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SYMPOSIUM: RENAL ASPECTS OF CARDIOVASCULAR PHARMACOTHERAPY

Treatment of Hypertension in Patients with Renal Disease

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Summary. **Management of hypertension in people with kidney disease is challenging and generally requires at least three different and complementary acting antihypertensive agents to achieve the recommended blood pressure goal by the JNC VI and WHO guidelines of <130/85 mmHg. This is also true for the recent blood pressure goal for diabetes of <130/80 mmHg recommended by both the National Kidney Foundation and American Diabetes Association for reduction of cardiovascular risk and preservation of kidney function. Commonly used combinations include an ACE inhibitor, which has compelling indications for use in people with kidney disease with a diuretic, generally a thiazide type agent. Angiotensin receptor blockers have clearly shown effectiveness for slowing nephropathy progression in Type 2 diabetes and clearly have a role as first-line agents in that disease. If additional therapy is required, either a beta blocker or calcium antagonist may be added to this antihypertensive 'cocktail'. Beta blockers are particularly effective in people with a high sympathetic drive, i.e. high pulse rates, to lower pressure and reduce cardiovascular risk. Moreover, in recent studies their benefits on kidney function both by reducing proteinuria and slowing decline of kidney function make them good agents to add in the appropriate clinical setting. Given recent data from an analysis of the NHANES III database showing only 11% of people being treated for hypertension with diabetic kidney disease have achieved the blood pressure goal of <130/85 mmHg, it's no wonder the incidence of people starting dialysis continues to climb. Physicians need to work harder and educate patients on the importance of achieving these lower blood pressure guidelines.**

Introduction

Hypertension is a common and serious problem and contributes in a major way to global cardiovascular morbidity and mortality. The degree and duration of elevation in either systolic or diastolic blood pressure (BP) substantially increases the risk of developing a cardiovascular event or renal disease [1–3]. Persons with a family history of hypertension or those who are obese are at particularly high risk of developing hypertension. Hypertension-induced vascular or target organ injury can be prevented or delayed by reducing arterial pressure to <140/90 mmHg. The management of hypertension is now second only to upper respiratory tract infection as an indication for visits to physicians in the United States [4].

In the setting of chronic renal parenchymal disease, hypertension is usually sustained and associated with a greater risk of cardiovascular morbidity and mortality than that conferred by essential hypertension in the absence of kidney disease [5,6]. Hypertension in patients with chronic renal parenchymal disease of either diabetic or nondiabetic etiology should be thought of as adding "gasoline to a burning fire"; it markedly accelerates the loss of renal function, as well as other processes, such as atherosclerosis.

The results of any clinical trial of the effects of antihypertensive treatment on renal disease progression must be considered in the context of the type and magnitude of intervention e.g. BP goal in the trial, ACE inhibitors versus other agents, as well as the stage of the disease at the inception of a trial. Renal function declines at different rates based on the etiology of the renal disease e.g. diabetes versus membranous nephropathy versus IgA nephropathy. Moreover, the timing of achieving BP goal is critically important in the prevention of the "avalanche effect" of renal disease progression. Specifically, intervention to a BP goal of <130/85mmHg in the very early stages of renal dysfunction, i.e. GFR >85 ml/min, is very likely to stop disease progression, whereas intervention when GFR is <50 ml/min will only slow its progression. The difference in timing of intervention is similar to an avalanche coming down a mountain; the farther down the mountain, the less likely it can be stopped.

This concept is exemplified by the results of the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, where the average levels of GFR were >80 ml/min at the start of the trial versus other diabetes trials where the GFR is generally <60 ml/min at baseline [7]. GFR decline was virtually stopped with early BP intervention in the ABCD trial, whereas in other trials of more advanced renal disease GFR, loss occurred at a rate of 2–7 ml/min/year [8]. Furthermore, BP levels attained in the ABCD trial averaged <130/80 mmHg.

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Thus, results of clinical trials in patients with advanced renal disease should not be extrapolated to patients with very early disease, since rates of decline in renal function are not uniformly linear. It is clear, however, that the earlier goal BP is achieved, the more likely renal function will be preserved and nephropathy progression halted.

