MetS/T2DM/HBP
ACEI vs ARB

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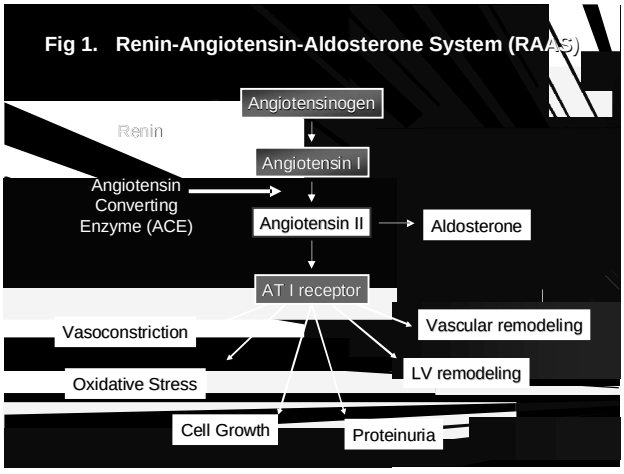
The recent angiotensin receptor blocker (ARB) trials have provoked these questions: Should ARBs replace angiotensin converting enzyme inhibitors (ACEIs)? – And if so, in which situations? This *Heartbeat* will explain the detrimental effects of angiotensin II (A II) and the beneficial effects of A II blockade, then explore our therapeutic options, comparing the benefits of ACEIs vs ARBs in high risk situations.

The renin-angiotensin-aldosterone system (RAAS) is largely responsible for maintaining the body's fluid homeostasis and vascular integrity. This system modulates the resistance of the circulatory system to the pumping output of the heart. One of the fundamental steps by which the RAAS exerts this control is through conversion of the inactive hormone angiotensin I to the powerful vasoconstrictor A II (Figure 1).

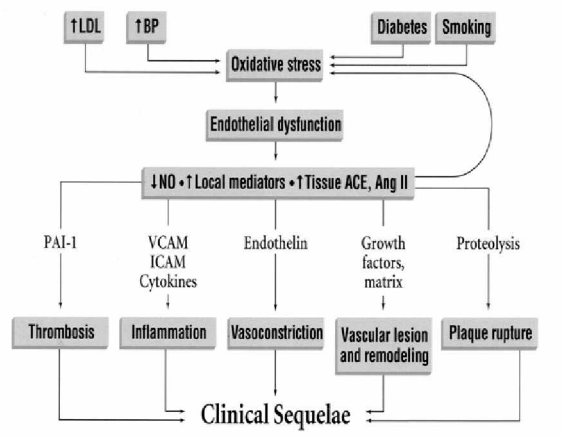
Fig 1. Renin-Angiotensin-Aldosterone System (RAAS)



Role of A II

A II modulates vascular plaque stability through a complex number of mechanisms mediated through the angiotensin type 1 (AT 1) receptor (Figure 1). When this carefully regulated system is out of balance, bad things happen. The most viable explanation involves endothelial function. The endothelium works to maintain vascular integrity by several mechanisms that regulate vascular structure and function. Endothelial health is largely a result of the balance between A II, a potent vasoconstrictor, and nitric oxide, a potent vasodilator. Our modern lifestyle, diet, genes, risk factors and oxidative stress, an unavoidable consequence of living in air, often shift this balance to A II, resulting in endothelial dysfunction (ED). The untoward effects of this imbalance are seen in Figure 2.

Fig 2. Detrimental Effects of A II.



The clinical sequelae are increased risk of cardiovascular disease (CVD), heart failure (HF) and chronic renal disease (CRD). The RAAS is a primary mediator of ED through its production of A II.

Benefits of A II Blockade

It comes as no surprise that blockade of the RAAS and A II, resulting in more normal endothelial function (more vasodilatory, anti-thrombotic, anti-inflammatory and growth inhibitory effects), is associated with decreased CVD and CRD risk. Four different classes of CV medications, shown to block A II, or some other part of the RAAS, are associated with improved CVD and CRD outcomes (Fig 3). **Beta-blockers** [which block renin (from the kidney) from converting angiotensinogen (from the liver) to angiotensin I], **ACEIs**, **ARBs** and **aldosterone antagonists** have all been shown, in many different

trials, to be associated with decreased CV and CRD morbidity and improved outcomes.

