REVIEW ARTICLE

Antihypertensive agents and renal transplantation

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Abstract

Advances in the field of kidney transplantation have led to a significant increase in the life of renal allograft with 1 - year graft survival rates of 93% to 99%.This increase in early graft survival has made it possible to observe the long-term morbidities that accompany renal transplantation.

Studies correlating the reduction of arterial blood pressure with patient and graft survival as well as the risk of cardiovascular disease do not exist. The recommendations come from the general population and from comparative studies of hypertensive and normotensive kidney graft recipients. It is known that in the general population hypertension is a risk factor for chronic kidney disease but at the same time a risk factor for death, ischaemic heart disease, chronic heart failure and left ventricular hypertrophy. We must always have in mind that there are many similarities between a kidney graft recipient and a patient with chronic kidney disease. Renal transplant recipients represent a patient population with a very high risk for development of cardiovascular disease which has been identified as the leading cause of death in these patients[1]. Of 18,482 deaths among renal allograft recipients, 38% had functioning renal allografts[2,3]. Successful renal transplantation (Rt) can result in partial regression of left ventricular hypertrophy (LVH) if it is associated with hypertension (HTN) remission or if HTN is controlled by medications. Frequently post transplant HTN is associated with failure of LVH to regress. Transplant clinicians must choose antihypertensive agents that will provide their patients with maximum benefit from renal allograft and cardiovascular perspective. The target must always be long term patient and graft survival and acceptable quality of life. The antihypertensive drugs usually used after kidney transplantation are diuretics, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and β – blockers. Most emphasis is given lately to ACEIs/ARBs and β – blockers because of their cardioprotecive effect. *Hippokratia 2007; 11, (1): 3-12*

Key words: *kidney transplantation, hypertension, anti – hypertensive agents*

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Posttransplant hypertension, perhaps the comorbidity with the greatest concern, occurs in about 70% to 90% of renal transplant recipients (Figure 1) in the cyclosporine era[4-6]. Systolic blood pressure[7] (Figure 2) as well as the pulse pressure (unpublished data) of recipients with graft function longer than 10 years is significantly lower compared with those of patients with graft survival >1 and < 10 years. Posttransplant hypertension has been recognized as an independent risk factor for chronic allograft dysfunction-nephropathy and graft

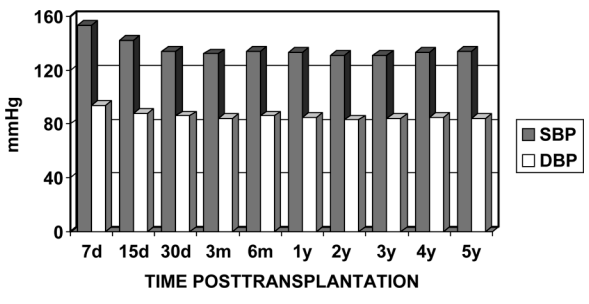


Figure 1. *Five year follow up of systolic and diastolic blood pressure after kidney transplantation*
- *272 patients, period 1987-1995 (normal blood pressure considered to be systolic > 140 mmHg and diastolic > 90 mmHg)*
- *Frequency on 7th pt day: 72.7%, on 5th year:67.6%*

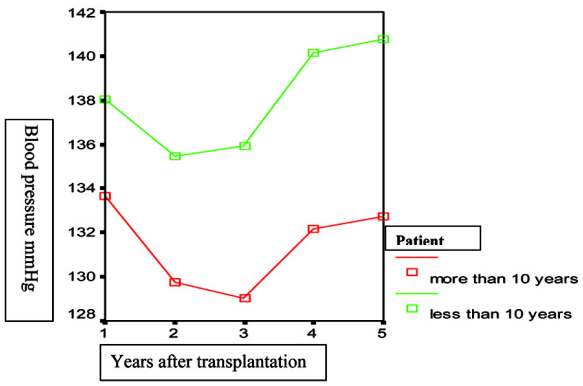


Figure 2. *Five year systolic blood pressure of patients with graft survival > 10 years and patients with graft survival >1 and < 10 years graft survival (p: 0.01)*

loss[8,9] (Figure 3). Finally hypertension causes cardiac

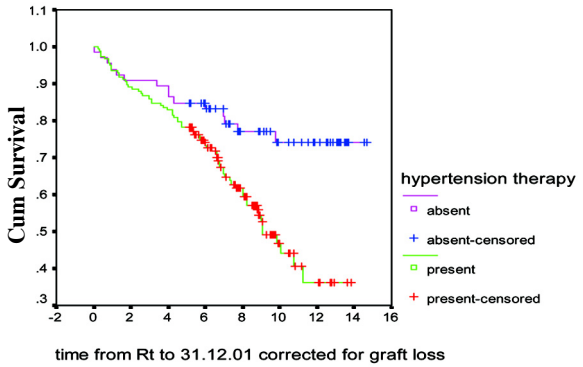


Figure 3. *Graft survival in patients with normal blood pressure (red line) and hypertension (green line)*[9]

hypertrophy and is associated with increased cardiac morbidity and patient mortality in both the general and transplant populations[2,8,10-12] (Table 1).

Table 1. *Cardiovascular disease as leading cause of death*[2,3]

Coronary artery disease,
Acute myocardial infarction
Arrhythmia, cardiomyopathy
Heart failure
Stroke

Etiology and mechanisms causing hypertension after renal transplantation

Many factors have been incriminated for the development of hypertension after renal transplantation (Table 2). Donor hypertension and death due to subarachnoid hemorrhage have been connected with higher blood pressure of the recipient. Recurrence of primary renal disease has been considered responsible for hypertension after a renal transplant. Hypertension is common among patients with acute or hyperacute rejection and this is due to impairment of graft excretory function. Renal artery stenosis may cause hypertension not responding to antihypertensive drugs.

