome and diabetes, the best strategy would be prevention of diabetes itself. As discussed earlier the renin-angiotensin system blockade intervenes at different stages of this disease process.

Preventing the complications of diabetes
mortality by around two-fold and can be identified as the underlying cause for up to 15% of all strokes with hypertension. There is a plausible scientific basis for the notion that inhibition of the renin-angiotensin-aldosterone system can reduce the incidence of AF. Possible mechanisms include reducing atrial stretch, limiting atrial fibrosis, inhibiting triggering from the pulmonary veins, and preventing atrial remodeling. Further potential mechanisms include increasing potassium concentrations, changing potassium currents and conduction, lowering end-diastolic left ventricular pressure, modifying the sympathetic tone, and direct antiarrhythmic effects.23

Secondary analyses of randomized trials performed for reasons other than AF prevention suggest that ACEIs and ARBs reduce the incidence of new onset AF. However, publication bias and heterogeneity of the trials renders the weak evidence to support their use weak for AF.

ACE inhibitors in secondary prevention – ACE inhibitors in postmyocardial infarction

Multiple prospective randomized trials have assessed the use of ACEIs following acute myocardial infarction (AMI). These trials (Table 4) could be divided into:

1. Those in which ACEIs were given to all AMI patients in a randomized fashion (ISIS-4, GISSI-3, and CONSENSUS II)19,20

2. Those that required evidence of asymptomatic or symptomatic left ventricular dysfunction before randomization (SAVE, TRACE, AIRE, and SMILE).15

In the ISIS-4 and GISSI-3 studies, oral use of captopril and lisinopril when compared with placebo resulted in a 7% (at 5 weeks) and 12% (at 6 weeks; 6.5% at 6 months) reduction in mortality, respectively. This outcome was accomplished above and beyond thrombolytic therapy. The negative result shown by the CONSENSUS II study was thought to be secondary to significant hypotension caused by intravenous enalapril at given in the first 24 h after AMI. Patients in AMI with and clinically evident congestive heart failure, ramipril reduced mortality and heart failure progression as compared with placebo. The SMILE study showed that in patients with anterior MI without thrombolysis, zofenopril reduced mortality and incidence of severe heart failure when the drug was started within 24 h after the onset of AMI. Meta-analysis of pooled data showed that use of ACEI was associated with a reduction in cardiovascular mortality (RR 0.83, 95% CI 0.72-0.96, P = 0.01), nonfatal myocardial infarction (MI) (RR 0.84, 95% CI 0.75-0.94, P = 0.003), all-cause mortality (RR 0.87, 95% CI 0.81-0.94, P = 0.003) and revascularization rates (RR 0.93, 95% CI 0.87-1.00, P = 0.44).21

ACE inhibitors in congestive heart failure

Enalapril in CONSENSUS, SOLVD treatment and prevention, and V-HeFT II (Table 4) demonstrated significant overall mortality reduction in patients with congestive heart failure.21 Compared with hydralazine and isosorbide dinitrate combination, enalapril was superior in terms of reducing mortality, as shown in the V-HeFT II study,21 although subsequent analysis showed that the mortality benefit was seen only in white patients with hypertension and higher PRA. Previous meta-analysis showed that ACE therapy increased survival, reduced heart failure-related hospitalizations, and improved symptoms in patients with left ventricular dysfunction or heart failure.

Diastolic heart failure

In vitro studies have suggested that ACEIs may improve cardiac dispensability and cause regression of left ventricular hypertrophy with time.30 Theoretically it was expected that similar effects would be duplicated in clinical studies but the trials so far have suggested otherwise.

ACE inhibitors in stroke

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Preventing the complications of diabetes

Diabetic nephropathy

Albuminuria is well known early sign of diabetic nephropathy. It represents a cardiovascular risk marker not only in diabetes, but also in hypertensives and general population.

Trials now indicate that reduction of albuminuria is associated with better renal and cardiovascular outcome (Figure 3).25

Role of ACE inhibitors in primary and secondary prevention of heart disease

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Figure 3. Change of albuminuria predicts occurrence of cardiovascular events and heart failure in patients with overt diabetic nephropathy. Blockade of the renin-angiotensin system prevents the onset of microalbuminuria in diabetic patients and reduces proteinuria. In addition to HOPE, the MICRO-HOPE substudy examined the effects of ramipril on the development of renal disease within the same diabetic cohort. Although ACE-I did not reduce the incidence of new onset microalbuminuria but there was a 24% relative
Table 5: Results of end points for all subjects and subjects with diabetes in recent cardiovascular and renal studies with angiotensin converting enzyme

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total subjects n</th>
<th>Diabetic subjects n (%)</th>
<th>Primary end point all</th>
<th>Primary end point diabetes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EUROPA-PERSUASIVE</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>1502 (12%)</td>
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<td><strong>PEACE</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triandopril 4 mg or placebo</td>
<td>8290</td>
<td>1409 (17%)</td>
<td>Data not provided</td>
<td>Open label ACE inhibitors for diabetes patients with overt proteinuria or hypertension and microalbuminuria</td>
<td></td>
</tr>
<tr>
<td><strong>DETAIL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan 80 mg vs enalapril 20 mg</td>
<td>250</td>
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</tr>
</tbody>
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Conclusions

Improvement of the patient’s cardiovascular risk by blockade of the renin-angiotensin system is caused by blood pressure reduction but includes additional non-hemodynamic effects. ARBs and ACEs are best proven in high-risk patients with advanced renal failure, especially if diabetic, and also decreased cardiovascular death by 37% and total mortality by 24%.

Similar findings were seen in post-hoc analysis of other trials example RENAAI (Table 5).

Patients with advanced renal failure, especially if diabetic, are at very high cardiovascular risk and blockade of the RAAS in these patients is safe and effective.

References


Address for correspondence

Dr. Rupert S. Wander. Email: drgs wander@yahoo.com
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Patients with advanced renal failure, especially if diabetic, are at very high cardiovascular risk and blockade of the RAAS in these patients is safe and effective.

**Conclusion**

Improvement of the patient’s cardiovascular risk by blockade of the renin-angiotensin system is caused by blood pressure reduction but includes additional non-hemodynamic effects. ARBs and ACEs are best proven interventions to reduce target organ damage in hypertension, atherosclerosis, and diabetes. New aspects of the renin-angiotensin system continue to emerge and could become targets for novel therapeutic strategies.

**References**