Should β-Blockers Be Used to Control Hypertension in People With Chronic Kidney Disease?

Peter D. Hart, MD* and George L. Bakris, MD†

Summary: Activation of the sympathetic nervous system is common in patients with chronic kidney disease, plays an important role in the genesis of hypertension, the rate of decrease of renal function, and is associated with the increased cardiovascular morbidity and mortality seen in these patients. β-blockers are potent antihypertensive agents but differ in their hemodynamic effects on renal function. The cardioselective β-blockers such as atenolol and metoprolol are known to retard the progression of renal diseases, but to a lesser degree compared with blockers of the renin-angiotensin-aldosterone system. However, the newer vasodilating β-blockers such as carvedilol and nebivolol have different effects on renal hemodynamics and function primarily because of its greater adjunctive α1-blocking activity. Carvedilol decreases renal vascular resistance and prevents reductions in the glomerular filtration rate and renal blood flow in patients with hypertension with or without impaired kidney function. In addition, carvedilol may retard progression of albuminuria, and provide cardiorenal protection in chronic kidney disease patients with hypertension, congestive heart failure, and at high risk for sudden cardiac death.

Keywords: β-blockers, hypertension, kidney disease

Hypertension is common in renal diseases and its prevalence increases with decreases in renal function such that about 50% to 75% of patients with chronic kidney disease (CKD) stage 3 or higher have blood pressure of 140/90 mm Hg or higher. Hypertension is also a well-known independent risk factor for both progressive loss of renal function and cardiovascular disease (CVD), which is associated with high morbidity and mortality. According to the National Kidney Fund task force for CKD, patients with CKD should be considered the highest risk group for subsequent CVD events, and effective interventions for the management of CVD in the general population also is recommended for these patients. β-blockers have been proven convincingly to reduce cardiovascular mortality in clinical trials and are recommended for patients with high-risk CVD such as myocardial infarction, but they are relatively underused in patients with CKD. This review focuses on the rationale for the use of β-blockers to control hypertension in patients with different stages of kidney diseases, to retard the progression of CKD, and to reduce the associated cardiovascular morbidity and mortality.

SYMPATHETIC NERVOUS SYSTEM AND KIDNEY DISEASE

The sympathetic nervous system (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 and the adrenergic receptors located in the preglomerular and postglomerular arterioles. The sympathetic nerves regulate capillary blood flow and
pressure by differentially affecting vasomotor tone to maintain a constant glomerular filtration (GFR). Afferent arterioles usually constrict to protect glomerular capillaries from acute increases in blood pressure. In the presence of CKD, however, efferent arterioles constrict more than afferents, which increases intraglomerular pressure to sustain adequate overall ultrafiltration at the expense of renal blood flow (RBF). The result is a net increase in filtration fraction.

Many experimental studies have indicated that the SNS is involved in the genesis of hypertension and progression of kidney disease. Di-Bona was the first to report the presence of chemoreceptors and baroreceptors in the kidney. Subsequently, in models of experimental renal damage, Campese and Krol and Ye et al showed that the activation of afferent signals emanating from damaged kidneys travel via the spinal cord into the hypothalamus, where local catecholamine turnover is up-regulated, 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 identified on sections of the dorsal roots. These afferent signals abrogate hypertension in subtotaly nephrectomized rats. Such afferent signals were seen with different types of kidney injury; notably that intra-injection of small amounts of phenol increased blood pressure; which resolved when the phenol-treated kidney was resected. Also, the role of the SNS in the progression of kidney disease has been documented by observations in subtotaly nephrectomized rats in which nonhypotensive doses of β-blockers ameliorated the development of glomerulosclerotic and cardiac lesions. Similar observations were documented with the central sympathicoplegic agent moxonidine.