Uncontrolled renin secretion from the native kidneys can be responsible for hypertension in the renal transplant recipient.

Table 2. *Etiology of hypertension after renal transplantation*[13]

Graft endogenous causes of hypertension
Donor age and hypertension
Acute rejection
Chronic allograft nephropathy
Recurrent or de novo glomerulonephritis
Drug – induced nephrotoxicity
Graft outflow obstruction
Graft exogenous causes of hypertension
Related to the native kidneys
Graft artery stenosis
Coexistent essential hypertension
Polycythemia?
Immunosuppressive therapy
-Corticosteroids
-Calcineurin inhibitors

Treatment of hypertension after renal transplantation

Treatment of elevated blood pressure in renal transplant recipients significantly reduces morbidity and mortality[14,15]. Aggressine treatment of hypertemsion must be voidel the first few days after transplantation. A systolic blood pressure of 140 – 160 mmHg and a diastolic < 90 mmHg is preferred in order to achieve a sufficient blood perfusion of the transplanted kidney. When the systolic blood pressure is > 200 mm Hg and diastolic blood pressure is > 120 mm Hg, hypertension may precipitate a medical emergency requiring rapid reduction of blood pressure to prevent vital organ damage.

The final regulation of blood pressure should be managed on an outpatient basis (Table 3) in a stable transplant recipient. Multiple factors may play important role in the fluctuation of blood pressure. It is important to take into account life style, the associated risk factors and the immunosuppressive regimen. So, the treatment of hypertension is individualized (Table 3, 4).

Table 3. *Therapeutic approach of hypertension in renal transplant recipients*

Life – style changes
↓Salt intake, ↓body weight, ↑exercise, give up smoking and alcohol intake
Strict blood pressure control
<130/80 mmHg, combined therapy is usually required
< 125/75 mmHg in recipients with proteinuria
Blockade of angiotensin II effects
Control of associated risk factors
Lipids (statins, fibrates)
Insulin resistance: insulin sensitizers (metformin, glitazones?)
Platelet aggregation: aspirin, others?

Table 4. *Adjustment of immunosuppressive medications*

Steroid withdrawal protocols favorably affect BP
Minimize dose of calcineurin inhibitors
Replace CsA by using less hypertensive and less nephrotoxic drugs (AZA, MMF, Tacrolmus, Sirolimus)

Immunosuppression manipulation and arterial hypertension

Corticosteroids

During the initial high dose corticosteroid therapy, sodium retention occurs and plasma volume increases substantially (mineralocorticoid action) and leads to an increase of blood pressure and cardiac output[16]. Other postulated mechanisms of corticosteroids causing hypertension include increased sensitivity to endothelin-1 and angiotensin II leading to increased vascular resis-

tance, increased density of glucocorticoid receptors in the vascular muscle and decreased production of vasodilatory prostaglandins[5,17,18]. The daily dose and cumulative dose of prednisone are related to blood pressure[19,20]. High long term maintenance dose may cause or aggravate hypertension. The estimated incidence of arterial hypertension induced by corticosteroids is 15%[21]. The conversion from every day to alternate day corticosteroid therapy may cause a reduction in arterial blood pressure. Steroid withdrawal is associated with fall of arterial blood pressure[22]. The lowest possible corticosteroid dose coupled with low salt diet and judicious use of diuretics is an interesting option.

Calcineurin inhibitors: Cyclosporine – tacrolimus

Both CsA and tacrolimus cause hypertension[17]. The mechanism is multifactorial, causes reduction in GFR and renal blood flow, and includes increase in sympathetic nervous tone, increase of intra-renal vascular resistance and increased sodium retention, a rise in peripheral vascular resistance and vasoconstriction of the afferent arterioles which produces vessel wall damage and impaired autoregulatory function[17,23,24].These may be the result of imbalance between vasoconstrictive (endothelin and thromboxane) and vasodilator factors (NO and prostacyclin) in CsA and tacrolimus treated patients[25,26]. Endothelin may play an important role in the development of hypertension in these patients[27]. Calcinurin is present in several tissues including the kidney, vascular smooth muscle and nervous system, all of which are targets for hypertension. Possibly, calcinurin inhibition in these tissues is the cause of the increased sodium and water retention, vasoconstriction and sympathetic activity[28]. Hypertension in patients taking cyclosporine in combination with corticosteroids has been described in 50% to 80% of cases[26]. CsA induced hypertension is characterized by nocturnal hypertension[25].

Tacrolimus has been associated with less systemic vasoconstriction and less arterial hypertension than CsA in liver transplant patients[29]. The most recent European multicentre study comparing tacrolimus with CsA microemulsion in kidney transplantation showed that the incidence of new onset or worsening hypertension was less common in the tacrolimus group[30]. In general, the existing data today suggest that renal transplant patients under tacrolimus based therapy show less arterial hypertension compared with patients under CsA immunosuppression[31].

Mycophenolate Mofetil

All the available literature support that MMF is not nephrotoxic and does not have any hypertensive effect, does not cause diabetes or hyperlipidaemia[22,32-34].

Sirolimus

In Phase III studies using sirolimus in combination with CsA, there was a higher frequency of hypertension than control groups. It is possible that sirolimus potentiates the nephrotoxic effect of cyclosporine, which would explain the increase of blood pressure[35].

Immunosuppressive protocols

Immunosuppression protocols using MMF or azathioprine with CsA and steroids did not show difference in the incidence of hypertension[36]. Protocols with steroid low dose and discontinuation present lower incidence of hypertension compared to triple scheme[37]. These protocols have the drawback of high acute rejection rate[38].

The dose reduction or discontinuation of cyclosporine, in protocols with MMF and steroids, results in lower systolic and diastolic blood pressure[39].

