Optimizing Cardiovascular and Renal Risk-reduction

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The goal of all our treatment strategies is risk-reduction resulting in *improved outcomes at the lowest cost*. Blocking angiotensin II (A II) should be one of the goals of all cardiovascular disease (CVD) and renal risk-reduction strategies. The major focus of this *Heartbeat* will be to show how and why blocking A II decreases risk and improves outcomes.

Double Threat

Hypertension and diabetes are well-known risk factors for both CVD and chronic renal disease (CRD). This risk is magnified when hypertension occurs concomitantly with diabetes (DM). Diabetes is recognized as a coronary heart disease (CHD) equivalent by almost all medical and healthcare organizations. This designation has evolved from data showing that diabetic individuals without CHD have the same risk for CVD events as patients who have a history of CHD or myocardial infarction (MI).[1] In addition, much of the clinical significance of hypertension and DM relates to its inextricable link to renal dysfunction. DM is the most common cause of end-stage renal disease (ESRD) in the US and Europe. The combination of DM and hypertension is associated with 6-times greater risk of ESRD than hypertension alone.[2]

Because of the increased risk for CVD and CRD, diabetic patients warrant more aggressive anti-hypertensive therapy and lower blood pressure goals than the general population (Table 1).

Table 1: BP Goals for Diabetic patients

Organization	Goal (mm hg)
National Kidney Foundation	<130/80*
American Diabetes Association	<130/80
JNC VI	<130/85*

* <125/75 for patients with renal insufficiency and proteinuria >1g.24 hr.

It is important to realize that achieving adequate control of blood pressure (BP) in diabetics will require combination therapy (multiple drugs, usually 3-4, administered in meaningful doses), which is more effective than higher doses of mono-therapy. Blood pressure control is even more important than glycemic control, since the slope of the relationship between glucose and CVD/CRD is relatively modest.

Renal Function: The Cinderella of CV Risk Profile

The presence of altered renal function in patients with HBP, DM, advanced heart failure (HF), and post- MI is associated with a higher CV morbidity and mortality.[3] Altered renal function is based on one or both of the following two findings:

1) Reduction of the glomerular filtration rate (GFR), reflected by an elevated serum creatinine (>1.5mg/dl in men; >1.4mg/dl in women) or a decreased creatinine clearance (<60-70ml/min).
2) Detection of elevated urinary excretion of albumin or protein, which points to a derangement in the glomerular filtration barrier.
   – Microalbuminuria, 30-300mg/day, usually correlates with the presence of nephrosclerosis (increased glomerular permeability which can be seen in pathologic circumstances, i.e. hypertension and DM), as well as a number of physiologic events, i.e. salt stress, exercise, pregnancy and diuresis.
   – Macroalbuminuria, >300mg/day, generally indicates established renal parenchymal damage.

As independent predictors of CV risk these parameters should routinely be measured in these clinical situations.

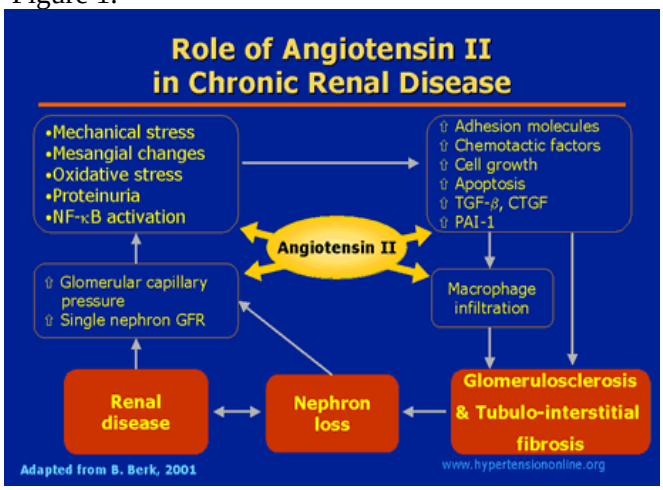
This information has several therapeutic implications. First, hypertensive kidney damage can be prevented by early and aggressive lowering of BP, particularly in those patients with microalbuminuria (Table 1). Secondly, anti-hypertensive agents that further reduce aggravation of high CVD/CRD risk should be used, especially in diabetics—ACE inhibitors. The most effective combination for lowering BP is an

ACE inhibitor and a dihydropyridine calcium channel blocker. In HF, the combination of an ACE-inhibitor and a beta-blocker seem to be most renal-protective. Renal and CV outcome are also improved by an ACE-inhibitor post-MI. Finally, **renal and CV outcome seem to run in parallel** in all of these situations.