**SYMPATHETIC HYPERACTIVITY**

Clinical studies have indicated that sympathetic hyperactivity is observed frequently in patients with a variety of renal diseases such as hypertensive adult polycystic chronic kidney disease (APCKD) patients with normal renal function, patients with advanced CKD, and in end-stage renal disease (ESRD) patients on dialysis. Indeed, 2 recent studies have confirmed the notion that sympathetic hyperactivity is common in hypertensive CKD patients. Furthermore, the role of the damaged kidney in causing sympathetic hyperactivity was illustrated by the observation that sympathetic activity returns to normal in hemodialyzed patients after bilateral nephrectomy. Conversely, sympathetic hyperactivity persists in renal allograft recipients and normalizes when the native shrunken kidneys are removed.

**INADEQUATE USE OF β-BLOCKERS IN CKD PATIENTS**

Coronary artery disease and congestive heart failure (CHF) are the most common causes of death in CKD patients, in part because of the occurrence of sympathetic hyperactivity and the relative lack of use of β-blockers. For example, a recent study by Zuanetti et al showed that β-blockers were used in less than 30% of patients on hemodialysis. This is alarming because β-blockers interfere with the deleterious actions of the SNS on cardiac end points, and are well-established, evidence-based treatment for reducing cardiovascular risk in hypertension and after myocardial infarction. Also, observational studies have suggested that the use of β-blockers in patients with advanced renal disease translates to improved survival. Furthermore, in a prospective, randomized study in hemodialyzed patients with CHF, Cice et al documented an impressive and significant reduction in death and hospitalization rates attributable to cardiovascular causes in patients on carvedilol compared with placebo. Nevertheless, β-blockers are used inadequately in patients with CKD, especially those with the most...
severe renal failure. 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. In another study, only 24% of patients with established coronary heart disease were treated with β-blockers. A similar trend occurs in the predialysis patients. A possible reason for this underuse may be concern of adverse hemodynamic effects on renal physiology or on glycemic control in patients with CKD with or without diabetes.

### RENAL HEMODYNAMIC AND PHARMACOLOGIC PROPERTIES OF β-BLOCKERS

β-blockers vary significantly in their pharmacologic properties and these differences may determine the efficacy and tolerability of the agents. Pharmacologic properties including lipid solubility, cardioselectivity, and routes of excretion, and the presence of adjunctive properties such as vasodilatory, antioxidant, and calcium-blocking activity all may influence the effect of the agent. Metabolic factors including lipoprotein and serum potassium levels and glycemic control also may differ with each β-blocker.

Table 1 depicts the pharmacologic and renal hemodynamic properties of the β-blockers that are used commonly for blood pressure control in hypertensive patients with diabetic and non-diabetic renal impairment. 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 adjustments in patients with ESRD. Hydrophilic agents may yield low blood levels owing to poor absorption after oral administration. β1-selective blockers are cardiospecific and result in reduced cardiac output, blood pressure, and heart rate. β1/β2-blockers antagonize the effects of catecholamine stimulation on β-adrenergic receptors in resistance vessels as well as the myocardium. β2-blockade has been shown to be particularly important in mediating the proarrhythmic effect of norepinephrine. However, inhibition of β2-vasodilation leaves the reflex α1-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.

The addition of α1-inhibiting activity to β-adrenergic antagonists blocks reflex vasoconstriction, and also may increase blood flow to skeletal muscle, thereby improving glucose availability and disposal. Although both nonselective and

### Table 1. Pharmacologic and Renal Hemodynamic Properties of β-Blockers

<table>
<thead>
<tr>
<th></th>
<th>Propranolol</th>
<th>Metoprolol</th>
<th>Atenolol</th>
<th>Labetalol</th>
<th>Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipophilic</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Nonselective (β1/β2)</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Cardioselective (β1)</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>α1-blockade</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Serum triglyceride level</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Serum HDL cholesterol level</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>Hyperkalemia in ESRD</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Renal effects in CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVR</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>RBF</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>GFR</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↑</td>
</tr>
</tbody>
</table>

Abbreviation: HDL, high-density lipoprotein.

↑, increases with use of drug; ↓, decreases with use of drug; ↔, remains the same with use of drug.