Management of hypertension in patients with renal disease is largely dependent on the excretory function of the kidneys. Management of this condition should focus on agents that not only lower BP but also reduce microalbuminuria (MA) and/or proteinuria. The presence of MA indicates an increased risk for CV events in all patients and the presence of nephropathy in those with type 1 diabetes [9,10]. MA is defined as a protein excretion of between 30–299 mg/day or 20–200 μg/min, present on two different occasions. Protein excretion >300 mg/day or >200 μg/min represents overt proteinuria [11]. Urinary protein excretion is best assessed by the albumin to creatinine (mg/g) ratio in a spot urine specimen. These values correlate with those obtained from 24 hour urine collections and are much more practical to collect. A guide to screening and management of MA is presented in Figure 1 [11].

Achievement of the recommended BP goal for those with diabetes and/or renal disease using agents that also reduce proteinuria or MA is suggested. A summary of goal BP values from various sets of treatment guidelines is presented in Table 1.

Nondiabetic Renal Parenchymal Disease

Renal dysfunction, both structural and functional, is often demonstrable in hypertensive patients, even those with minimally elevated arterial pressure. The remarkable pathological changes are hyalinization and sclerosis of the walls of the afferent arterioles, the hallmark of hypertensive nephrosclerosis. Involvement of the kidney is usually asymptomatic, with the first objective sign being MA, a marker of impaired endothelial responsiveness [12–14]. Moreover, MA may be a likely factor in the initiation and progression of tubulointerstitial renal injury [15].

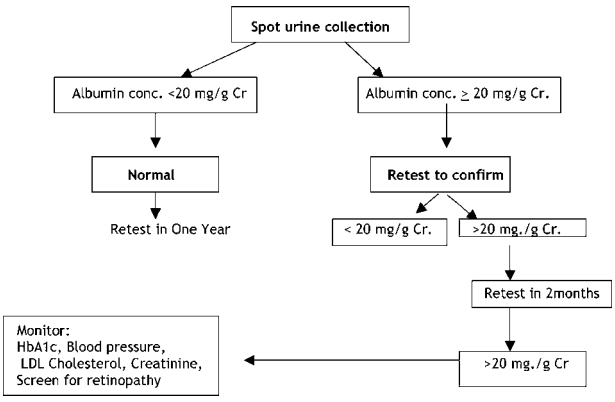

Fig. 1. *Evaluation and work-up of microalbuminuria. Adapted from Keane WF and Eknoyan G, Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Am J Kidney Dis 1999;33:1004–1010.*

Table 1. *Summary of Practice Guideline recommendations for blood pressure and initial treatment*

Group	Goal BP (mmHg)
• British HTN Soc.	<140/80
• Canadian HTN Soc.	<130/80
• Am. Diabetes Assoc	<130/80
• Natl. Kidney Foundation	<130/80
• JNC VI	<130/85
• WHO/ISH	<130/85

Only a small minority of patients with essential hypertension develop progressive renal insufficiency, but the incidence of renal insufficiency does rise progressively with every 10 mmHg increment in systolic pressure [2,16]. African-American patients and those with diabetes have a higher likelihood of developing progressive renal disease than the general population [16,17]. In the recently completed African-American Study of Kidney Disease (AASK) trial it was noted that an old concept, i.e. drugs that inhibit the renin-angiotensin system would not protect African-Americans against renal disease progression because they don't lower blood pressure as well, was proven false [18]. Moreover, the dihydropyridine CCBs that were thought to yield better blood pressure lowering failed to show significant benefit against renal disease progression [18]. The renal outcome in this trial strongly correlated with changes in proteinuria.

The Ramipril Efficacy in Nephropathy (REIN), Angiotensin Converting Enzyme Inhibitor and Progressive Renal Insufficiency (AIPRI) and Modification of Dietary Protein in Renal Disease (MDRD) trials, as well as other smaller trials, established the ability of antihypertensive therapy to slow the progression of nondiabetic renal disease [19–21]. A recent meta-analysis of all clinical trials in patients with nondiabetic renal disease also demonstrated that BP reduction that includes the use of an ACE inhibitor markedly slows renal disease progression [22].