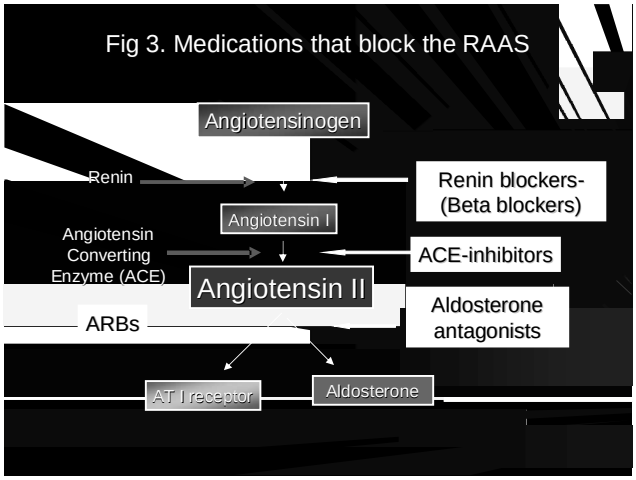


Fig 3: Blocking A II can be done in two ways:

- By blocking the conversion of angiotensin I to angiotensin II, through inhibition of the enzyme (from the lung) that catalyzes that conversion, using angiotensin-converting enzyme (ACE) inhibitors.

- By preventing the circulating angiotensin II from binding to its receptors in vessel walls, using angiotensin II (type 1) receptor blockers (ARBs).

ACE Inhibition

ACE inhibition goes far beyond reducing BP. In early studies it had substantially improved morbidity and mortality in patients with HF and left ventricular (LV) dysfunction.[1] The unexpected 23% reduction in MI risk, along with the expected 20% reduction of mortality from HF, led to further ACE inhibitor studies. The resultant landmark trial, the **HOPE (H**eart **O**utcomes **P**revention **E**valuation) study[2] included 9297 patients, followed for 4½ years, with CVD or diabetes and one risk factor (all with normal LV function). The ACE group had a 22% reduction in the primary endpoint, comprised of MI, stroke or death from CVD compared to placebo. Patients with hypertension (47%) were controlled with other medication, before starting ramipril. *It is important to note no benefit was obtained with the 2.5 mg dose of ramipril, and the 10mg dose showed significantly better results than the 5mg dose*.
The diabetic patients in HOPE (38%, >3500 patients) were evaluated in a sub-study called **MICRO-HOPE**.[3] Greater reduction of CV events (25%), were observed in MICRO-HOPE compared with the overall HOPE population, reflecting the higher risk of diabetics. **MICRO-HOPE is the only study to show a reduction in total mortality in T2DM with A II blockade.** In addition, reductions were also observed in such micro-vascular complications as overt nephropathy (24%) and the combined outcome of overt nephropathy, dialysis, or laser therapy (16%). Mean BP in the active treatment group was decreased by 3.3/1.9mm Hg over the course of the study, suggesting that the **benefits** were not BP related and **due largely to vascular-protective effects** (improved ED).

The results of the **EUR**opean trial **O**n reduction of cardiac events with **P**erindopril in stable coronary **A**rtery disease (**EUROPA**)[4] extended the findings of the HOPE trial to demonstrate the benefits of therapy with ACE inhibitors to nearly all patients with CAD. In contrast to HOPE, which used the ACE inhibitor ramipril (Altace) 5-10 mg, EUROPA used perindopril (Aceon) 8 mg once daily. It demonstrated a 20% reduction in combined frequency of CV death, MI, and cardiac arrest within 4·2 years in 12,218 high-risk (but slightly lower than HOPE) patients.

WHOOPS…HOPE for PEACE?

