Beta blockers in the management of chronic kidney disease

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The sympathetic nervous system modulates renal function through its receptors namely β_1 (cardiac output and renin release), α_1 (systemic and renovascular constriction), and β_2 renovascular dilation. Sympathetic overactivity is commonly seen in chronic kidney disease (CKD) and is an important contributor to increasing the risk of cardiovascular events as well as increasing renal disease progression. Recent evaluations of drug use in people with CKD shows a remarkably low percentage of patients receiving β-blockers, especially in more advanced stage CKD when cardiovascular risk is higher. This is in large part due to tolerability of these agents. Moreover, water-soluble β-blockers such as atenolol and metoprolol are dialyzable and require supplementation to avoid exacerbation of arrhythmias following dialysis. Newer vasodilating β-blockers have better tolerability and different effects on renal hemodynamics as well as metabolic variables. These effects are related to the relative α_1-blocking effect of agents such as carvedilol and labetolol, with carvedilol having relatively greater α-blocking effects. Few studies evaluate β-blockers on cardiovascular risk in CKD patients. Studies with carvedilol demonstrate attenuated increases in albuminuria as well as reduction in cardiovascular events in CKD patients with hypertension. This paper reviews the animal and clinical trial data that evaluate β-blockers in CKD highlighting the vasodilating β-blockers. It is apparent that greater use of this drug class for blood pressure control would further enhance reduction of risk of heart failure, the most common cause of death in the first year of starting dialysis.

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Given the high prevalence of cardiovascular disease in people with chronic kidney disease (CKD) and the clear benefits of mortality reduction observed for most β-blockers in clinical trials, they are relatively underused in CKD patients. The reasons for this relative lack of β-blocker use as well as the role of newer subclasses of this antihypertensive group in people with CKD are discussed.

In order to understand the rationale for use of β-blockers in patients with CKD, it is useful to review some background information on sympathetic overactivity in such patients as well as elucidate its role in the genesis of hypertension and progression of kidney disease as well as potentially of cardiovascular complications. Experimental evidence focused on the role of the sympathetic system will be initially presented followed by data from clinical studies and trials.

Studies by DiBona[1] identified chemoreceptors and baroreceptors in the kidney. In models of experimental renal damage, Campese and Krol[2] and Ye *et al.*[3] documented that the activation of afferent signals emanating from damaged kidneys, travel via the spinal cord into the hypothalamus, where local catecholamine turnover is upregulated, leading to increased efferent sympathetic nerve traffic into the periphery.

The activation of the hypothalamic centers which occurs in response to afferent signals has been proven by experiments with sections of the dorsal roots (rhizotomy), which abrogated hypertension in subtotally nephrectomized rats.[4] Such afferent signals were seen with different types of kidney injury; most impressive was the observation that injection of as little as 20 μl phenol raised blood pressure; this hypertension was abrogated several weeks later by resection of the phenol-treated kidney.[5] Sympathetic overactivity in kidney disease is involved in the genesis of hypertension, in the progression of kidney disease, and in the cardiac complications of kidney failure. The role of the sympathetic nervous system (SNS) in the progression of nephropathy has been documented by observations in subtotally nephrectomized rats in which nonhypotensive doses of β-blockers ameliorated the development of glomerulosclerotic and cardiac lesions.[6] Similar observations concerning kidney disease progression were noted with the central sympathicoplegic agent moxonidine.[7] Additionally, moxonidine also reduced

albumin excretion in patients with type I diabetes, despite causing no change in ambulatory blood pressure.[8,9]

In a separate model of kidney disease (spontaneously hypertensive rats with adriamycin nephropathy), α-/β-blocker carvedilol decreased systolic blood pressure, decreased renal vascular resistance (RVR), and significantly increased renal blood flow (RBF). Moreover, it significantly decreased interstitial infiltration in the early phase of the study, slowed development of interstitial fibrosis and tubular atrophy, and decreased blood vessel changes. These changes strongly correlated with slowed nephropathy progression as well as decreases in proteinuria. The addition of captopril to carvedilol improved its effects, especially on prevention of tubulointerstitial changes.[10]

In subtotally nephrectomized rats with known microangiopathy, β-blockers increased the capillary density in the heart.[11] This is an important observation, as β-blockers clearly improve cardiac function and reduce cardiovascular events in hemodialyzed patients.[12]