An analysis of randomized clinical trials of renal disease progression that included an ACE inhibitor arm showed that a rise in serum creatinine limited to 25 to 30% within the first four months of starting therapy correlated with marked preservation of renal function over a mean follow-up period of three or more years [8]. This correlation between a limited early rise in serum creatinine and long-term preservation of renal function was restricted to patients with baseline serum creatinine values of $\leq$3.5 mg/dl. If acute increases in serum creatinine of >30% occur in less than four months of ACE inhibitor therapy, the physician should rule

out (a) volume depletion, (b) worsened heart failure, or (c)bilateral renal artery stenosis as etiologies [8]. These acute changes in renal function may also occur with angiotensin receptor blockers (ARBs).

Diabetes and renal disease

Hypertension is common and is closely related to the development of renal disease in patients with diabetes. In Type 1 diabetes, the incidence of hypertension rises from five percent at ten years to 33 percent at 20 years and 70 percent at 40 years, but hypertension is present in only 2–3% of those without clinically evident renal involvement. Such patients may have underlying essential hypertension. The findings are somewhat different in Type 2 diabetes.

Patients with diabetes who are at risk of developing nephropathy can be identified by the detection of MA. MA is a predictor of both progressive renal damage and overall cardiovascular morbidity [9–11]. Development of proteinuria, in spite of adequate BP control, is a clue that renal disease is present and progressing. The presence of >2.5 gm of proteinuria is an uncommon consequence of hypertension alone and should prompt a renal biopsy to determine the etiology of renal disease. More than 35% of diabetic patients develop persistent proteinuria, a decline in GFR, and an increased arterial pressure, the syndrome of diabetic nephropathy. The relationship between arterial pressure and diabetic nephropathy in Type 2 diabetes is not as clear as in Type 1 diabetes [23]. The presence of nephropathy is associated with increased morbidity and mortality due to both increased cardiovascular events and end stage renal failure [11].

Diabetics with albuminuria are 20 times more likely to die of cardiovascular disease than those without albuminuria. Hence, treatment is aimed at both *lowering arterial pressure to a stated goal* and *reducing proteinuria by at least 30 to 50% from baseline* [11,24]. The person with diabetes should be started on antihypertensive medications even if the BP is in the high normal range (>135/85 mmHg) because of the greatly heightened cardiovascular and renal risk in this group [25].

Therapeutic Approaches to Hypertension

Sodium restriction

Sodium retention is a major pathophysiological mechanism of hypertension development in chronic renal disease. Therefore, limitation of daily sodium intake to 2–4 grams/day is a logical initial therapeutic approach. Salt restriction is also important because excessive dietary sodium intake attenuates the protective effects of ACE inhibitors and calcium channel blockers (CCBs) in these patients [26]. Further, because African-Americans with essential hypertension demonstrate greater angiographic and histological evidence of arteriolar nephrosclerosis than whites and both normotensive and hypertensive African-Americans excrete a lower sodium load than their white counterparts, sodium restriction is particularly important in African-Americans with essential hypertension [27,28]. This sluggish response to sodium loading is associated with a higher prevalence of salt sensitive hypertension and lower plasma renin activity compared with white hypertensives. Interestingly, calcium channel blockade has been shown to reverse the abnormal renal adaptation to a high sodium diet in salt sensitive African-American patients [28]. In addition, sodium restriction clearly contributes to the maintenance of BP reductions in elderly patients with established hypertension [29].

Antihypertensive Treatment

There is no single methodology by which to achieve BP goals in all individuals. Clearly, in those with diabetes and/or nephropathy, multiple drug approaches must be used to achieve the lower recommended goals. Moreover, both the JNC VI and the National Kidney Foundation (NKF) guidelines state that all such patients should be started on an ACE inhibitor while lifestyle modifications and dietary charges are addressed [24,25]. Figure 2 illustrates a consensus approach put forth by the NKF to achieve the BP goal of <130/80 mmHg, recommended by this group for such patients [30]. In those with renal insufficiency, the goal should be <130/85 [17,21]. This approach takes into account trial data that optimize preservation of renal function as well as reduction of CV risk. In addition to this approach, other factors that contribute to BP control, such as salt restriction, should be addressed.

