

## SAFE AND EFFECTIVE ANTI-HYPERTENSIVE DRUG THERAPY IN DIABETIC NEPHROPATHY- A META ANALYSIS

Dr. Keshav Kunwar<sup>1\*</sup>, Dr. Sina Zare<sup>1</sup>, Dr. Miriam L. Hnamte<sup>1</sup> and Bhubneswari Bhatt<sup>2</sup>

<sup>1</sup>Pharm.D, Department of Pharmacy Practice, Krupanidhi College of Pharmacy, Bangalore-560035, India.

<sup>2</sup>B Pharm, Dayanandsagar College of Pharmacy, Bangalore-560068, India.

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### \*Corresponding Author

**Dr. Keshav Kunwar**

Pharm.D, Department of  
Pharmacy Practice,  
Krupanidhi College of  
Pharmacy, Bangalore-  
560035, India.

### ABSTRACT

Diabetic nephropathy is a critical medical problem and the leading cause of end-stage renal disease. Some patients are characterized with albuminuria and renal failure where other patients are not as considering a long history of diabetes. Slowing progression of renal failure is an important factor to consider when selecting antihypertensive medications for patients with renal failure and proteinuria. Proteinuria is a sensitive and independent predictor for the progression of nephropathy and cardiovascular disease. Higher levels of proteinuria are associated with increased progression of renal and cardiovascular disease and that reductions in proteinuria are associated with a decrease in the rate of renal function deterioration and

cardiovascular events Both the angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been shown to have these effects. However, the evidence for the renoprotective effects of calcium antagonists is more equivocal. Nondihydropyridine calcium antagonists (NDCAs) are superior to Nondihydropyridine calcium antagonists (DCAs) in reducing proteinuria. NDCAs, alone or in combination with an ACE inhibitor or an ARB, should be preferred over DCAs for treating hypertensive patients with proteinuric renal disease or renal insufficiency. Effective antihypertensive treatment postpones renal insufficiency in diabetic nephropathy. Both angiotensin converting enzyme (ACE) inhibitors and the nondihydropyridine calcium antagonists, (non-DHPCAs) reduce both arterial pressure and proteinuria in those with diabetic nephropathy significant reductions in proteinuria, findings not observed in the atenolol group. Spironolactone daily added to recommended antihypertensive treatment including ACE inhibitors and/or ARBs is

well tolerated by reductions in blood pressure and albuminuria in type 2 diabetic patients with nephropathy.

**KEYWORDS:** Diabetic nephropathy, Hypertension, albuminuria, End-stage renal disease.

## INTRODUCTION

Diabetic nephropathy is the leading cause of end-stage renal disease. Interruption of the renin–angiotensin system slows the progression of renal disease in patients with type 1 diabetes, but similar data are not available for patients with type 2, the most common form of diabetes. Over the past 20 years, while deaths attributed to hypertensive vascular disease have declined in the United States, the incidence of end-stage renal disease (ESRD) associated with hypertension has increased.<sup>[1]</sup>

About 40% of all insulin dependent diabetic patients develop persistent proteinuria, a decline in their glomerular filtration rate, and increased blood pressure, collectively constituting the clinical syndrome of diabetic nephropathy. Increased blood pressure accelerates the development of diabetic glomerulopathy. About 40% of all insulin dependent diabetic patients develop persistent proteinuria, a decline in their glomerular filtration rate and increased blood pressure, collectively constituting the clinical syndrome of diabetic nephropathy.<sup>[2]</sup>

The concept that the combination of an ACE inhibitor with a non-DHPCA reduce proteinuria to a greater extent than either agent alone. This added antiproteinuric effect occurs at lower doses of each drug and is independent of further reductions in arterial pressure. These findings could have ramifications for slowing renal disease progression in patients with nephropathy from type 2 diabetes. In persons with renal insufficiency secondary to NIDDM, similar levels of blood pressure control with either lisinopril or NDCCBs slowed progression of renal disease to a greater extent than atenolol. Moreover, this enhanced slowing of renal disease progression correlated with sustained and significant reductions in proteinuria, findings not observed in the atenolol group.<sup>[3]</sup>

Mostly the blood pressure remain normal in patients who do not have perceptible renal failure whereas hypertension is seen in those patients with nephropathy. The increase in progression of nephropathy and cardiovascular events are highly correlated to the degree of proteinuria in the patients. It has been shown that reduction in progression of nephropathy

correlates with the reduction of blood pressure and proteinuria in a post hoc analyses of recent studies.<sup>[3]</sup> The obstruction of the renin–angiotensin system delays the progression of renal disease in patients with type 1 diabetes, but similar informations are not available for patients with type 2 diabetes. The common risk factors for diabetic nephropathy includes Microalbuminuria and Hypertension.<sup>[10]</sup> It has been found that long term antihypertensive treatment results in reduction of progressive decline of kidney function in diabetic nephropathy.<sup>[6,9]</sup> As a result, the safe and effective use of anti-hypertensive drugs in diabetic nephropathy will be summarized.

### **Classifications of Anti-hypertensive Drugs**

1. Diuretics.
2. Beta adrenergic blockers.
3. Calcium channel blockers.
4. Angiotensin converting enzyme inhibitors.
5. Angiotensin receptor blockers.
6. Sympatholytics and adrenergic blockers.
7. Direct arterial vasodilators

### **DIURETICS**

#### **Mechanism of action.**

- Initial effects: through reduction of plasma volume and cardiac output.
- Long term effect: through decrease in total peripheral vascular resistance.

