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Evidence Base for Combining ACE Angiotensin Converting Enzyme Inhibitor with ARB Angiotensin Receptor Blocker

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Abstract: RAS (Renin Angiotensin System) cascade though important in maintaining salt and water balance could be deleterious if it is over active. Angiotensin II, produced by ACE and non-ACE pathways could contribute to progress of hypertension, renal and cardiac failure.

The conventional ACE Inhibitors reduce the levels of Angiotensin II but, over a period of time, due to ACE escape, become ineffective. Adding Angiotensin Receptor Blocker (ARB) the RAS activity is substantially suppressed. Besides stimulation of AT₂ receptor would be an added benefit. *The controversy of using Dual blockade is now gradually yielding impressive data in its favor. Several trials support the use of ACE and ARB in preventing progress of congestive cardiac failure, renal failure, diabetic and non-diabetic nephropathy.*

The use of Dual blockade in uncomplicated hypertension is not recommended.

A final answer in the use of ACE with ARB would be available in 2007 when the results of ONTARGET/TRANSEND trials are published.

Renin Angiotensin System (RAS) has evolved to maintain salt, water and electrolyte balance.¹ Excess activity of RAS is fraught with deleterious effects. The target organs damaged are heart, kidney, brain and peripheral vessels.

RAS cascade (Figs 34.1 and 34.2) is activated by variety of stimuli due to decrease effective blood volume resulting from low sodium diet, diuretics, congestive cardiac failure, cirrhosis, nephrotic syndrome.

RAS contributes to the pathophysiology of² (Figs 34.3 and 34.4):

- Systemic hypertension
- Diabetic nephropathy
- Congestive cardiac failure (Fig. 34.3).

Angiotensinogen is converted to angiotensin by two distinct pathways:²

- A. ACE dependent (angiotensin converting enzyme)
- B. Non-ACE or alternate pathway

Non-ACE dependent is due to trypsin, kallikrein, tonin and chymase

ACE dependent Angiotensin regulates:

- A. Electrolytes
- B. Blood pressure

Non-ACE dependent are mostly concentrated in tissues and are involved in cellular and tissue repair.

There are several Angio II receptors viz. AT₁, AT₂, AT₃ and AT₄. In humans two main types viz: Angiotensin type I (AT₁) and angiotensin type II are of great importance.⁵ The significance of AT₃ and AT₄ is not known at present.

AT₁ receptor is responsible for:

- Vasoconstriction
- Aldosterone synthesis
- Vascular smooth cell proliferation
- Cardiac contraction/hypertrophy

AT₂ receptor counter acts AT₁ is responsible for:

- Tissue repair
- Inhibition of cell growth proliferation
- Modulation of extracellular tissue repair

RAS blockade is achieved either by blocking renin, aldosterone or production of Angio II. ACE inhibitor effectively blocks conversion of Angiotensin I to Angiotensin II.

As indicated earlier, ACE Inhibitor does not block Angiotensin I. conversion at tissue level through alternate pathway. Hence, the concept of angiotensin receptor blockade was conceived to suppress Angiotensin II activity.

Differences between ACE Inhibitor/ARB:

- Action on angio II:* ACE inhibitor reduces production of Angiotensin II, but does not inhibit syntheses from non-ACE pathway. While ARB blocks the receptors and inhibits action of Angio II regardless of the source.
- ACE inhibitor, by blocking conversion of Angio I to Angio II* reduces levels of angio II, while with ARB Angio II is elevated. Since AT₂ receptors are not blocked, elevated Angio II stimulates AT₂ receptor to provide protective, action against AT₁ receptor.
- ACE inhibitors increase bradykinin which mediates the side effects of ACE inhibitor.

Dual Blockade

It is observed that ACE inhibitor does not reduce the angio II levels formed by non-ACE pathway and at tissue levels. 80% of tissue angiotensin II is formed by non-ACE pathway in left ventricle and 40% in kidney.

To offset the disadvantage of increased levels of tissue Angio II by alternate pathway, usage of ARB is logical. The combination of ARB/ACE inhibitor will achieve more complete RAS blockage than ACE inhibitor alone. Besides, Angio II escape commonly seen with ACE inhibitor is offset by using ACE inhibitors and ARB together.