Role of Angiotensin II

The most viable explanation has to do with endothelial function. The endothelium works to maintain vascular integrity through a variety of 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 increased A II on endothelial function are shown below.

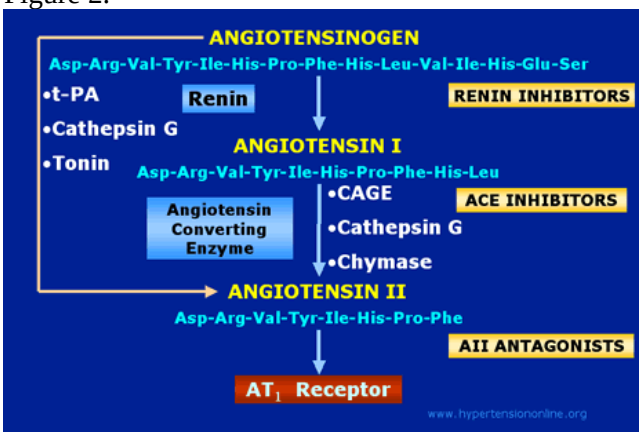
Figure 1.



Blocking A II through inhibition of the renin angiotensin system (RAS) results in more normal endothelial function (more vasodilatory, anti-thrombotic, anti-inflammatory and growth inhibitory effects) and resultant decreased CVD and CRD risk. **All** CVD risk factors as well as CRD are associated with endothelial dysfunction (ED). The renin angiotensin system (RAS) is one of the primary mediators of ED through its production of A II.

Three different classes of medications have been shown to block A II (Figure 2). **It is no coincidence that beta-blockers** (renin inhibitors), angiotensin converting enzyme (**ACE)-inhibitors** (which block the conversion of angiotensin I to angiotensin II) **and angiotensin receptor blockers** (ARBs) - A II antagonists—**have been shown to be associated with decreased CV and CRD risk.**

Figure 2.



Management of CVD and CRD risk will require an aggressive approach to multiple abnormalities. No single type of intervention will work. Aggressive treatment of all risk factors—HBP, DM, dyslipidemia and tobacco dependence—along with a diet and exercise program, is necessary. Emerging knowledge about the wide-ranging pathophysiologic effects of A II creates a virtual mandate to include an agent that blocks A II as a necessary component of therapy when high risk is identified.

ACE Inhibition

The benefits of ACE inhibition appear unrelated to BP reduction. ACE inhibition has been shown to substantially improve morbidity and mortality in patients with HF and left ventricular (LV) dysfunction.[4] 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** study[5] (**H**eart **O**utcomes **P**revention **E**valuation) included > 9000 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. The results of

this trial were very definitive, giving the clinician great comfort in their reliability.

The diabetic patients in HOPE (38%, >3500 patients) were evaluated in a sub-study called MICRO-HOPE. [6] Greater reductions (25%) were observed in MICRO-HOPE compared with the overall HOPE population, reflecting the higher risk of diabetics. 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).

Further sub-analysis revealed substantial CV risk reduction in patients (965) with renal insufficiency (40% mortality risk reduction in patients with renal insufficiency compared to 10% in those without). **CRD is a risk factor for CVD, and it is more than coincidence that ACE inhibitors are both cardio-protective and renal-protective**.