Early clinical trial data suggested that at similar levels of BP control, ACE inhibitors provide better preservation of renal function than other antihypertensive drugs [20,22,30–32]. This is especially true in patients with Type 1 diabetes. Moreover, clinical trial data in hypertensive patients indicate that use of an ACE inhibitor confers greater protection against renal disease progression at BP levels of 140/90 mmHg but not at BP levels <130/80 mmHg [7,8,22,33,34].

Three meta-analyses of clinical trials clearly support the use of ACE inhibitors as antihypertensive agents in patients with diabetic nephropathy, in part because they reduce proteinuria and markedly slow the progression of nephropathy [9,22,31]. Diabetics with the most advanced nephropathy generally have severe proteinuria and may derive the greatest benefit from BP reduction with ACE inhibitors [30]. In the REIN trial of non diabetic renal disease, patients who had serum creatinine values of >2.0 mg/dl and >3.0 grams per day of proteinuria had a 62% reduction in renal disease progression. In contrast, over the same 42-month follow-up, those with MA had only a 22% reduction in renal disease progression [19].

Two separate studies and a meta-analysis in patients with nondiabetic renal disease further emphasize the

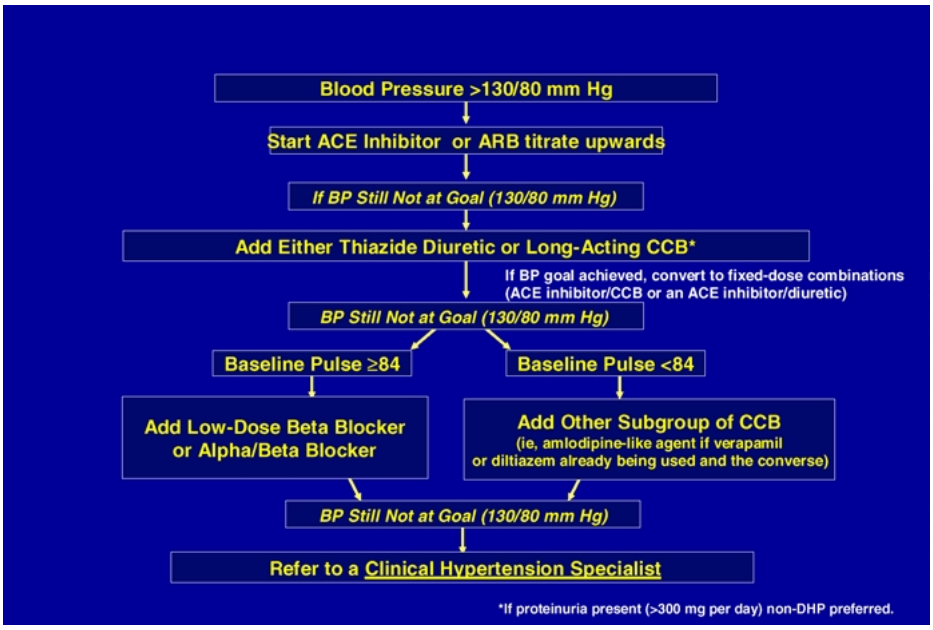

Fig. 2. *An approach to lower arterial pressure in patients with renal disease to goal. Taken from the NKF recommendations (Bakris GL et al., Am J Kidney Dis. Sept. 2000). #Everyone with diabetes and /or renal insufficiency should be instructed on lifestyle modifications as per the JNC VI. Everyone, however, should be started on therapy if blood pressure is greater than 130/80 mmHg. Note: If BP <15/10 mmHg above goal (130/80 mmHg) then ACE inhibitor alone may be used. *Non-dihydropyridine CCBs (verapamil, diltiazem have been shown to reduce both CV mortality, proteinuria and diabetic nephropathy progression independent of an ACE inhibitor). Beta blockers may be substituted for calcium channel blockers if the patient has angina, heart failure or arrhythmia necessitating their use. Beta blockers with proven efficacy to reduce CV events and the lowest side-effect profile are preferred. Note that use of a beta-blocker with a nondihydropyridine CCB should be avoided in the elderly and those with conduction abnormalities. Otherwise such combinations are safe and particularly effective for lowering blood pressure. Note: Other agents such as minoxidil, hydralazine and clonidine or methyldopa can also be used as adjunctive agents to help achieve goal blood pressure. Clonidine should Not be used with beta blockers for numerous reasons, not the least of which is a high likelihood of severe bradycardia.*