Protocols based on sirolimus (plus steroid and azathioprine/MMF) show lower systolic and diastolic blood pressure but renal function at two years was lower in sirolimus treated compared to cyclosporine treated patients[40].

Use of antihypertensive drugs

The selection of antihypertensive therapy in the kidney transplant recipient should be guided, in part, on prior history of success of antihypertensive medications in facilitating blood pressure control before the transplant. In spite the use of new antihypertensive agents, the best treatment of arterial blood pressure after transplantation is not known yet. No single antihypertensive agent (Table 5) has been found to be more efficacious and better tolerated than the others used in the treatment of posttransplant hypertension and the initial antihypertensive therapy must aim at the patient's risk factors. We diagnose hypertension when the blood pressure is > 130 / 85 mmHg in Rt recipients without proteinuria, or it is > 125 / 75 mmHg in Rt with proteinuria[41-43].

Table 5. *Pharmacological therapy*

Diuretics
Calcium channel blockers (CCBs)
ACE Inhibitors (ACE-I)
Angiotensin receptor blockers (ARBs)
Other antihypertensive drugs
– β-blockers
– α-adrenergic receptor antagonists
– Centrally acting α-2 receptor agonists
– Direct vasodilators

Diuretics (Table 6,7)

A careful assessment of blood volume is important in all kidney transplant recipients because they frequently

Table 6. *Diuretics*[50]

Natriuretic action
Risk reduction of cardiovascular events
Restore or increase the antiproteinuric effect of ACE-I
Treat hyperkalemia and hypercalcaemia
Decrease urinary calcium loss
Side effects
Hypokalemia, hypomagnesemia
Hyperuricemia, hyperlipidemia
Insulin resistance

receive corticosteroids and calcinurin inhibitors which may interfere with sodium and water excretion. Depending on the level of the kidney function a thiazide or a loop diuretic may be appropriate.

The mechanism by which diuretics reduce blood pressure is not known. The first period after starting diuretic therapy, the control of blood pressure is by volume depletion. Later possibly there is a vascular hyporesponsiveness to the sympathetic nervous system[44]. The use of diuretics is mandatory in the immediate post-transplant period in case of hypertension and fluid overload. Loop diuretics are the drugs of choice, alone or in combination with CCBs, especially in cases with urine output less than 50 ml/h and gross haematuria. Sodium load, food-drug interactions and drug-drug interactions may lessen or ablate the effectiveness of diuretic therapy[45-47]. Loop diuretics can cause prerenal azotemia, hypokalemia, hyperuricemia, hypocalcaemia and exacerbate hyperparathyroidism. A potential problem associated with hypokalemia is interference with insulin release and subsequent impairment of glycemic control. The extended use of diuretics and calcineurin inhibitors may require close electrolyte monitoring to avoid gout and cardiac mortality associated with low magnesium levels[48]. On the contrary thiazide diuretics may induce hypercalcaemia and potassium sparing agents hyperkalemia. The use of cyclosporine, FK506, ACE inhibitors, b-blockers and cotrimoxazole has been connected with hyperkalemia. Hyperuricaemia and hypomagnessaemia are complications of cyclosporine and tacrolimus therapy[49].

Table 7. *Dose, renal effects, dosage adjustment in renal failure of the more commonly used diuretics in renal transplantation*

Diuretics	usual dose mg/d	renal effects GFR RBF RVR	percentage of normal dosage in renal failure >50	10-50	<10	toxicity (most frequent)
Furosemide	20-320	acutely decrease GFR and RBF	100	100	100	hypercholesterolemia hyperglycemia hypokalemia hyperuricaemia
Hydrochlorothiazide	12.5-50	>>	100	100	avoid	>>
Chlorothiazide	125-500	>>	100	100	avoid	>>
Ethacrynic acid	25-200	>>	100	q^{12hr}	avoid	>>
Bumetanide	0.5-10	>>	100	100	100	>>
Amiloride	2.5-10	>>	100	100	avoid	>>
Indapamide	1.25-25	improve GFR	100	100	avoid	>>

Calcium channel blockers (CCBs)

CCBs are usually well tolerated and it has been proved that reduce mean arterial pressure and total renal vascular resistance, provide selective afferent glomerular arterioral dilatation, increase renal blood flow and GFR, reduce cyclosporine toxicity and combat the vasoconstrictive effect of CNIs, cause natriuresis, decrease perfusion injury and the rate of acute tubular necrosis immediately after transplantation because they offer protection to tubular epithelium and may reduce CsA induced hyperuricaemia[51-56]. The main action of these drugs is the inhibition of entrance of calcium into the smooth muscles of vasoconstricted arterioles through voltage potential-dependent channels (Table 8). For the above reasons, it has been supported that calcium antagonists are the drugs of choice. The use of CCBs after the recovery of cold ischemia time acute tubular necrosis (ATN) and normalization of graft function must target to normal levels of systolic blood pressure (< 130 mmHg) because the afferent arteriolar dilatation conveys the systemic blood pressure into the glomerulus and in long term may result in kidney damage if the systolic blood pressure is not well controlled. However, in a comparative clinical trial, it was found that a calcium antagonist, an ACE-I and an a-blocker were equally effective in reducing blood pressure[57] and patient and graft survival did not show difference with the use of b-blockers and / or calcium antagonists in a 5-year follow up[58]. In a recent longitudinal study it has been suggested that beta blockers as well as ACEIs may have a beneficial effect on cardiovascular mortality and on patient and graft survival over calcium antagonists[59].