In models of chronic renal damage, norepinephrine (NE) content was decreased, yet increased NE release was noted upon stimulation of renal nerves.[13] This is consistent with increased NE discharge from reduced numbers of sympathetic nerves, possibly because of partial denervation from incipient polyneuropathy. Patchy denervation from autonomic polyneuropathy with denervation supersensitivity to catecholamines may also be relevant in the heart of uremic patients.[14] These observations may explain, at least in part, the propensity for sudden death,[15] a frequent cause of death in dialysis patients, and the benefit derived from treatment with β-blockers.[12,14]

Further abnormalities of the sympathetic system in renal failure include reduction of β- and α-receptor responsiveness.[16–18] Direct evidence of sympathetic overactivity was provided using the methodological gold standard of microneurography of the sural nerve in hemodialyzed patients,[19] in patients with advanced renal failure,[20] and even in the earliest stage of renal disease, that is, patients with polycystic kidney disease despite no reduction in glomerular filtration rate (GFR).[21] The role of the damaged kidney in causing sympathetic overactivity is illustrated by the observation that sympathetic activity is completely normal in hemodialyzed patients with bilateral nephrectomy.[19] Conversely, sympathetic overactivity is still present in renal allograft recipients and normalizes when their own shrunken kidneys are removed.[22]

THE USE OF β-BLOCKERS IN CKD PATIENTS

As there is overwhelming evidence for sympathetic overactivity in patients with kidney disease, coronary heart disease and heart failure (HF) are the most common causes of death in these patients.[23] This may be due to inadequate treatment, as demonstrated by a recent study in which β-adrenergic blockade was used in fewer than 30% of patients on hemodialysis.[24] This is surprising, as β-blockers interfere with the deleterious actions of the SNS on cardiac end points,[14] and are well-established, evidence-based therapy for reducing cardiovascular risk in hypertension[25] and after myocardial infarction.[12,26]

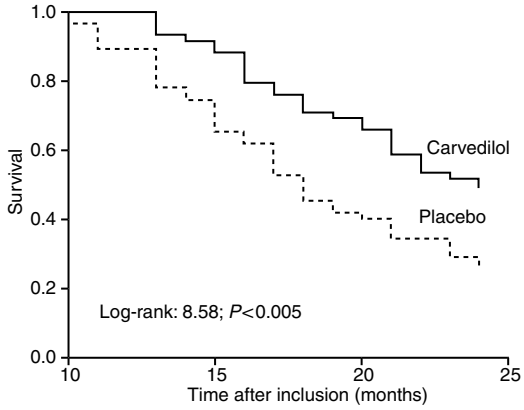

Figure 1 | Kaplan–Meier curve for all-cause mortality during 24-month follow-up in hemodialysis patients with cardiomyopathy according to the use of carvedilol. Used with permission.[12]

Observational studies suggest definite survival benefits derived from the use of β-blockers in patients with severe renal disease.[27,28] Furthermore, in a prospective, randomized study in hemodialyzed patients with HF, Cice *et al.*[12] documented an impressive and significant decrease in death and hospitalization rates attributable to cardiovascular causes in patients on carvedilol compared to placebo (Figure 1). Nevertheless, β-blockers are inadequately used in patients with CKD, especially those with the most severe renal failure.[29] For example, the United States Renal Data System Dialysis Morbidity and Mortality Study found that only 20% of chronic dialysis patients were receiving β-blocker therapy.[24] In another study, only 24% of patients with established coronary heart disease were treated with β-blockers.[30] A similar trend occurs in the predialysis patients.[31] One reason for this underutilization may be fear of adverse hemodynamic effects on renal physiology or on glycemic control in patients with diabetes.

β-blockers vary significantly in their pharmacologic properties. These differences may determine how well an agent will work and how tolerable it will be in patients with CKD. Pharmacological properties including lipid solubility, cardioselectivity and routes of excretion, and the presence of adjunctive properties such as vasodilatory, antioxidant, and calcium-blocking activity will all influence the effect of the agent. Metabolic factors including lipoprotein and serum potassium levels and glycemic control may also respond differently to each β-blocker. This review will discuss the different properties and effects of several commonly used β-blockers in the management of CKD: propranolol, metoprolol, atenolol, labetalol, and carvedilol.

