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Management of hypertension in patients with chronic kidney disease

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1. Introduction

Chronic kidney disease (CKD) is an important area simply because reduced Glomerular filtration rate (GFR) and/or proteinuria is so very common in clinical practice. GFR below 60 is a very important part of care concern. In the United States (US), the relative percentage of people in each stage of CKD varies. Lower prevalence of patients with GFR below 30 ml/min/1.73 m^2 is probably because cardiovascular (CV) disease like strokes and heart attacks contribute to the deaths in such patients. Diagnosis of CKD is more likely to be predictive of CV events than even having a diagnosis of diabetes. CKD is more ominous from a prognostic standpoint.

2. Blood pressure and risk of renal injury

Glomeruli, the filtering units are vascular units within the kidney (Fig. 1). An afferent arterial goes in and an efferent arterial leaves out the glomerulus. It is an artery–artery connection. The afferent arteriole functions to limit the flow of blood going into the filter. The filter likes to operate at about one-half to two-thirds of systemic blood pressure. Efferent arterial can vasoconstrict during situations of diminished effective arterial blood volume. That obviously, is very important for maintaining necessary pressure for filtration. So for this whole system to work, healthy blood vessels are needed so that one can modulate the amount of blood flow going in and modulate the amount of blood flow exiting.

The problem lies in the eccentric development of vascular disease which is quite important along the afferent arteriole. Increasing severity of the disease limits the ability of the kidney to auto-regulate its blood supply and thus, the kidneys' filters become more vulnerable to the effects of systemic blood pressure (BP). Experimental evidence of this had already been established using radio-telemetric techniques in various rodent models of hypertension (HTN). The amount of glomerulosclerosis directly correlates with BP. Studies have even shown glomerulosclerosis may differ depending on use of a calcium channel blocker (CCB) like amlodipine which is an afferent arteriolar dilator versus renin angiotensin system (RAS) blocker which preferentially dilates the efferent arterial. Using CCB as a monotherapy dilates the afferent arteriole; if BP not lowered enough, then the risk for glomerular injury is markedly enhanced (Fig. 2). Thus practically one need to use RAS blockers first and then add CCB.

Determinants of hypertensive renal injury are related to BP load, BP transmission, and variety of other factors like local BP independent susceptibility mechanisms. There is probably very tight relationship between SBP and risk for renal injury suggesting that there is no right number but that lower indeed may be better.

3. Non-diabetic kidney disease

Increasing proteinuria increases more the likelihood of kidney disease progression and can happen more quickly. This allows opportunity to study effect of proteinuria on kidney outcomes with smaller number of patients and for a shorter period of time. On the other hand, in presence of microalbuminuria, it is unlikely to observe progression of kidney disease as such patients are more likely to die of CV events like strokes and heart attacks. Thus there is need of larger, longer duration studies which have not been done. In non-diabetic kidney disease, probably the best data comes from the MDRD (The Modification of Diet in Renal Disease) study which was

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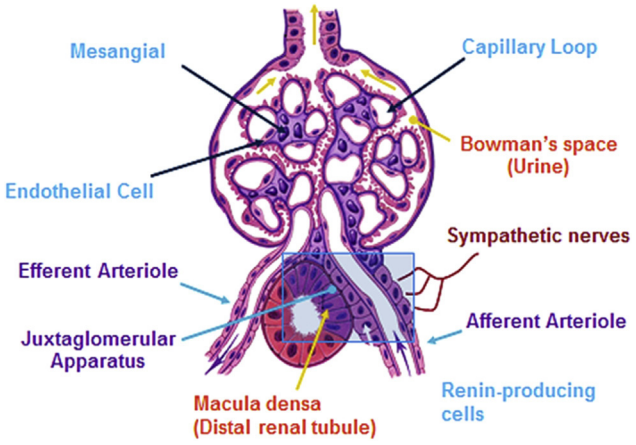

Fig. 1 – The glomerular apparatus of the kidney.

originally designed to look at the effect of diet on the progression of renal disease. Study also looked at two different BP – 140/90 versus 125/75 mmHg. Over a 36-month, for ≥3 g of proteinuria, benefit of 125/75 versus 140/90 was observed in just 8 month. On the other hand, for proteinuria between 1 and 3 g, again 125/75 looks better than 140/90 but it took nearly two years to start to see the benefit. For lower levels of proteinuria, it is unlikely to see any effect of BP within a three-year period of time.