Table 8. *Characteristics of CCBs*[60]

Counteract afferent arterial vasoconstriction caused by calcineurin inhibitors
Ameliorate interstitial fibrosis caused by calcineurin inhibitors
Reduce the incidence of delayed graft function
Modulate the immune system??
Improve graft function??
side effects
Impair calcineurin inhibitor's metabolism
Verapamil, diltiazem, nicardipine, amlodipine
Gingival hyperplasia
Peripheral oedema
Skeletal muscle weakness
Tachycardia

Isradipine (Lomir) and nifedipine (Coracten, Macorel, Adalat) are probably the most effective drugs among calcium channel antagonists and do not

cause increase of cyclosporine levels as it happens with diltiazem, verapamile and nicardipine[24,61,62]. These drugs are potent vasodilators and may cause dizziness, flushing, headache, leg oedema and gum hyperplasia[63-65].

These adverse effects (Table 9) can be minimised by the use of slow release formulations or with agents of a slow onset of action. It has been reported that short – acting calcium antagonists, given in non-transplanted patients, may increase the mortality in those with a recent history of acute myocardial infarction or coronary heart disease[66]. Recently, safety has proved not to be a problem with calcium channel blockers in hypertensives treated in the ALLHAT study even in those with chronic renal failure[67]. CCBs present robust antihypertensive action even in the presence of concomitant salt consumption. Clinical trials have shown that nondihydropyridine CCBs are more effective in reducing proteinuria compared with dihydropyridines (such as nifedipine). The combination of CCBs with an ARB or ACE-I reduces further the proteinuria[68,69].

Table 9. *Dose, renal effects, dosage adjustment and toxicity of the more commonly used CCBs in renal transplantation*

CCBs	usual dose mg	renal effect GFR	RBF	RVR	percentage of normal dosage in renal failure >50	10-50	<10	toxicity
Nifedipine	30-120	↑↑	↑↑	↓↓	100	100	100	GH, HD, OE, FL
Felodipine	5-20	>>			100	100	100	>>
Amlodipine	5-10	>>			100	100	100	>>
Isradipine	2.5-10	>>			100	100	100	>>
Nicardipine	60-120	>>			100	100	100	>>
Diltiazem	60-350	>>			100	100	100	>> + CA
Verapamil	180-240	>>			100	100	100	>>

GH: Gingival Hyperplasia, HD: Headache, OE: oedema, FL: Flashing, CA: Conduction abnormality

Angiotensin converting enzyme inhibitors (ACE-I)

The basic haemodynamic effect of ACE-I is vasodilatory via suppression of angiotensin II production and inhibition of bradikinin inactivation (Table 10). Also, it has been suggested that ACE inhibitors retard the evolution of glomerulosclerosis and chronic decline of renal function, controlling arterial blood pressure and possibly normalizing intraglomerular hemodynamics[70,71].

The use of ACE-Is in post-transplant hypertension had been a matter of debate for a long time. In recent clinical studies with a long term follow up in renal transplant patients, ACE-Is have been shown to be effective in the treatment of post-transplant hypertension. There was no difference between ACE-Is' and calcium antagonists' antihypertensive effect. Also adrenal plasma flow and GFR were similar in both groups of patients[70,74]. Mourard compared nifedipine plus atenolol with lisinopril plus furosemide and found no differences between the two groups as far as the antihypertensive efficacy, the adverse drug reaction profile, the effect on plasma renal flow and GFR. It has been shown that ACE-Is reduce significantly the proteinuria of transplanted patients with chronic allograft nephropathy[75].

Table 10. *Characterists of ACE-I*[72,73]

Suppress angiotensin II production
– Act on afferent and efferent arteriols
Inhibit bradykinin inactivation
Reduce proteinuria
Inhibit the expression of TGF-β1
Risk reduction of cardiovascular events
– Reduce left ventricular hypertrophy
Natriuretic action
Antagonize erythrocytosis
side effects
Acute decrease in GFR
Hyperkalemia
(In patients with risk factors for hyperkalemia)
Chronic - dry cough (10% pts)
Anemia

The decline of renal function (20% - 30%) is due to foll of glomerular capillary pressure and GFR. If there is a more than 30% decrease after treatment with ACE inhibitors it is possibly related to the existence of renal artery stenosis or it may happen in grafts with normal parenchyma when the patient is dehydrated[76-78]. The use of these drugs has been connected with hyperkalemia, especially in diabetics, and anemia[79] (Table 11).

Angiotensin II receptor antagonists (ARBs)

ARBs reduce the capillary pressure, the GFR and the systemic blood pressure by blocking the physiological response to angiotensin II[80,81] (Table 12). It is best to start these drugs during the posttransplant period when kidney function and immunosuppression is stable.

Table 11. *Dose, renal effects, dosage adjustment in renal failure and toxicity of most commonly used ACE-Is in renal transplantation*

ACE inhibitors	usual dose mg/d	renal effects GFR	RBF	RVR	percentage of normal dosage in renal failure >50	20-50	<10	toxicity
Captopril (Capoten)	50-100	No/↓	No/↓	↓	100	75	50	CA, C, A, H, An
Enalapril (Renitec)	2.5-20	>>			100	75	50	>>
Lisinopril (Prinivil)	10-20	>>			100	50	25	>>
Fosinopril (Monopril)	20-40	>>			100	100	75	>>
Cilazapril (Vascace)	0.5-5	>>						

CA:conduction abnormality, C:cough, A:angioedema, H:hyperkalaemia, An:anaemia

Table 12. ***Angiotensin receptor blockers***

Blockade angiotensin II receptor 1
– Act on afferent and efferent arteriols
Inhibit the expression of TGF-β1
Reduce proteinuria
Risk reduction of cardiovascular events
– Reduce left ventricular hypertrophy
Natriuretic action
Antagonize erythrocytosis
side effects
Acute decrease in GFR
Hyperkalaemia
(In patients with risk factors for hyperkalaemia)
Anaemia

The recent successful use of angiotensin II receptor antagonists type I has added a new group of drugs in the treatment of renal transplant hypertension[71,82,83].