PHARMACOLOGIC PROPERTIES OF β-BLOCKERS

Controlling hypertension is a mainstay in the management of CKD. Table 1 displays the pharmacologic and renal

Table 1 | Pharmacologic properties of β-blockers

	Propranolol	Metoprolol	Atenolol	Labetalol	Carvedilol
Lipophilic	Y	Y	N	Y	Y
Nonselective (β_1/β_2)	Y	N	N	Y	Y
Cardioselective (β_1)	N	Y	Y	N	N
α_1-blockade	N	N	N	Y	Y
Insulin sensitivity	↓	↓	↓	↔	↑
Serum triglycerides	↑	↑	↑	↔	↓
Serum HDL cholesterol	↓	↓	↓	↔	↑
Hyperkalemia in ESRD	Y	N	N	Y	N
Renal effects in CKD					
RVR	↑	↓	↔	↔	↓
RBF	↓	↔	↔	↔	↑
GFR	↓	↔	↔	↔	↑

↑, increases with use of drug; ↓, decreases with use of drug; ↔, remains the same with use of drug; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; N, no; RBF, renal blood flow; RVR, renal vascular resistance; Y, yes.
Sources:[32–42]

hemodynamic properties of several β-blockers that have been used to lower blood pressure in hypertensive patients with diabetic and nondiabetic renal impairment.[32–42] Lipophilic agents undergo extensive first-pass hepatic metabolism with relatively little being excreted unchanged in the urine. Hydrophilic agents are excreted primarily by the kidneys and require dose adjustment in patients with end-stage renal disease (ESRD). Hydrophilic agents may yield low blood levels due to poor absorption after oral administration.[43,44] β1-selective blockers are cardio-specific and result in reduced cardiac output, blood pressure, and heart rate. β1-/β_2-blockers antagonize the effects of catecholamine stimulation on β-adrenergic receptors in resistance vessels as well as the myocardium. β_2-blockade has been shown to be particularly important in mediating the proarrhythmic effect of NE.[45] However, inhibition of β_2-vasodilation leaves the reflex α_1-mediated vasoconstrictor response to arterial underfilling unopposed in the face of decreased blood pressure or cardiac output. In general, the effects of β-blockade are amplified by reduction of plasma renin release through inhibition of β-adrenergic receptors located in the renal juxtaglomerular apparatus.[37]

The addition of α_1-inhibiting activity to β-adrenergic antagonists blocks reflex vasoconstriction, and may also increase blood flow to skeletal muscle, thereby improving glucose availability and disposal.[46] Whereas both nonselective and β_1-selective blockers can increase insulin resistance, the addition of sufficient α_1-blocking activity may improve insulin sensitivity in both diabetic and nondiabetic patients.[46]

β_1- and α_1-stimulation have opposite effects on specific enzymes involved in lipid metabolism. Whereas β_1-selective and -nonselective β-blockers tend to increase blood levels of triglycerides and lower levels of high-density lipoprotein cholesterol, α_1-blockers can lower triglycerides and raise high-density lipoprotein cholesterol levels.[46] Consequently, the addition of α_1-blocking activity to certain β-blockers may impact both diabetes and arteriosclerotic cardiovascular disease by promoting better glycemic control with less compensatory hyperinsulinemia and fewer proatherogenic changes in serum lipids.[38,39]

Nonselective β-blockers (as opposed to β_1-selective blockers) may also promote hyperkalemia in patients with ESRD, especially after exercise, and in patients taking mineralocorticoid receptor blockers. The risk is higher in patients with acidosis and patients with tubulointerstitial disease and can be reduced by administering loop diuretics. α_1-Blockade protects against increases in serum potassium levels.[24,47,48] CKD is associated with increased oxidative stress.[49] Adjunctive antioxidant activity may help β-blockers protect cell membrane constituents against damage by oxygen-free radicals and has been shown to attenuate microalbuminuria.[50,51] β-blockers in general reduce urinary sodium excretion, primarily as a result of lowered blood pressure, but their adjunctive calcium-blocking activity may attenuate this antinatriuretic effect, thereby leading to a reduction in sodium retention.[52] α_1-Blockade improves RBF and enhances sodium excretion.[45]

EFFECTS ON KIDNEY FUNCTION

The SNS exerts important control over normal renal function and plays a key role in the development and progression of CKD. The renal vasculature is richly innervated with sympathetic nerves.[53] Adrenergic receptors located in the pre- and postglomerular arterioles regulate capillary blood flow and pressure by differential vasomotor tone (renovascular autoregulation) in order to maintain a constant rate of GFR.[37] Afferent arterioles normally constrict to protect glomerular capillaries from acute increases in blood pressure; in the presence of CKD, efferent arterioles constrict more than afferents, which increases intraglomerular pressure in order to sustain adequate overall ultrafiltration at the expense of RBF, thereby increasing the filtration fraction.