A meta-analysis of 12 trials of ACE inhibition in patients with normal BP and type I DM and microalbuminuria revealed findings that suggest ACE inhibition may help reverse renal disease in diabetics and that the benefit is independent of BP reduction.[7]

Another recent meta-analysis supports the role of ACE inhibitors as the anti-hypertensive agent of first choice in patients with non-diabetic renal disease and also suggests that ACE inhibitors may also be of benefit in patients with CRD in the absence of hypertension or elevated serum creatinine.[8] Most recently, in a post hoc, secondary analysis of the **R**amipril **I**n **N**ephropathy **T**rial (REIN) the following conclusions were made: [9]

1) ACE inhibitors prevent ESRD, regardless of baseline GFR and severity of renal insufficiency.
2) The risk of ESRD and absolute number of events decreased by ramipril is highest in the cases with the lowest GFR.
3) Treatment started at earlier stages stabilizes renal function and prevents need for dialysis.

The authors commented, "ACE inhibition should be offered to all patients with chronic nephropathies, regardless of renal function.... even when GFR approximates levels requiring replacement therapy." They observe that, "This message will never be emphasized enough, given the fact that < 20% of patients in need are currently offered this renal-protective treatment, a figure that decreases to 11-12%, if the GFR is severely impaired."

Angiotensin II Receptor Blockers

Three new studies ([10] [11] [12]) show that ARBs can slow the progression of renal disease among patients with type II DM, both those with HBP and microalbuminuria and those with macroalbuminuria, a marker of more advanced disease. (This is not surprising given the information presented previously about A II blockade.) In an editorial accompanying the publication, Dr Thomas Hostetter states that he believes that the observed effects occurred because of inhibition of the RAS, and he suggests that ACE inhibitors, which are known to prevent kidney disease in type I DM, would achieve the same effect more cheaply.[13] 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 type I DM.[14] He couldn't get peer-reviewed funding to study the type II diabetic population so he went to the pharmaceutical industry.

Dr Hostetter further states, " We must focus more attention on the regrettable tendency of study sponsors to drop good drugs from important trials when their patents expire and the drugs therefore become less profitable. The legitimate need to develop and profit from new compounds must be explicitly balanced against the obligation to test established and effective, but cheaper, agents." Even more importantly, despite the mounting evidence for their efficacy, established treatments for the maintenance of renal function "remain woefully underutilized."

Conclusions / Recommendations:

1) When developing a clinical strategy to optimize both CVD and CRD risk, think cardiovascular and renal-protection simultaneously. It seems that the two disease entities are inextricably related, and the presence of one is associated with or propagates the other. ED is the common denominator. All risk factors must be aggressively treated (HBP, dyslipidemia, DM

and tobacco dependence) and a diet that emphasizes sodium and protein restriction (where applicable) to reduce glomerular hypertension, and a specifically tailored exercise program should be recommended. Each of these modalities will improve ED.

2) The double threat of HBP and DM together cannot be over emphasized with regard to CVD and CRD risk. These people are at markedly higher risk for HF, heart attacks, strokes and ESRD. HBP poses more of a risk to diabetic patients than hyperglycemia (sugar still has to be treated aggressively). Treat HBP to newer and lower target levels with combination therapy.

3) Think A II blockade as part of this treatment program because of the vascular-protective effects. When we choose agents, BP lowering or a decrease in proteinuria alone does not indicate success. Improved outcomes when available should determine the choice. When addressing combined cardio-renal-protection, an ACE inhibitor is the A II blocker of choice. Beta blockers should be used in HF, post MI and as an ad-on for HBP. ARBs can be used as an add-on where indicated and are the drug class of choice when an ACE inhibitor cannot be tolerated in any of these clinical situations.

4) ACE inhibitors should be used for all HF, and CVD or high-risk CVD patients. This covers by definition all diabetics and patients with renal disease. ACE inhibitors are "the last best hope" for preventing ESRD and dialysis and decreasing cardiac events. The difficulty in initiating therapy is usually worth the effort. From a practical standpoint, acute elevations of creatinine that may occur in these patients are generally not clinically significant and stabilize quickly with volume repletion and/or discontinuation of diuretics. *Patients with a persistently greater than 20% increase of BUN/creatinine should be evaluated to rule out renal artery stenosis.*

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