These agents have a significant control on the blood pressure, reduce the need for other antihypertensive agents[82,83] and reduce statistically significantly proteinuria (Figure 4, Table 13) of patients with chronic allograft disease[84]. These agents do not seem to interfere with any of the immunosuppressive agents.

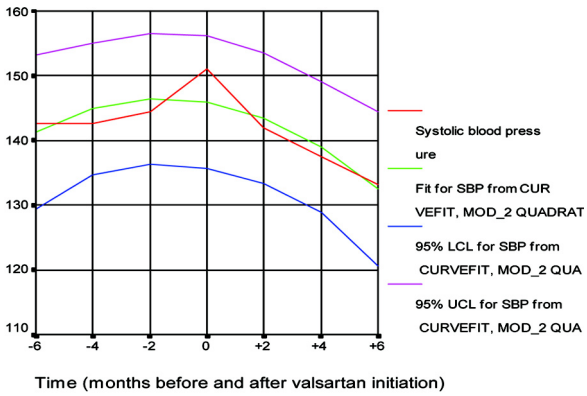


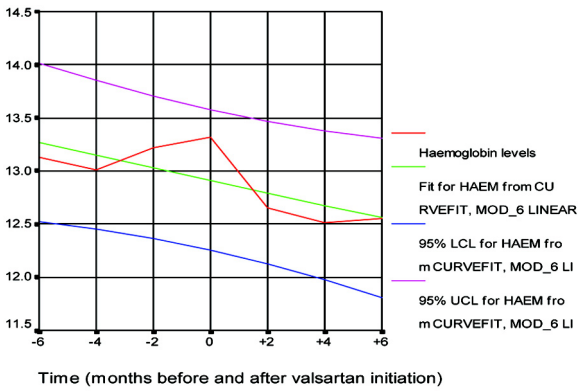
Figure 4. *The systolic blood pressure six months before and six months after valsartan treatment Vergoulas G, et al. Hippokratia 2001; 5:61-68*

Table 13. *Proteinuria and number of antihypertensive drugs at baseline and six months after treatment with ARBs*[84]

	Baseline	Six months later
24 hour urine protein (g)	0.76 ±0.77[1]	0.61±0.63[1]
range	0.25-2.50	0.00-1.80
Number of antihypertensive agents	2.27±0.89[2]	1.83±0.85[2]

[1]p: 0.024 [2]p:0.007

Stimulation of AT1 receptors of erythroid progenitor cells by Ag II is believed to increase red blood cell mass independently from circulating erythropoietin. AT1 blockers cause statistically significant fall of Ht and Hb (Figure 5) and are very useful in hypertensive patients



Figue 5. *Hb levels six months before and six months after valsartan treatment. Vergoulas G, et al. Hippokratia 2001; 5:61-68*

with erythremia[82,83]. It is believed that the blockade of AT1 receptors results in a decrease of red blood-cell mass independently of erythropoietin and initial haemoglobin levels[85,86].

In some patients supplementation with erythropoietin may be required and some may consider this as an inappropriate trade-off. However the opportunity to reduce both kidney and cardiovascular risks simulta-

neously in patients with greater cardiovascular burden may be an important consideration.

These drugs have the ability to lower significantly the levels of TGF-β1 in the plasma of transplanted patients with chronic allograft nephropathy[87]. Usually, they do not cause hyperkalemia or hyperuricaemia and cause a slight but significant rise of serum creatinine level[88] (Table 14). A rise of serum creatinine of 20-30% is acceptable but always must be kept in mind the possibility that the rise is due to rejection. The reduction of GFR correlates with stabilization of kidney function over time possibly due to an anatomical protection of kidney[89]. Serum creatinine level increase by more than 30% could indicate diminished effective arterial blood volume because of diuretic use or renal artery stenosis. From the first four drugs of this class of antihypertensives (losartan, valsartan, irbersartan, candesartan) it seems that losartan has the weaker antihypertensive effect and candesartan the stronger[90-92].

The drugs of this category could be proved valuable not only for the treatment of hypertension of renal transplant recipients but also for the intervention in the evolution of chronic allograft nephropathy by interfering with profibrogenic and scarring processes within the kidney[93-95] and this possibly is the great difference between ARBs and ACE-Is because much production of angiotensin II takes place by non-ACE pathways both systemically and at the tissue level. These alternative pathways include direct formation from angiotensinogen, cathepsin G, and tissue plasminogen activation. Angiotensin I also can be converted to angiotensin II at the tissue level by chymase and cathepsin G. These local pathways are very important because tissue levels of angiotensin II are nearly 1,000 times greater than the levels in the circulation. Angiotensin II converting enzyme inhibitors have no effect on angiotensin II formed by these alternate pathways[96-100]. Another point in favour of ARBs is the high percentage of patients that can not tolerate ACE-I[101,102].

There have been some concerns about the early administration of ACEIs and ARBs after transplantation because of the fear of ATN development or DGF. Recently it has been supported that the early administration of ACEis/ARBs after transplantation is associated with faster decrease of serum creatinine levels, faster recovery time from delated graft function (DGF) and lower proteinuria[103].

It must be noticed that ACEIs/ARBs improve left ventricular function and reduce left ventricular hypertrophy due to hypertension in general population and possibly they have the same effect on the kidney transplant recipients with hypertension[104-106].

Table 14. *Dose, renal effects, dosage adjustment in renal failure and toxicity of ARBs in renal transplantation*

ARB	usual dose Mg/d	renal effects			percentage of normal dosage in renal failure			toxicity
		GFR	RBF	RVR	>50	20-50	<10	
Losartan (Cozaar)	50-100	No/↓	No/↓	↓	100	100	75	anaemia,
Irbersartan (Aprovel)	150-300		>>		100	100	100	>>
Candesatan (Atacand)	4-32		>>		100	100	75	>>
Eprosartan (Teveten)	200-400		>>		100	100	75	>>
Telmisartan (Pritor)	40-120		>>		100	100	100	>>
Valsartan (Diovan)	40-160		>>					>>

B – blockers (Table 15)

The precise mode of action of β-blockers in reducing blood pressure is not known. In a small study of the effect of β-blockers on hypertensive renal transplant recipients, a blood pressure reduction was noticed only in hypertensive patients with their native kidneys in situ[107]. Native kidneys may play an important role in activation of renin - angiotensin system mediated by activation of the sympathetic nervous system. In a randomized study renal transplant recipients received atenolol or quinapril. In both groups blood pressure control was achieved. However quinapril lowered significantly albumin excretion[108].