Reprinted with permission from Bakris et al.
β₁-selective blockers can increase insulin resistance, the addition of sufficient α₁-blocking activity may improve insulin sensitivity in both diabetic and nondiabetic patients.37

β₁- and α₁-stimulation have opposite effects on specific enzymes involved in lipid metabolism. Although β₁-selective and β₁-nons selective β-blockers tend to increase blood levels of triglycerides and lower levels of high-density lipoprotein cholesterol, α₁-blockers can decrease triglyceride levels and increase high-density lipoprotein cholesterol levels.37 Consequently, the addition of α₁-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 β₁-selective blockers) also may 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, but α₁-blockade protects against increases in serum potassium levels.26,40,41 CKD is associated with increased oxidative stress42 and adjunctive antioxidant activity may help β-blockers protect cell membrane constituents against damage by oxygen free radicals and has been shown to attenuate microalbuminuria.43,44 β-blockers in general reduce urinary sodium excretion, primarily as a result of decreased blood pressure, but their adjunctive calcium-blocking activity may attenuate this antinatriuretic effect, thereby leading to a reduction in sodium retention.45 Of note, α₁-blockade improves renal blood flow and enhances sodium excretion.36

USE OF β-BLOCKERS IN PATIENTS WITH HYPERTENSION AND NORMAL RENAL FUNCTION

β-blockers traditionally have been a cornerstone of antihypertensive therapy. However, nonselective β-blockers, such as propranolol, generally decrease GFR and RBF by decreasing cardiac output, thereby reflexively increasing SNS activity and increasing systemic and renal vascular resistance via α₁-receptors. In addition, blocking β₂-vasodilatation leaves α₁-vasoconstriction unopposed.37 In hypertensive patients with normal renal function, this class of β-blockers produce no significant effect on renal perfusion or glomerular filtration and are not associated with increases in serum creatinine or blood urea nitrogen levels.46,47 However, acute dosing with these β-blockers can produce minor decreases in the GFR, presumably as a desirable consequence of the reduction of glomerular hypertension. In parallel, a decrease of urinary sodium excretion is observed.48

The β₁-cardioselective blockers such as atenolol or metoprolol have been studied in patients with essential hypertension and normal renal function. A number of small studies have shown consistently that the cardioselective blockers do not produce significant reduction in the GFR or RBF, while effectively decreasing blood pressure in patients with essential hypertension, although an increase in renal vascular resistance (RVR) occurs.49,50 In patients with renovascular hypertension, decreasing blood pressure with metoprolol has been associated with a decrease in plasma renin activity.51

Nonselective β-blockers with adjunctive α₁-blocker activity (vasodilating) such as labetalol and carvedilol attenuate renal nerve activity and could preserve RBF and GFR, and they have been evaluated in hypertensive patients with and without renal impairment.

Labetalol has been available for clinical use for a long time,46,47,52 but there are 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 a total of 81 patients with normal renal function and 6 patients with impaired renal function. A decrease in the RVR led to increased RBF in 1 placebo-controlled study of 24 patients with normal renal function.53 Another study of 17 patients confirmed a decrease in RVR in the group with normal renal function (n = 11), but inconsistent responses were found in those with more impaired renal function (n = 6).54 By contrast, in 18 patients with essential hypertension, labetalol diminished RBF and GFR by 20%.55 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.56,57

Carvedilol is a relatively new vasodilating β-blocker with antioxidant activity.58,59 Its renal effects have been documented in a number of clinical trials involving patients with hypertension and normal renal function. In a randomized, double-blind, placebo-controlled study, carvedilol was administered for 4 weeks to 20 patients with mild to moderate essential hypertension and, despite the therapeutic decrease of blood pressure, RBF and GFR remained unchanged, whereas RVR decreased by 13%.58 In a longer-term trial, 10 patients with mild to moderate hypertension were treated for an average of 17 weeks and no changes in RBF or GFR occurred, but a significant decrease in RVR was observed.60 In summary, all subclasses of β-blockers appear efficacious and safe for the treatment of hypertension in patients with normal renal function.