Increased SNS activity increases the release of NE from presynaptic sympathetic neurons and epinephrine from the adrenal medulla. Presynaptic β_2-receptors further augment the release of NE at synaptic junctions. Postsynaptic sympathetic neurons innervate the muscular layer of

resistance vessels controlling systemic and local circulations. NE stimulation of α_1-adrenergic receptors in vascular smooth muscle results in an increase in renal as well as peripheral vascular resistance.[53] β1-activation stimulates cardiac output through its effects on myocardial contractility, and subsequent blood pressure fluctuations modulate RBF as a function of cardiac output.

As discussed above, increased sympathetic activity has been reported consistently in patients with moderate renal failure as well as in those with ESRD undergoing renal dialysis. The level of sympathetic activity is an independent predictor of total as well as cardiovascular mortality in patients with ESRD.[19,54]

Nonselective β-blockers

β-blockers have traditionally been a cornerstone of antihypertensive therapy. However, nonselective β-blockers, such as propranolol, generally decrease GFR and RBF by lowering cardiac output, thereby reflexively increasing SNS activity and raising systemic and RVR via α_1-receptors. In addition, blocking β_2-vasodilation leaves α_1-vasoconstriction unopposed.[37] These effects could potentially exacerbate established renal dysfunction in hypertensive patients.

In persons with normal renal function, β-blockers produce no important effect on renal perfusion or glomerular filtration and are not associated with increases in serum creatinine or blood urea nitrogen levels.[55,56] However, acute dosing with many β-blockers can produce minor decreases in GFR, presumably as a desirable consequence of the reversal of glomerular hypertension. In parallel, a decrease of urinary sodium excretion is observed.[57] The nonselective β-blocker propranolol diminishes renal perfusion by lowering cardiac output and renal perfusion pressure, thereby stimulating reflex α_1-vasoconstrictor activity while blocking β_2-mediated vasodilation. Most studies have shown that the chronic administration of propranolol results in the reduction of RBF and GFR.[55]

Cardioselective β-blockers

The β_1-selective blockers metoprolol and atenolol were the first blood pressure-lowering agents to be used in studies with patients with renal disease, specifically diabetic nephropathy, with dramatically beneficial effects on the rate of decline of renal function.[58,59] Today, β-blockers are recommended as antihypertensive agents in patients with CKD.[60]

The β_1-cardioselective blockers such as metoprolol and atenolol have been studied in patients with essential hypertension and normal renal function, hypertensive and diabetic nephropathy, and ESRD with dialysis or transplantation. A number of small studies have consistently demonstrated that neither metoprolol nor atenolol produce significant reduction in GFR or RBF while effectively lowering blood pressure in patients with essential hypertension, although both can increase RVR.[61–65] In patients with renovascular hypertension, lowering blood pressure with metoprolol has been associated with a fall in plasma renin activity.[66] Lowering blood pressure with atenolol in patients with microalbuminuria owing to diabetic nephropathy has been shown to prevent the usual progression to macroalbuminuria.[67]

In patients with impaired renal function, antihypertensive therapy with metoprolol has beneficial hemodynamic effects, including a significant reduction in RVR.[68] In a clinical trial of metoprolol plus hydralazine and diuretics in patients with diabetic nephropathy, the rate of decline in GFR and increase in albuminuria was significantly reduced compared to the pretreatment control period.[56] Studies with metoprolol and atenolol in patients with ESRD on chronic dialysis or after renal transplantation have demonstrated no adverse effects on renal hemodynamics.[69–71] However, although atenolol needs to be reduced by one-half to three quarters of its normal dose owing to diminished renal clearance, metoprolol dosing does not need to be altered, even though one of its less active metabolites may accumulate.[72,73] One study reported, however, that long-term atenolol therapy in renal transplant recipients was associated with a significant increase in urinary protein excretion, but whether this resulted from progressive transplant nephropathy or from the drug *per se* remains unresolved.[74] In patients on long-term maintenance hemodialysis with dilated cardiomyopathy, left ventricular size and function improved and levels of atrial natriuretic and brain natriuretic peptides decreased following 4 months of treatment with metoprolol.[75]