β-Blockers may mask the symptoms of hypoglycaemia and thyrotoxicosis and cause sexual dysfunction, muscle weakness, tiredness and fatigue. Abrupt discontinuation of β-blockers may exacerbate rebound hypertension and so the dosage should be reduced slowly over a 1- to 2-week period.

They can also complicate the lipid profile in renal transplant recipients. The beneficial effect of β-blockers on transplant recipients, with a history of MI, CHD, hypertrophic cardiomyopathy or systolic heart failure outweigh the risk of their adverse effects[109].

The use of mTOR inhibitors may complicate further the problem of hyperlipidemia. Newer third generation β-blockers such as carvedilol (Dilatrend®) may solve the problem since they have neutral or positive effect on dyslipidemia and insulin resistance[110]. β-Blockers should be considered first choice treatment together with the ACI / ARBs for patients with a renal transplant and a history of coronary heart disease.

Table 15. *β-Blockers*[111,112]

Antagonize the catecholamines at b1-adrenergic receptors
Risk reduction of cardiovascular events (myocardial infarction, sudden death)
Reported decrease of the expression of TGF-b1
Side effects[113,114]
Blunting of clinical picture of hypoglcaemia
Dyslipidaemia
Diabetes mellitus

References

1. U.S. Renal Data System. USRDS 1998 annual report. Bethesda, MD: The National Institutes of Health- National Institute of Diabetes, Digestive and Kidney Diseases 1998
2. Ojo AO, Hunson GA, Wolfe RA, et al. Long – term survival in renal transplant recipients with graft function. Kidney Int 2000; 57:307-313
3. Riggato C, Folley RN, Kent GM, Guttman R, Parfrey PS. Long-term changes in left ventricular hypertrophy after renal transplantation. Transplantation 2000; 70:570-575
4. Jarowenko MV, Flechner SM, Van Buren CT, et al. Influence of cyclosporine on posttransplant blood pressure response. Am J Kidney Dis 1987; 10:98-103
5. Zeier M, Mandelbaum A, and Ritz E. Hypertension in the transplant patient. Nephron 1998;80:257-268
6. Vergoulas G, Miserlis Gr, Karasavvidou F, et al. The blood pressure after renal transplantation. A single centre experience. Hippokratia 2002; 6:62-70
7. Vergoulas G, Tasiopoulou C, Angelou A, et al. Risk factors affecting ten year kidney graft survival. 2nd World Congress on "Quality in Clinical Practice", Porto Carras, Chalkidiki, 3-6 June 2004, abstracts p. 108 (poster)
8. Opelz G, Wujciak T, Ritz E. Association of chronic kidney graft failure with recipient blood pressure. Kidney Int 1998; 53:217-222
9. Vergoulas G, Miserlis Gr, Atmatzidis E, et al. Clinical risk factors on patient and graft survival after kidney transplantation. BANTAO Journal 2003; 1:261-263
10. Psaty BM, Smith NL, Siscovick DS, et all. Health outcomes associated with antihypertensive therapies used as first line agents: a systematic review and meta - analysis. JAMA 1997; 277:739-745
11. Howard RJ, Patton PR, Reed AI, et al. The changing causes of grft loss and health after kidney transplantation. Transplantation 2002; 73:1923-1928
12. Mange KC, Cizman B, Joffe M, Feldman HI. Arterial hypertension and renal allograft survival. JAMA 2000; 283:633-638
13. Vergoulas G, Miserlis Gr, Karasavvidou F, et al. The blood pressure after renal transplantation. A single centre experience. Hippokratia 2001; 6:62-70
14. Kokado Y, Takahara S, Kameoka H, et al. Hypertension in renal transplant recipients and its effect on long term allograft survival. Transplant Proc 1996;28:1600-1602
15. Cosio FG, Falkenhain ME, Pesavento TE, et al. Relationships arterial hypertension and renal allograft survival in African-American patients. Am J Kidney Dis 1997; 29:419 – 417
16. WhitworthJA. Mechanisms of glucocorticoid - induced hypertension. Kidney Int 1987; 31:1213-1224
17. Kutkuhn B, Hollenbeck M, Weskoff A, et al. Renin secretion and captopril stimulation in hypertensive renal transplant recipients. Urol Int 1994; 52:82-86
18. First MR, Neylan JF, Rocher LL, Tejani A. Hypertension after renal transplantation. J Am Soc Nephrol 1994; 4(Suppl 1):S30-S38
19. Taler SJ, Textor SC, Canzanello VJ, et al. Role of steroid dose in hypertension early after liver transplantation with tacrolimus and cyclosporine. Transplantation 1996; 62:1588-1592
20. Fryer JP, Granger DK, Leventhal JR, et al. Steroid related complications in the cyclosporine era. Clin Transplant 1994; 8:224-228
21. Veenstra DL, Best JH, Hornberger J, et al. Incidence and long term cost of steroid related side effects after renal transplantation. Am J Kidney Dis 1999; 33:829-833
22. Kasiske BL, Ballantyne CM. Cardiovascular risk associated with immunosuppression in renal transplantation. Transplant Rev 2002; 16:1-21
23. van den Dorpel MA, van der Meiracker AH, Lameris TW, et al. Cyclosporine A impairs the nocturnal blood pressure fall in renal transplant recipients. Hypertension 1996; 28:304-307
24. de Mattos AM, Olyaei AJ, Bennett WM. Pharmacology of immunosuppressive medications used in renal diseases and transplantation. Am J Kidney Dis 1996; 28:631-637
25. Taler SJ, Textor SC, Canzanello VJ, et al. Cyclosporine – induced hypertension: Incidence, pathogenesis and management. Drug Saf 1999; 20:437-457
26. Haas M, Mayer G. Cyclosporine A – associated hypertension. Pathomechanisms and clinical consequences. Nephrol Dial Transplant 1997; 12:395-397
27. Takeda Y, Mitamori I, Wu P, et al. Effects of an endothelin receptor antagonist in rats with cyclosporine induced hypertension. Hypertension 1995; 26:932-937
28. Sander M, Lyson T, Thomas GD, et al. Sympathetic neural mechanisms of cyclosporine induced hypertension. Am J Hypertens 1996; 9(Suppl):S124-S127
29. Textor SC, Weisner R, Wilson DJ, et al. Systemic and renal hemodynamic differences between FK506 and cyclosporine in liver transplant recipients. Transplantation 1993; 55:1332-1337
30. Margreiter R. Efficacy and safety of tacrolimus compared with cyclosporine microemulsion in renal transplantation. A randomized multicentre study. The European Tacrolimus vs Ciclosprine micoeulsion Renal Transplantation Study Group. Lancet 2002; 359:741-746
31. Morales JM. Influence of the new immunosuppressive combinations on arterial hypertension after renal transplantation. Kidney Int 2002; 62(Suppl 82):S81-S87
32. Platz DP, Sollinger HW, Hullet DA, et al. RS-61443, a new potent immunosuppressive agent. Transplantation 1991; 51:27-31
33. European Mycophenolate Mofetil Cooperative Study Group: Placebo-controlled study of mycophenolate mofetil combined with cyclosporine and corticosteroids for prevention of acute rejection. Lancet 1995; 345:131-1325
34. Ojo AO, Meier –Kriesche HU, Hanson JA, et al. Mycophenolate mofetil reduces late renal allograft loss independently of acute rejection. Transplantation 2000; 69:2405-2409
35. Kahan BD Camardo JS. Rapamycin: Clinical results and future opportunities. Transplantation 2001; 72:1181-1193
36. Sollinger HW, U.S. Renal Mycophenolate Mofetil Study Group. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. Transplantation 1995; 60:225-232
37. Vanrenterghem Y, Lebranchu Y, Hene R, et al. Double blind comparison of two cortical regimens plus mycophenolate ofetil and cyclosporine for prevention of acute renal allograft rejection. The Steroid Dosing Study Group. Transplantation 2000; 70:1352-1359
38. Steroid Withdrawal Study Group. Prednisone withdrawal in