USE OF β-BLOCKERS IN PATIENTS WITH CKD

Optimal blood pressure control is the most important strategy for the management of CKD and, currently, β-blockers are recommended as antihypertensive agents in these patients.61

The nonselective β-blocker propranolol diminishes renal perfusion by decreasing cardiac output and renal perfusion pressure, thereby stimulating reflex α1-vasoconstrictor activity while blocking β2-mediated vasodilatation. Most studies have shown that chronic administration of propranolol results in the reduction of RBF and GFR.62 These effects potentially could exacerbate established renal dysfunction in hypertensive patients and hence they are not safe in CKD patients.

The β1-selective blockers such as atenolol and metoprolol were the first blood pressure-decreasing agents to be used in studies with patients with renal disease, specifically diabetic nephropathy, with dramatically beneficial effects on the rate of decrease of renal function.62,63

In patients with impaired renal function, antihypertensive therapy with metoprolol has beneficial hemodynamic effects, including a significant reduction in RVR.64 In a clinical trial of metoprolol plus hydralazine and diuretics in patients with diabetic nephropathy, the rate of decrease in GFR and increase in albuminuria was reduced significantly compared with the pretreatment control period.65 These agents are used routinely for blood pressure control in CKD patients.

The vasodilating β-blocker carvedilol is also a potent and safe agent for decreasing blood pressure in patients with CKD. In a nonblinded clinical trial using carvedilol at doses that reduced systolic blood pressure by an average of 22 mm Hg given over 2 to 4 weeks, there was no increase in serum creatinine or blood urea nitrogen levels.65 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.66 In the group on carvedilol monotherapy, blood pressure decreased significantly from 166/102 to 150/94 mm Hg, and in the combined group the blood pressure decreased significantly from 175/103 to 142/85 mm Hg. Serum creatinine levels were not worsened, despite such major reductions in blood pressure.

A key question is how does the renoprotective effect of β-blockers compare with that of renin-angiotensin-aldosterone system (RAAS) blockers such as angiotensin converting enzyme (ACE) inhibitors? Both metoprolol and atenolol have been compared with 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.67-71 The African American Study of Kidney Disease and Hypertension compared metoprolol, the ACE inhibitor ramipril, and the calcium channel blocker amlodipine in 1,094 participants with hypertensive nephropathy (GFR, 20-65 mL/min per 1.73 m²), followed up for a mean of 4 years.72 The primary analysis of the GFR slope did not establish a definitive difference among the 3 agents. Significant benefits were seen, however, with ramipril compared with metoprolol and amlodipine on the
clinical composite outcome of decrease 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 metoprolol or amlodipine. The metoprolol-treated patients had a significantly lower rate of ESRD or death than those treated with amlodipine.72

USE OF β-BLOCKERS IN PATIENTS ON DIALYSIS AND RENAL ALLOGRAFT RECIPIENTS

Studies with atenolol and metoprolol in patients with ESRD on chronic dialysis or after renal transplantation have shown no adverse effects on renal hemodynamics.73-75 However, although atenolol needs to be reduced by about 50% of its normal dose because of diminished renal clearance, dose adjustment is not required with metoprolol even though one of its less active metabolites may accumulate.76,77 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 chronic allograft nephropathy or from the drug per se remains unresolved.78 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 after 4 months of treatment with metoprolol.79

Labetolol has been used as antihypertensive therapy in patients with advanced CKD but a serious adverse effect seen in patients on hemodialysis or after renal transplantation is severe hyperkalemia.80,81 In contrast, carvedilol is relatively safe in ESRD patients on dialysis. A pharmacokinetic study found that in CKD renal clearance of carvedilol is reduced by approximately 70%, but the mean 24-hour 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.82 In addition, carvedilol does not accumulate during continuous daily administration, and because it is 96% protein bound it does not cross the dialysis membrane.83,84 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, the time to the maximum carvedilol blood concentration, and the area under the time-concentration curve during long-term treatment were all within the range observed in normal persons.85 Importantly, in contrast to propranolol and labetalol, serum potassium levels during exercise did not increase in hemodialysis patients on carvedilol.86