How does the renoprotective effect of β-blockers compare with that of angiotensin-converting enzyme (ACE) inhibitors? Both metoprolol and atenolol have been compared to ACE inhibitors in patients with CKD. In both diabetic and nondiabetic patients, the rate of GFR decline and progression of albuminuria were attenuated to a greater extent by antihypertensive therapy with an ACE inhibitor than by metoprolol or atenolol.[76–80] The African American Study of Kidney Disease and Hypertension compared the long acting, once daily formulation of metoprolol, the ACE inhibitor, ramipril, and the calcium channel blocker, amlodipine in 1094 Black subjects with hypertensive nephropathy (GFR 20–65 ml/min per 1.73 m^2) followed for a mean of 4 years.[81] The primary analysis of the GFR slope did not establish a definitive difference among the three agents. Significant benefits were seen, however, with ramipril compared to metoprolol and amlodipine on the clinical composite outcome of decline of GFR, ESRD, and death. The results of the secondary analyses indicated that ramipril treatment slowed the progression of hypertensive kidney disease to a greater extent than either once daily metoprolol or amlodipine. The once daily metoprolol-treated patients had a significantly lower rate of ESRD or death than those treated with amlodipine.[81]

Vasodilating β-blockers

Lowering blood pressure with nonselective (propranolol) or selective (metoprolol, atenolol) β-blockers is associated with compensatory stimulation of the SNS and renin–angiotensin

systems, leading to elevated NE and renin levels. Subsequent activation of vascular α-adrenergic receptors results in an increase in systemic as well as RVR. Vasoconstriction is further exacerbated with nonselective β-antagonists because of the blockade of β_2-mediated vasodilation. It has been known for a long time that propranolol increases RVR and reduces RBF and GFR.[59,82] Conversely, α_1-blockers such as prazosin and doxazosin enhance renal perfusion.[59] In addition, whereas β-blockers reduce insulin sensitivity and promote proatherogenic lipoprotein changes, α_1-blockers have the opposite effect.[46] Consequently, nonselective β-blockers with adjunctive α_1-blocker activity have been developed that attenuate renal nerve activity and could preserve RBF and GFR. Two such agents, labetalol and carvedilol, have been evaluated in hypertensive patients with and without renal impairment.

Labetalol, a nonselective β-antagonist with α_1-inhibiting activity (β/α ratio estimated to be between 3:1 and 7:1) has been available for clinical use since the mid-1980s.[58,59,83] In spite of this long duration of availability, there is very little data available on renal outcomes or hemodynamics with this agent. Moreover, in hypertensive patients labetalol has yielded conflicting results. Five studies have been reported, which included 81 patients with normal renal function and six patients with impaired renal function. A fall in RVR led to increased RBF in one placebo-controlled study of 24 patients with normal renal function.[41] Another study in 17 patients confirmed a decrease in RVR in subjects with normal renal function ($n = 11$), but inconsistent responses were found in those with more impaired renal function ($n = 6$).[84] By contrast, in 18 patients with essential hypertension labetalol diminished RBF and GFR by 20%[85] Two studies in patients with normal renal function, one including 17 patients and the other including 11 patients, found no significant effect of labetalol on GFR, RBF, or body fluid volumes.[36,86]

The effects of labetalol on carbohydrate and lipid metabolism have also been evaluated in small studies. Labetalol administration resulted in a variable increase in serum glucose levels without a measurable effect on circulating insulin levels.[87–89] Several authors report a lack of significant changes in cholesterol or triglyceride levels,[40,90,91] whereas another group observed a slight decrease in high-density lipoprotein cholesterol levels.[88] Labetalol has been used as antihypertensive therapy in patients with severe chronic renal failure. Although this drug is removed by dialysis, the procedure does not significantly increase its total body clearance.[92] A disturbing side effect of labetalol in patients on hemodialysis or after renal transplantation is serious hyperkalemia.[93,94]