kidney transplant recipients on cyclosporine and mycophenolate mofetil. A prospective randomised trial. Transplantation 1999; 68:1865-1874
39. Schnuelle P, Van Der Heide JH, Tegzess A, et al. Open randomized trial comparing early withdrawal of either cyclosporine or mycophenolate mofetil in stable renal transplant recipients initially treated with a triple drug regimen. J Am Soc Nephrol 2002; 13:536-543
40. Morales JM, Wramner L, Kreis H, et al. Sirolimus does not exhibit nephrotoxicity compared to cyclosporine in renal transplant recipients. Am J Transplant 2002; 2:436-442
41. National Kidney Foundation k/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004; 43 (suppl): 176-182
42. Mailloux LU, Levey AS. Hypertension in patients with chronic renal disease. Am J Kidney Dis 1998; 32(Suppl 5): S120-S141
43. European best practice guidelines. Nephrol Dial Transpalnt 2002; 17(Suppl 4): S25-S26
44. Neutel JM. Metabolic manifestations of low-dose diuretics. Am J Med 1996; 101:71S-82S
45. Johnson AG, Nguyen TV, Day RO. Do non steroidal antiinflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289-300
46. Swan SK. Diuretic strategies in patients with renal failure. Drugs 1994;48:380-385
47. Ellison DH. The physiologic basis of diuretic synergism: its role in treating diuretic resistance. Ann Intern Med 1991;114:886-894
48. Hoes AW, Grobbee DE, Lubsen J, et al. Diuretics, beta blockers and the risk for sudden cardiac death in hypertensive patients. Ann Intern Med 1995;123:481-487
49. West C, Carpenter BJ, Hakala TR. The incidence of gout in renal transplant recipients. Am J Kidney Dis 1995;123:481-487
50. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension Diabetes Executive Committees Working Group. Am J Kidney Dis 2000; 36:646-661
51. Dawidson I, Rooth P. Improvement of cadaver renal transplantation outcomes with verapamil. A review. Am J Med 1991; 90:37S
52. Bia MJ, Tyler K. Evidence that calcium channel blockade prevents cyclosporine-induced exacerbation of renal ischemic injury. Transplantation 1991;51:293-295
53. Dawidson I, Rooth P, Always C, et al. Verapamil prevents post-transplant delayed function and cyclosporine A nephrotoxicity. Transplant Proc 1990;22:1379-1380
54. Dawidson I, Rooth P, Lu C, et al. Verapamil improves the outcome after cadaver renal transplantation. J Am Soc Nephrol 1991; 2:983-990
55. Romero JC, Raij L, Granger JP, et al. Multiple effects of calcium entry blockers on renal function in hypertension. Hypertension 1987; 10:140-151
56. Chanard J, Toupance O, Lavaud S, et al. Amlodipine reduces cyclosporine – induced hyperuricaemia in hypertensive renal transplant recipients. Nephrol Dial Transplant 2003; 18:2147-2153
57. Martinez – Castelao A, Hueso M, Sanz V, et al. Treatment of hypertension after renal transplantation: long-term efficacy of verapamil, enalapril and deoxazocin. Kidney Int 1998;68 Suppl:S130-S134
58. Morales JM, Rondriguez-Paternina E, Araque A, et al. Long-term protective effect of a calcium antagonist on renal function in hypertensive renal transplant patients on cyclosporine therapy: a 5-year prospective randomized study. Transplant Proc 1994;26:2598-2599
59. Tutone VK, Mark PB, Stewart GA, et al. Hypertension, antihypertensive agents and outcomes following renal transplantation. Clin Transplantation 2005; 19:181-192
60. Baroletti SA, Gabardi S, Magee CC, Milford EL. Calcioum channel blockers as the treatment of choice for hypertension in renal transplant recipients: fact or fiction. Pharmacotherapy 2003; 23:788-801
61. Pesavento TE, Jones PA, Julian BA, et al. Amlodipine increases cyclosporine levels in hypertensive renal transplant patients: results of a prospective study. J Am Soc Nephrol 1996;7:831-835
62. Guan D, Wang R, Lu et al. Effects of nicardipine on blood cyclosporine levels in renal transplant patients. Transplant Proc 1996;28:1311-1312
63. Grekas D, Dioudis C, Kalevrosoglou I, et al. Renal hemodynamics in hypertensive renal allograft recipients: Effect of calcium antagonists and ACE inhibitors. Kidney Int 1996, 49:597
64. Vanderschaaf MR, Hene RJ, Floor M, et al. Hypertension after renal transplantation: Calcium chanel blocker or converting enzyme blockade? Hypertension 1995,25:77
65. Bochicchio T, Sandoval G, Ron O, Perez-Grovas H, Bordes J, Herrera-Acosta J. Lisinopril prevents hyperfiltration and decreases proteinuria in post-transplant hypertensives. Kidney Int 1990,38:873
66. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. JAMA 1995;274:620-625
67. ALLHAT study. Major outcomes in high-risk hypertensive patients randomized to angiotensin –converting enzyme inhibitor or calcium channel blocker vs diuretic: The antihypertensive and lipid lowering treatment to prevent heart attack.JAMA 2002; 288:2981-2997
68. Bakris G, Copley JB, Vicknair N, et al. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int 1996; 50:1641-1650
69. Bakris G, Weir MR, Shanifar S, et al. Effects of blood pressure level on progression of diabetic nephropathy: Results from the RENAL study. Arch Intern Med 2003; 163:1555-1565
70. Mourad G, Ribstein J, Mimran A. Converting-enzyme inhibitor versus calcium antagonist in cyclosporine-treated renal transplants. Kidney Int 1993;43:419-425
71. del Castillo D, Campistol JM, GuiradoL,et al.Efficacy and safety of losartan in the treatment of hypertension in renal transplant recipients. Kidney Int 1998,54(Suppl 68):S135
72. Suwelack B, Gerhardt U, Hausberg M, Rahn KH, Hohage H. Comparison of quinaril versus atenolol: effects on blood pressure and cardiac mass after renal transplantation. Am J Cardiol 2000; 86:583-585
73. Navar GL. The intrarenal rennin – angiotensin system in hypertension. Kidney Int 2004; 65:1522-1532
74. Sennesael J, Lamote J, Violet I, et al. Comparison of perindopril and amlodipine in cyclosporine – treated renal allograft recipients. Hypertension 1995;26:436-444
75. Bochicchio T, Sandoval G, Ron O, et al. Fosinopril prevents hyperfiltration and decreases proteinuria in post-transplant hypertensives. Kidney Int 1990;38:873-879
76. Meyer MM. Post-transplant hypertension. In Bennett WM, McCarron DA, eds. Pharmacology and management of hypertension. New York, Churchill Livingstone, 1994:181-215,
77. Traindl O, Falger S, Reading S, et al. The effect of lisinopril on renal function in proteinuric renal transplant recipients. Transplantation 1993;55:1309-1313
78. Bergman SM, Curtis JJ. Possible mediators in hypertension: Renal factors. Semin Nephrol 1996;16:134-1390
79. Gaston RS, Julian BA, Curtis JJ. Post-transplant erythrocytosis: an enigma revisited. Am J kidney Dis 1994;24:1-11
80. Ritz E, Orth SR, Strzelezyk P. Angiotensin converting en-