point that the level of BP reduction rather than the antihypertensive agent used determines renal protection [22,32]. A double blind, prospective trial in patients with nondiabetic renal disease followed for an average of three and a half years demonstrated no difference in the slope of GFR decline between ACE inhibitor and beta blocker treatment despite comparable BP control [33]. Moreover, a retrospective analysis of data from clinical trials indicated that if the BP goal of <130/85 mmHg is achieved, decline in renal function is maximally slowed regardless of the agents used (Fig. 3) [11]. Clinicians should strive to achieve goal BP with medications that can be given once daily and which have the fewest adverse effects, thus optimizing adherence.

There is impressive clinical trial evidence that angiotensin receptor blockers (ARBs) in people with Type 2 diabetes with nephropathy have specific renoprotective properties [35,36]. Both these trials show that ARBs markedly reduce the time to dialysis and transplantation.

A simple way to conceptualize the benefits of ACE inhibitors to the kidney is through an analogy with cardiac function. ACE inhibitors reduce the maximal response of a given nephron to excrete metabolic waste products by reducing its baseline GFR, analogous to beta-blocker induced reduction in baseline heart rate, blunting the maximal increase in heart rate and BP during exercise, in part, by decreasing the work of the heart and improving coronary flow. When beta-blockers are stopped, heart rate and myocardial work increase. We postulate that ACE inhibitors, in much the same way, reduce the work of individual functional nephrons, and thus, preserve nephron function.

These trials, taken together with other long-term studies that have evaluated progression of renal disease in the context of BP reduction, clearly provide guidance in the management of hypertensive patients with renal dysfunction. They demonstrate that in diabetic hypertensive patients with normal renal function, a systolic BP <130 mmHg and diastolic BP <80–85 mmHg will offer optimal renal protection. Secondly, they reveal that the number of antihypertensive agents needed to achieve the recommended goal BP of <130/85 mmHg is an average of three (Fig. 4) [11].

ACE inhibitors frequently need other agents to achieve the blood pressure goals previously mentioned. Diuretics are the oldest class of antihypertensive

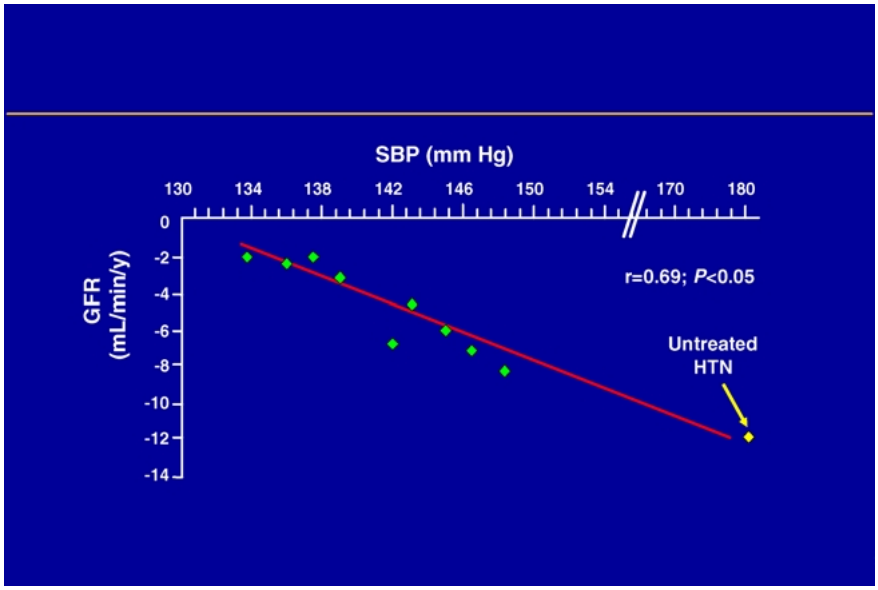

Fig. 3. *The relationship between level of BP control and rate of decline in renal function. Adapted from (Bakris GL et al., Am J Kidney Dis, Sept. 2000)*