The **P**revention of **E**vents With **A**ngiotensin-**C**onverting-**E**nzyme Inhibition (**PEACE**) trial using trandolapril 4mg vs placebo to evaluate lower risk CAD patients—most were post revascularization on good risk reduction treatment (antiplatelet therapy, beta-blockers and statins)—resulted in no benefit.[5] Does PEACE raise concerns about the beneficial effects of ACEIs? The answer is absolutely, "No."

ACE inhibitors have the broadest impact of any drug in CV medicine. They reduce risk of death, MI, stroke, diabetes and renal impairment in patients with HF or LV dysfunction (LVEF < 40%), post MI, PAD, diabetes, stroke or TIA & AAA and renal dysfunction. ***The absolute benefit depends on baseline risk.*** HOPE demonstrated benefit with ramipril in a broad range of patients with CVD and preserved LV function, who were at high-risk for CV events. EUROPA extended this finding to include perindopril and a population of patients at slightly lower risk. ***Together, 22,515 high risk patients with established CVD or DM randomized to ramipril 10mg or perindopril 8mg vs placebo had a relative risk reduction of 22% and 20% respectively in CV death, MI, stroke or cardiac arrest.***

The PEACE trial involved patients at much lower risk, and the benefits shown were not clinically significant. The study was under-powered. It's probable that with longer follow-up, clinical benefit would be shown in this low-risk group. Data from HOPE showing dose-dependent effects of ramipril on CVD suggest that a higher trandolapril dose might have provided additional benefit.

HOPE, EUROPA and the two hypertension trials, ALLHAT[6] and ANBP2[7] have all shown decreased incidence of T2DM with ACE inhibition.

Conclusions and Clinical Implications Re ACEI Therapy: Clinical data support the use of ACEIs in a broad range of CVD and CRD patients—even those with serum creatinine values approaching those associated with incipient need for dialysis. The dosage of trandolapril needed for vascular protection cannot be concluded from PEACE. ***The absolute benefit obtained depends on baseline risk. Selection of ACEI should depend on clinical judgment (risk along with cost and compliance issues) in conjunction with data from clinical outcomes trials.***

Angiotensin Receptor Blockers

To achieve a more targeted blockade of the actions of A II for possibly even more benefit, ARBs were developed. They act selectively by blocking binding of A II to the angiotensin type 1 (AT1) receptors. By acting at the receptor level, ARBs provide more complete blockade of the RAAS than ACE inhibitors do, and they do not potentiate bradykinins, which are thought to mediate the ACEI-induced cough. ARBs have effects similar to those of the ACE inhibitors with regard to hemodynamics, neurohormones, and exercise capacity, and in some patients they may be better tolerated.

A series of large-scale clinical trials have established the efficacy of ARBs as an alternative to ACE inhibitors or as an add-on to treatment of systolic HF and show they are beneficial even in those with preserved LV function (Table 1). The results of the **CHARM C**andesartan in **H**eart failure **A**ssessment of **R**eduction in **M**ortality & morbidity study (largest ARB study) further emphasize the importance of blocking the deleterious effects of the RAAS on the CV system. [8] [9] [10] [11]

Table 1. CHARM Program Results

End point	Alternative trial (n=2028)	Add-on trial (n=2548)	Preserved trial (n=3025)
All-cause mortality	Trend to benefit	Trend to benefit	No effect
CV death/HF hospitalization	Significant benefit (P < 0.004	Significant benefit P = 0.011	Trend to Benefit P = 0.118
CV death benefit	Significant benefit P = 0.072	Significant benefit P = 0.029	No effect
HF hospitalization	Significant benefit P < 0.001	Significant benefit P = 0.014	Trend to benefit P < 0.072

Most notably, these benefits were achieved on top current state-of-the art HF therapy, including beta-blockers, diuretics, digitalis, spironolactone, and/or ACE inhibitors, at dosages close to current recommended levels. New-onset T2DM was reduced by 28% in the candesartan-treated patients.

Other trials have demonstrated efficacy and non-inferiority, but not superiority, of ARBs in various clinical situations.

- The Valsartan in Acute Infarction trial (VALIANT), which randomized 14,703 patients, concluded that an ARB (valsartan) is as effective as ACEI (captopril) in patients at high risk for CV events post MI, but combining them increased risk.[12] This study and another post MI study, OPTIMAAL[13] demonstrate the beneficial effects of ARBs along with better tolerability.