In renal transplant patients carvedilol is effective for blood pressure control and has been shown to reduce the oxidative stress and subsequent up-regulation of profibrotic cytokines that occur in renal transplant patients receiving cyclosporine A.87 However, carvedilol increases cyclosporine A blood levels by as much as 20% so that careful dose adjustment of the immunosuppressive agent is required.88 In a randomized cross-over study of 12 renal allograft recipients on cyclosporin A with hypertension and chronic stable graft rejection in which carvedilol was compared with metoprolol, adequate blood pressure control was obtained with both β-blockers, but carvedilol resulted in an increase in RBF and a decrease in RVR.89

USE OF β-BLOCKERS IN PATIENTS WITH CKD AND CHF

CHF occurs frequently in patients with CKD because both conditions are linked closely to common underlying factors including hypertension, diabetes, and arteriosclerosis. CHF also can exacerbate renal dysfunction by reducing cardiac output and increasing SNS and RAAS activity.90 Also, congestive heart failure is either present at the initiation of chronic dialysis or develops subsequently in 25% to 33% of patients with ESRD and substantially impacts survival.91 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.92 By the end of the sec-
ond year of the trial, 49% fewer carvedilol-treated patients had died compared with those receiving placebo ($P < .01$).

**USE OF $\beta$-BLOCKERS FOR THE REDUCTION OF ALBUMINURIA**

Microalbuminuria is recognized as a powerful predictor of cardiovascular morbidity and mortality in patients with hypertension and/or diabetes. Moreover, its progression to macroalbuminuria or proteinuria signifies the presence of kidney disease and increased risk for the development of kidney failure. The RAAS blockers currently are recommended as first-line agents for the control of albuminuria in patients with kidney disease, but $\beta$ blockers may have an additive role. The vasodilating $\beta$-blocker carvedilol was compared with the $\beta_1$-selective blocker atenolol in a randomized, open-label study involving 140 patients with mild to moderate essential hypertension. 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 of 10 mg/L or greater remained unchanged in the atenolol group, but was reduced by 40% with carvedilol. Carvedilol also has been shown to abrogate microalbuminuria in 58% of nondiabetic hypertensive patients who had tested positive by dipstick before the start of 3 months of treatment. In a multicenter trial of 245 patients with mild to moderate essential hypertension and microalbuminuria treated with carvedilol for 6 to 12 weeks, there was a blood pressure–independent reduction and complete resolution of urine albumin excretion in 56% and 48% of the patients, respectively.

A recent, large-scale, randomized, clinical trial compared carvedilol and metoprolol tartrate added to a treatment regimen containing a RAAS antagonist in 1,235 diabetic patients with established hypertension. After 5 months of maintenance therapy, blood pressure was 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 ($\leq 30$ mg/g) at baseline, 47% fewer carvedilol-treated patients progressed to microalbuminuria (>$30$ mg/g/d) than those receiving metoprolol tartrate ($P = .03$). 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 $\beta_1$-selective blockers. One plausible explanation for these observations is that oxidative stress appears to be a blood pressure–independent determinant of microalbuminuria in hypertensive patients, 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.

**CONCLUSIONS**

CKD, with the frequently associated conditions of hypertension, diabetes, and CHF, is a state of sympathetic hyperactivity and $\beta$-blockers should play an important role in its management. Antihypertensive regimens including $\beta$-blockers slow the deterioration of renal function as assessed by decreasing GFR and worsening albuminuria. These agents currently are underprescribed and given the high prevalence of CVD and its associated morbidity and mortality in patients with CKD, a greater use of $\beta$-blockers, especially the vasodilating agents such as carvedilol, is recommended strongly.

**REFERENCES**

4. Antman EM, Anbe DT, Armstrong PW, et al. A guideline for the management of patients with ST-eleva-
24. Eknayan G. On the epidemic of cardiovascular disease in patients with chronic renal disease and pro-
25. Zuanetti G, Maggioni AP, Keane W, et al. Nephrologists neglect administration of beta blockers to dialy-
28. Foley RN, Herzog CA, Collins AJ. Blood pressure and long-term mortality in United States hemodialysis pa-