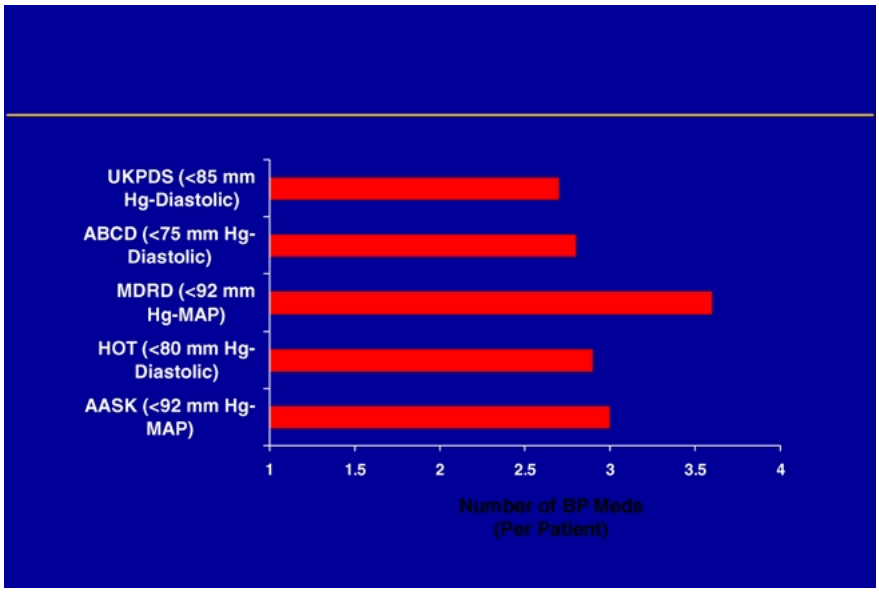

Fig. 4. *Number of antihypertensive medications required to achieve BP goals in all clinical trials that randomized to two different levels of BP. Adapted from Sheinfeld GR and Bakris GL, Am J Hypertension 1999;12:80S–85S.*

agents that have consistently demonstrated their ability to reduce CV mortality. These are excellent agents to add to ACE inhibitors or ARBs to achieve BP goals. In diabetes these agents must be part of the antihypertensive cocktail in order to achieve the desired BP control in most clinical circumstances. Moreover, they have been shown to reduce CV mortality in patients with diabetes [37].

Diuretics must gain entry to the tubular fluid and have access to the luminal side of the nephron to work. In general, if the glomerular filtration rate (GFR) is <50ml/min or the serum creatinine is 1.8–2.0 mg/dl, only loop diuretics are effective for volume removal and BP reduction. In diuretic-resistant patients, combining a diuretic that inhibits sodium transport at the loop of Henle with one that acts at the proximal/distal tubule,

i.e., furosemide with metolazone, may effect a response when neither is effective alone [38].

ACE inhibitors and, to a lesser extent, beta-blockers and angiotensin receptor blockers, may also increase serum potassium levels. Diuretics have a role in minimizing the risk of hyperkalemia in patients treated with these agents. Patients who develop elevated serum potassium levels on ACE inhibitors may the benefit instead from use of an angiotensin receptor blocker to inhibit the renin angiotensin-aldosterone system [39,40]. In a multicenter clinical trial of patients with normal and abnormal renal function, those with a mean GFR of >44 ml/min showed a 0.1 mEq/l rise in serum potassium above the baseline of 4.6 mEq/L on an angiotensin receptor blocker as compared to a 0.3 mEq/L rise with an ACE inhibitor [39]. Moreover, fewer patients developed potassium levels >5 mEq/L with the angiotensin receptor blocker.