Carvedilol is a nonselective vasodilating β-adrenergic antagonist with α_1-blocking activity (β/α ratio estimated to be approximately 7:1).[95] In addition, carvedilol has antioxidant activity.[96,97] The renal effects of carvedilol have been documented in a number of clinical trials involving patients with the following conditions: essential hypertension, renal hypertension, hypertension with evidence of CKD, hemodialysis, renal transplantation, congestive HF, and hypertension with diabetes. Carvedilol was administered for 4 weeks to 20 patients with mild-to-moderate essential hypertension in a randomized, double-blind, placebo-controlled study.[96] Despite the therapeutic lowering of blood pressure, RBF and GFR remained unchanged, whereas RVR fell by 13%.[96] In a longer-term trial, 10 patients with mild-to-moderate hypertension were treated for an average of 17 weeks: there were no changes in RBF or GFR and a significant decrease in RVR.[98]

The efficacy and safety of carvedilol in lowering blood pressure has been established in several clinical trials of patients with CKD. In doses that reduced systolic blood pressure by an average of 22 mmHg given over 2–4 weeks, carvedilol caused no increase in serum creatinine or blood urea nitrogen levels.[99] In another study, carvedilol, alone or in combination with a diuretic, was evaluated in 52 patients with either renal hypertension or essential hypertension accompanied by renal failure.[100] In the group on carvedilol monotherapy, blood pressure decreased significantly from 166/102 to 150/94 mmHg and in the combined group, the blood pressure decreased significantly from 175/103 to 142/85 mmHg. Serum creatinine levels were not worsened, despite such major reductions in blood pressure.

A pharmacokinetic study found that in CKD, renal clearance of carvedilol is reduced by approximately 70%, but the mean 24-h plasma concentration–time curves for the parent drug and its major metabolites did not differ significantly between patients with essential hypertension and normal renal function and those with renal insufficiency.[101] Carvedilol does not accumulate during continuous daily administration. Because it is 96% protein bound it does not cross the dialysis membrane.[102,103] A study of 15 ESRD patients with moderate hypertension receiving chronic dialysis treated with carvedilol for 12 weeks found no relevant changes in major pharmacokinetic parameters. The maximum carvedilol blood concentration (C_{max}), the time to C_{max}, and the area under the time–concentration curve during long-term treatment were all within the range observed in normal persons.[104] Importantly, in contrast to propranolol and labetalol, serum potassium levels during exercise did not increase in hemodialysis patients on carvedilol.[105]

Hypertension adversely affects renal allograft survival, and effective blood pressure control is important to improve outcomes. Cyclosporin A, which is frequently used to reduce renal allograft rejection, is known to increase blood pressure and RVR while decreasing RBF and GFR.[106] Carvedilol increases cyclosporin A blood levels by 20% so that careful dose regulation of the antirejection agent is required.[107] Conversely, carvedilol has been shown to reduce the oxidative stress and subsequent upregulation of profibrotic cytokines that occur in renal transplant patients receiving cyclosporin A.[108] Carvedilol was compared with metoprolol in a randomized crossover study involving 12 renal allograft recipients on cyclosporin A. These patients had hypertension and chronic stable graft rejection. Adequate blood pressure

control was obtained with both β-blockers, but carvedilol resulted in an increase in RBF and a decrease in RVR.[106]

HF may be encountered frequently in patients with CKD, as both conditions are closely linked to common underlying factors including hypertension, diabetes, and arteriosclerosis. HF can also exacerbate renal dysfunction by reducing cardiac output and stimulating SNS and renin–angiotensin system overactivity.[109] Because of its pharmacological properties, the renal effects of carvedilol have been investigated in patients with HF and normal renal function. A randomized, placebo-controlled comparison was performed during 6 months of treatment with either carvedilol or metoprolol in 14 patients with moderately severe HF (New York Heart Association Class III), severe left ventricular systolic dysfunction (ejection fraction 16%), and no evidence of significant kidney impairment.[110] Although the ejection fraction increased comparably with both drugs, only carvedilol improved RBF and GFR. A subsequent randomized clinical trial compared carvedilol and enalapril in 572 patients with chronic left ventricular dysfunction and mild symptoms of HF (approximately 65% of patients were classified as NYHA Class II) for 18 months. Enalapril alone, carvedilol alone, and the combination of carvedilol and enalapril were all well tolerated. In this study, there were no significant differences among the three study arms with regard to either blood pressure or the number of patients achieving target drug dose. Serum creatinine levels were normal at the onset of the study, but increased slightly in patients receiving enalapril alone ($+2.3\,\mu$mol/l) and reduced in the group receiving carvedilol alone ($-2.5\,\mu$mol/l).[111]