This discussion is important is because one needs to be cautious and know about the clinical trial design before making assumptions about clinical trial data.

4. Clinical studies in non-diabetic kidney disease: Effect of BP on renal outcomes

There are actually only three studies. These are MDRD (The Modification of Diet in Renal Disease) study, REIN-2 (Ramipril Efficacy in Nephropathy) trial, the AASK (The African American Study of Kidney Disease and Hypertension) study and a meta-analysis of a number of the clinical trials.

4.1. *MDRD study*

In this trial 840 patients with quite low GFR (13–55 ml/min/1.73 m^2) were randomized in to two target BP groups (140/90 versus 125/75). Over mean 2.2 years of follow up, lower BP goal was associated with reduced rate of GFR loss compared to the higher goal which was most apparent in people with more than 1 g of protein excretion per. But study did not look at hard end points of like doubling of creatinine, end-stage renal disease (ESRD) or death. Also there was the confounding observation that 48% of the patients in the lower goal BP group were on an angiotensin converting enzyme inhibitor (ACEI) compared to 26% in the goal BP group. There is also a 10-year follow-up MDRD. It also shows more (32%) reduction in ESRD in the lower blood pressure group. But there were limited BP measures and a little higher use of ACE inhibitors in the lower blood pressure group. So, people tended not to really believe the data.

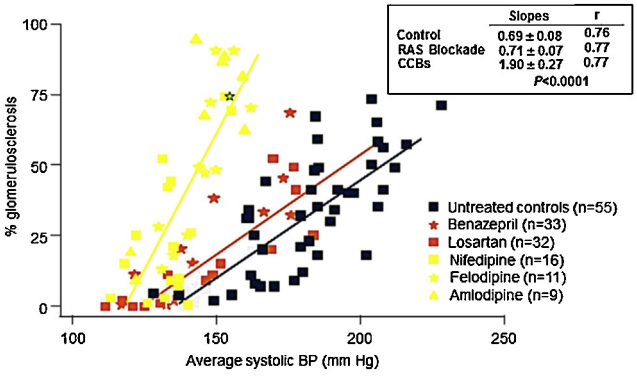

Fig. 2 – Relationship of renal damage to blood pressure.

4.2. *REIN-2 study*

In the ramipril efficacy in nephropathy (REIN) trial, 338 patients with lower GFR, proteinuria were randomized to two different blood pressure goals; 129.6 (intensified) versus 133.7 (conventional). This is not exactly what can be described as a world of difference. Because this is still quite close, it did not really have any evidence of benefit. 23% of patients in the intensified group and 20% in the conventional group progressed to ESRD (hazard ratio 1.00 [95% CI 0.61–1.64]; p = 0.99) over a median follow-up of 19 months. So again this is not definitive probably because the goal blood pressures were so close to one another.

4.3. *The AASK study*

The African American Study of Kidney Disease and Hypertension was a bit larger (1094 patients) and like MDRD had a much wider splay in terms of blood pressure target (140/90 versus 125/75). Achieved BP was 141/85 in the conventional group and 128/78 mmHg in the lower BP group. The lower BP goal did not reduce the clinical composite of 50% reduction of GFR, ESRD, and death compared to the usual BP goal. Over 10 years, those people with more protein in the urine clearly demonstrated a slowing of the rate of progression of kidney disease with the lower blood pressure goal (hazard ratio in the intensive-control group, 0.73; 95% confidence interval [CI], 0.58 to 0.93; P = 0.01) (Fig. 3: upper panel). In contrast, in people with very low amounts of protein in the urine, there is no significant difference (Fig. 3: lower panel). The clue here is the important observation that more the proteinuria, lower should be the goals.

Although all three trials looking at two levels of blood pressure don't appear to convincingly show the benefit of a lower goal, with the clear exception in people with more proteinuria. This is why, on face value the current evidence-based guidelines set goal 140/90 is fine. But some experts might not agree with that. In a meta-analysis of 11 randomized control trials in non-diabetic kidney disease involving 1860 people, it was observed that more the proteinuria, more are the events and vice-versa. What they looked at was doubling of serum creatinine or ESRD, what they did not show is that there was a conclusive benefit below 110 but they did raise the question that systolic BP between 110 and 129 may be beneficial in the patients with more than 1 g of proteinuria per day.