- In ELITE II, losartan (50mg) was found not to be superior to captopril (50mg Tid) in improving survival in elderly HF patients, but was significantly better tolerated.[14]

- Three recent studies show that ARBs can slow the progression of CRD among patients with T2DM (with HBP and microalbuminuria).[15] [16] [17] In an editorial accompanying these publications, Dr Thomas Hostetter states that he believes that the observed effects occurred because of inhibition of the RAAS, and he suggests that ACE inhibitors, which are known to prevent kidney disease in type I DM, would achieve the same effect more cheaply.[18] Interestingly, Dr Edmund J Lewis, principal investigator of one of the newly published studies, said that his group had previously reported that the ACE inhibitor captopril prevented kidney disease in patients with TIDM.[19] He couldn't get peer-reviewed funding to study the T2DM population, so he

went to the pharmaceutical industry (where the money is).

- The ARB vs ACEI in T2DM and nephropathy (DETAIL) trial—250 randomized patients—concluded that these two classes of A II blockade were equally effective in stemming urinary albumin loss and decrease in glomerular filtration rate (GFR).[20] In addition, a dramatic reduction in predicted mortality was seen with the use of either drug emphasizing the importance of A II blockade in this setting.

- Emerging evidence from the LIFE[21] and CHARM trials has shown respective 25% and 28% reductions in the incidence of T2DM with ARBs.

Conclusions and Clinical Implications: There are many other studies, not recounted here, in which both ACEIs and ARBS demonstrate the benefits of A II blockade in multiple clinical situations. ARBs appear non-inferior to ACE inhibition in clinical situations where A II blockade is indicated. They are better tolerated.

Criteria for Choice of Agent (ACEI vs ARB):

- Should reduce BP over 24 hours (i.e. be long-acting) in order to reduce end-organ damage and the incidence of early morning cardiovascular events. **It's a draw.**

- Should have direct protective properties on end organs, such as the heart, brain and kidney**. Another draw**

- Should have a favorable interaction profile and be well tolerated and safe. **A draw** (even though ARBS are better tolerated)

- Should have proven CV morbidity and mortality benefits. **ACEI is the winner** because it is the only form of A II blockade with proven mortality benefit in a large study—MICRO-HOPE. Both decrease morbidity, mortality and progression of disease. We anticipate that ARBS will be proven equal but doubt they will be proven better.

- Cost. **ACEI is the winner** because the cost of ARBs can be 2-4 times higher than generic ACEIs.

Summary/Conclusion:

- A II Blockade is good. No Evidence of superiority of ARB over ACEI.

- We should not place comfort above efficacy and safety (i.e. ACEIs are the only agents with ↓ mortality benefit in DM).

- Cost should always be part of the equation.

- ACEIs are first choice, but use ARBs in situations where ACEI can't be tolerated, and maybe as an add-on or in combo for patients with HF and T2DM/ microalbuminuria, where benefits appear additive.

- ACEIs remain the logical first-line therapy for **high-risk patients** post MI, CVD (CAD, PAD, carotid vascular disease and cerebral vascular disease); **all** patients with T1 or T2DM; **all** CRD patients; and **all** with LV dysfunction (LVEF < 40%) with or without HF. ACEIs should be first choice for MetS and hypertension for all the same reasons.

- The good news is: ARBs are a safe and almost equally effective alternative.

- All high-risk patients are going to need poly-pharmacy in conjunction with A II blockade to decrease risk. Therapy should include aspirin, statins, beta blockers and combination treatments for BP and glucose control where indicated, in addition to therapeutic lifestyle changes—diet, exercise and tobacco cessation.

- Choice of ACEI: If cost is the issue, enalapril 20mg 2x daily (40mg) or captopril 50mg 3x daily (150mg) is optimal. If it is compliance and cost, lisinopril 40mg daily is optimal. Without cost constriction, ramipril 10mg is the choice because of the known effective dosages used in the clinical trials.

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