HF is either present at the initiation of chronic dialysis or develops subsequently in one-quarter to one-third of patients with ESRD and substantially impacts survival.[112] In chronic hemodialysis patients with established dilated cardiomyopathy, carvedilol has been associated with improvements in left ventricular size and function. After 1 year of treatment with carvedilol, left ventricular ejection fraction increased 39%, and left ventricular systolic and diastolic volumes decreased 16 and 6%, respectively, compared with no change shown with placebo.[12] By the end of the second year of the trial, 49% fewer carvedilol-treated patients had died compared with those receiving placebo ($P<0.01$).

Microalbuminuria is recognized marker of increased cardiovascular risk in patients with CKD, hypertension, and/or diabetes; progression to macroalbuminuria (>300 mg/day) indicates presence of kidney disease. Carvedilol was compared with the β_1-selective blocker atenolol in a randomized, open-label study involving 140 patients with mild-to-moderate essential hypertension.[113] Despite an equivalent reduction in blood pressure, carvedilol was associated with a significantly greater reduction in urinary albumin excretion. After 2 months, the proportion of patients with urine albumin levels $\geqslant 10$ mg/l (could not verify unit) remained unchanged in the atenolol group, but was reduced by 40% with carvedilol. Carvedilol has also been shown to eliminate microalbuminuria in 58% of nondiabetic hypertensive patients who had tested positive by dipstick before the start of 3 months of treatment.[114] In a multicenter trial of 245 patients with mild-to-moderate essential hypertension and microalbuminuria treated with carvedilol for 6–12 weeks, there was a blood pressure-independent reduction in urine albumin in 56% of patients; urine albumin disappeared completely in 48% of the patients.[115]

A recent large-scale, randomized clinical trial compared carvedilol and metoprolol tartrate added to a treatment regimen containing a renin–angiotensin system antagonist in 1235 diabetic patients with established hypertension.[116] After 5 months of maintenance therapy, blood pressure had decreased to the same extent in both groups, yet the mean urinary albumin/creatinine ratio of the carvedilol group had decreased by 1%, whereas the albumin/creatinine ratio of the metoprolol tartrate group increased by 2.5%. Of those patients with trace protein loss (30 mg/g or less) at baseline, 47% fewer carvedilol-treated patients progressed to microalbuminuria (>30 mg/gm/day) than those receiving metoprolol tartrate ($P=0.03$).[117] The study also confirmed previous reports that carvedilol improves insulin sensitivity and glycemic control while producing significantly fewer proatherogenic changes in serum cholesterol and triglyceride levels than β_1-selective blockers.[116]

Oxidative stress appears to be a blood pressure-independent determinant of microalbuminuria in hypertensive patients,[118] and the antioxidant activity of carvedilol (free-radical scavenging as well as sequestration of iron in ferric ion-induced oxidation), may play an additive role in its protection against glomerular damage leading to albuminuria.[119]

Nebivolol is a relatively new lipophilic β_1-blocker approved for hypertension that is devoid of intrinsic sympathomimetic or membrane stabilizing activity but is unique in that it has nitric oxide-mediated vasodilatory effects. The drug does not significantly influence glucose or plasma lipid metabolism and appears to have a protective effect on left ventricular function. The most common adverse events reported with this agent are similar to other vasodilating β-blockers and includes headache, fatigue, paraesthesias, and dizziness.[120]

The effects of this novel β-blocker on kidney function are limited to animal models as of this writing. In two separate studies, one in Sprague–Dawley rats nebivolol was shown to increase both renal plasma flow and GFR.[121–122] Additionally, sodium and chloride excretion were increased in a dose-dependent manner, as was potassium, albeit not dose-dependent. The mechanism by which this increase in renal plasma flow occurs is presumably through the 5-HT1A receptor/NO pathway.[121–122]

CONCLUSION

CKD, with the frequently associated conditions of hypertension, diabetes, and HF, is a state of overactivity of the SNS. Antiadrenergic drugs play an important role in its management. Antihypertensive regimens including β-blockers slow

the deterioration of renal function as assessed by decreasing GFR and worsening albuminuria. It is therefore deplorable that β-blockers are still underutilized out of fear of adversely affecting renal function and glycemic control.

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