#### **Types**

- Thiazides and related diuretics:Hydrochlorothiazide, chlorthalidone
- Loop diuretics:Furosemide, Torsemide
- Potassium sparing diuretics:Spironolactone, Amiloride

#### **Studies showed that**

1. Low dose of diuretic based (chlorthalidone) treatment is effective in preventing major Cardiovascular disease. A Systolic Hypertension in the Elderly Programme (SHEP) antihypertensive drug regimen was carried out where they assess the effect of low-dose, diuretic-based antihypertensive treatment on major cardiovascular disease (CVD) event rates in older, non-insulintreated diabetic patients with isolated systolic hypertension (ISH), compared with nondiabetic patients. The blood pressure of both diabetic and nondiabetic

patients lowered, with few adverse effects. For both diabetic and nondiabetic patients, all outcome rates were lower for participants randomized to the active treatment group than for those randomized to the placebo group.<sup>[10]</sup>

2. That spironolactone safely adds to the reno- and cardiovascular protective benefits of treatment with maximally recommended doses of ACE inhibitor and ARB by reducing albuminuria and blood pressure in type 2 diabetic patients with nephropathy.<sup>[8]</sup>

## **CALCIUM CHANNEL BLOKERS**

### **Mechanisms of action**

- Decrease in the concentration of free intracellular calcium ions results in decreased contraction and vasodilation.
- Diuretic effect through increase in renal blood flow and glomerular filtration rate.
- Inhibition of aldosterone secretion.

### **Types**

- Dihydropyridine: Nifedipine, amlodipine, felodipine, nicardipine, lacidipine.
- Non dihydropyridine: - Phenylalkylamine: verapamil. - Benzothiazepine: diltiazem.

### **Studies showed that**

1. A systematic review was conducted to assess the differential effects of DCAs and NDCAs on proteinuria in hypertensive adults with proteinuria, with or without diabetes, and to determine whether these differential effects translate into altered progression of nephropathy. This analysis supports (1) similar efficacy between subclasses of calcium antagonists to lower blood pressure, and (2) greater reductions in proteinuria by NDCAs compared to DCAs in the presence or absence of diabetes. Based on these findings, NDCAs, alone or in combination with an angiotensin.<sup>[1]</sup>

2. The treatment of hypertension with ACE inhibitors in diabetic patients reduces proteinuria and slows progression of nephropathy compared with agents that do not maintain declines in proteinuria. Calcium channel blockers (CCB5) have variable effects on proteinuria. Result shows in persons with renal insufficiency secondary to non-insulin dependent diabetes mellitus NIDDM, similar levels of blood pressure control with either lisinopril or nondihydropyridine CCBs NDCCBs slowed progression of renal disease to a greater extent than atenolol. Moreover, this enhanced slowing of renal disease progression correlated with

sustained and significant reductions in proteinuria, findings not observed in the atenolol group.<sup>[1]</sup>

## **BETA ADRENERGIC BLOCKERS**

### **Mechanisms of Action**

- Initial decrease in cardiac output, followed by reduction in peripheral vascular resistance.
- Other actions include decrease plasma renin activity, resetting of baroreceptors, release of vasodilator prostaglandins, and blockade of prejunctional beta-receptors. Common examples are propranolol, metoprolol, atenolol.

### **A study showed that**

It could not evaluate whether effects on nephropathy of the present treatment, which included beta-blockers, were due solely to reduction in blood pressure, since beta-blockers have several other vascular and metabolic effects.

It was found that propranolol has a considerable disadvantage in diabetic patients-namely, an increased tendency to hypoglycaemic unawareness. Once changed to metoprolol (a cardioselective beta-blocker) hypoglycaemic unawareness was not a problem for the patients during many months of treatment.<sup>[5]</sup>

## **ACE INHIBITORS**

### **Mechanism of Action**

- Inhibition of circulating and tissue angiotensin- converting enzyme.
- Increased formation of bradykinin and vasodilatory prostaglandins.
- Decreased secretion of aldosterone; help sodium excretion.

### **Studies showed that**

1. Ace inhibitors and nondihydropyridine calcium antagonists NDPCA reduce both arterial pressure and proteinuria in those with diabetic neuropathy. Combination of Ace inhibitor + verapamil produces greater reduction in proteinuria.<sup>[13]</sup>
2. Enalapril or metoprolol usually combined with frusemide. Enalapril has an antiproteinuric effect independent of the effect on systemic blood pressure. Enalapril can reduce the rate of decline in kidney function in patients with diabetic nephropathy more than equally effective antihypertensive treatment with metoprolol. This points to a specific renal protective effect of angiotensin converting enzyme inhibitors in diabetic nephropathy.<sup>[4,15]</sup>

## ANGIOTENSIN RECEPTOR BLOCKERS

### Mechanism of action

They act by blocking type I angiotensin II receptors generally, producing more blockade of the renin - angiotensin - aldosterone axis.

Example: Losartan, Olmesartan, Irbesartan.

### Studies showed that

1. Losartan reduced incidence of a doubling of serum creatinine concentration but no effect on rate of death. Level of proteinuria declined by 34% with Losartan. Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and it was generally well tolerated.<sup>[5,14]</sup>
2. Irbesartan is renoprotective independently of its blood-pressure-lowering effect in patients with type 2 diabetes and microalbuminuria.<sup>[10,5]</sup>

## CONCLUSION

Diabetes and hypertension frequently occur together. There is substantial overlap between diabetes and hypertension in etiology and disease mechanisms. Obesity, inflammation, oxidative stress, and insulin resistance are thought to be the common pathways. Greater reductions in proteinuria by NDCAs compared to DCAs in the presence or absence of diabetes. NDCAs, alone or in combination with an ACE inhibitor or an ARB, should be preferred over DCAs for treating hypertensive patients with diabetic nephropathy. Irbesartan, enalapril, atenolol, Lisinopril, spironolactone are safe and effective antihypertensive drug in diabetic nephropathy.

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