Clinical Studies

Dual Blockade in Hypertension^{6a}

Hypertension is a key risk factor for cardiac, renal, cerebral and eye complication. Monotherapy does not control the blood pressure as satisfactorily as with dual therapy.

In view of complete block of RAS activity, a combination of ACE/ARB has been used in several trials.

Combination is extremely effective in hypertension with comorbid condition like diabetes and microalbuminuria,⁷ diabetic nephropathy, and non-diabetic nephropathy. Combination of candesartan and lisinopril reduced albumin urinary excretion (CALM study).⁸ It is also seen that the combination of ACE/ARB is more effective than doubling the dose of ACE inhibitors. However no studies exist to see whether ACE / ARB combination is superior to ACE inhibitor in combination with an another antihypertensive like a diuretic.⁴

Renal Disease

Renin angiotensin system contributes to diabetic nephropathy by exerting both hemodynamic and non-hemodynamic effects on renal cells thus contributing to progress of nephropathy by:

- Glomerular hypertension
- Alteration in glomerular basement membrane filtration
- Altering immune system, renal growth factor, profibrogenic factors, fibrosis and scarring.

Several studies suggest combination therapy is demonstrated to be more effective in preventing end stage renal disease (ESRD). CALM study,⁸ i.e. candesartan and lisinopril in patient with hypertension, diabetes mellitus and micro- albuminuria, indicate a greater reduction of blood pressure and micro-albuminuria than with monotherapy. The urinary albumin creatinine ratio decreased by 50% in combination, while with candesartan and lisinopril separately the reduction was only 24% and 39% respectively.

The transforming growth factor B₁ in proteinuric patient with renal failure increased in spite of adequate dose of lisinopril but with addition of losartan (50 mg/day) the levels of elevated B₁ growth factor reduced by 38% after a month.

The current American Diabetes Association position statement asserts that B level evidence to support that combination of ACE inhibitors and ARBs which will decrease albuminuria more than either agent alone.

Systolic Heart Failure (HF)

Central to use of RAS antagonist in HF is demonstration of high levels of RAS activity with substantial increase in renin, aldosterone and angiotensin II. The increase levels are seen despite adequate doses of ACE inhibition.⁹ Hence the usage of ACE and ARB were proposed.

The CHARM¹⁰ and Val He FT¹¹ trials, acting on this premise added candesartan and valsartan respectively to ACE inhibitor. CHARM added trial showed 15% reduction in risk of cardiovascular deaths in a median follow-up of 41 months. The blood pressure reduction was 4.6 mm/3.7 mm. Hg at 6 months interval.

The Val He FT study indicates reduced hospital admission by 27.5% though the reduction of mortality was not significant.

It was also observed that reduction in morbidity and mortality were impressive when the LV ejection fraction is less than 30%.

Ongoing Trials

Ontarget/transend trials: ONTARGET (on going Telmisartan alone and in combination with Ramipril global end-point trial) is launched on a massive scale.¹² The study population consists of 28,400 patients spread across 40 countries. The results are due to be published in 2007.

Ontarget study is an international double blind, multicentric study. It has two aims:

- a. A principal study (ONTARGET)
- b. A parallel TRANSCEND, trial i.e. Telmisartan.

Randomized Assessment study in ACE inhibitor intolerant patient with cardiovascular disease. The end points of the studies are death caused by cardiovascular disease, acute myocardial infarction, stroke and hospitalization due to congestive cardiac failure. The secondary end points include newly diagnosed heart failure, Type-2 Diabetes mellitus, nephropathy, dementia and atrial fibrillation. This is a definitive study to answer benefits of dual therapy in prevention of vascular events.

In conclusion ACE inhibitors and ARB have different mode action acting at different sites. ACE inhibitor though effective, over a period of time, cause ACE escape resulting in blunting of its response. Adding ARB to ACE inhibitors will substantially suppress the RAS activity and is more effective than ACE Inhibitor alone.

The current recommendation with dual blockade are as follows:⁸

- a. Hypertension with possibly LVH, micro albuminuria, diabetes mellitus
- b. Systolic heart failure when symptoms persist despite use of diuretic beta blockers and ACE Inhibitors
- c. Nephroprotection in diabetic and non- diabetic.

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