Calcium channel blockers (CCBs) are not as well studied as ACE inhibitors in diabetic nephropathy. However, available data from both pre-clinical and clinical studies indicate that dihydropyridine CCBs, e.g. amlodipine, do not reduce albuminuria to the same extent as nondihydropyridine CCBs, e.g., verapamil or diltiazem [41–44]. Moreover, in the recent Irbesartan Diabetio Nephropathy Trial (IDNT) they failed to protect against renal disease progression to the same extent as the ARB, irbesartan [35]. This was also seen in a subanalysis of the RENAAL trial. The dihydropyridine CCBs have not been shown to slow renal disease progression or prevent glomerular scarring in any animal model of renal insufficiency or in humans with diabetes compared to nondihydropyridine CCBs or ACE inhibitors [45,46]. Further, CCBs that reduce albuminuria (nondihydropyridine-type) also reduce cardiovascular events [47,48]. Dihydropyridine CCBs that have neutral effects on albuminuria also have neutral effects on cardiovascular events when used in the absence of an ACE inhibitor [41,42,46,49]. Taken together, these findings suggest that dihydropyridine CCB's are inferior to ACE inhibitors in preventing renal endpoints in patients with established nephropathy from Type 2 diabetes or nondiabetic renal disease associated with hypertension.

Beta blockers have a clear role as adjunct therapy in patients with renal disease, primarily because they reduce CV risk and events but slow, to a lesser extent than ACE inhibitors, progression of nephropathy. In the UKPD Study of patients with Type 2 diabetes, atenolol was as effective as captopril in both arterial pressure lowering and protection against micro- and macrovascular disease [50].

Newer agents in this class have neutral or beneficial effects on metabolic and renal profiles. One α, β blocker of note, carvedilol, has been shown to not only reduce CV mortality but also reduce MA and not adversely affect glucose tolerance or lipid profiles in patients with hypertension or diabetes [51,52]. This may be a very useful beta-blocker to use in such high-risk patients.

Treatment Recommendations and Caveats

The goal BP for patients with renal disease and/or diabetes as outlined by JNC VI is ≤130/85 mmHg. More recently, both the National Kidney Foundation and the Canadian Hypertension Society stated that BP should be reduced to <130/80 mmHg in those with renal disease from diabetes [24,53]. A summary of guidelines for control of hypertension in patients with diabetes from various international consensus committees is summarized in Table 1.

The National Kidney Foundation guidelines make the point that antihypertensive agents with the ability to reduce both BP and albuminuria are preferred first line agents to preserve renal function [24]. Thus, the optimal initial therapy for hypertensive diabetic patients is usually an ACE inhibitor because of proven efficacy in both of these areas and excellent tolerability. When an ACE inhibitor does not produce the desired BP goal, drugs that have additive or synergistic effects on BP and proteinuria, such as diuretics or non-dihydropyridine CCBs, should be added. A beta-blocker should be added if goal BP has not been achieved and pulse rate is >84 beats per minute [54]. A central alpha-adrenergic agonist like clonidine is appropriate if beta-blockers are contraindicated.

It is estimated that only about 11 percent of patients with renal insufficiency or diabetes achieve a BP goal of <130/85 mmHg. This may be due, in part, to physician indifference, fear or ignorance as well as patient failure to adhere to medication schedules. Doses of ACE inhibitors generally used in every day practice do not provide the same preservation of renal function as noted in clinical trials. One of the main reasons for the failure to achieve adequate drug dosing relates to "emotion based" rather than "evidence based" medicine. Physicians recall that there are increased side effects of drugs as doses increase. While this is true for older antihypertensive agents, it is not true for ACE inhibitors or angiotensin receptor blockers. Thus, to optimize CV and renal risk reduction, physicians should set BP, lipid, and glucose goals with their patients and state them on paper, keep a copy in the chart, and give one to the patient. At each visit, the patient and the physician are aware of the treatment goals and the patient's progress towards them.

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