zyme inhibitors, calcium channel blockers and their combination in the treatment of glomerular disease. J Hypertens 1997;15:Suppl:S21-S26
81. Moser M. Angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and calcium channel blocking agents. J Am Coll Cardiol 1997;29:1414-1421
82. Vergoulas G, Miserlis Gr, Trellopoulos G, Antoniadis A. Evaluation of losartan in patients with renal transplantation. Hippokratia 2000;4:67-72
83. Vergoulas G, Miserlis Gr, Gakis D, Atmatzidis E, Anoniadis A. The use of valsartan in hypertensive renal transplant recipients. Hippokratia 2001; 5:61-68
84. Vergoulas G, Miserlis Gr, Papanikolaou V, et al. Angiotensin II type I receptor antagonists reduce proteinuria of hypertensive renal transplant recipients. Hippokratia 2001; 5: 165-171
85. Ducloux D, Saint-Hillier Y, Chalopin GM. Effect of losartan on haemoglobin concentration in renal transplant recipients: a retrospective analysis. Nephrol Dial Transplant 1997; 12:2683-86
86. Home S, Holzer H, Horina J. Losartan and renal transplantation. Lancet 1998; 351:285
87. Campistol JM, Inigo P, Jimenez W, et al. Losartan decreases plasma levels of TGF-β1 in transplant patients with chronic allograft nephropathy. Kidney Int 1999;56:714-719
88. Vergoulas G, Miserlis Gr, Papanikolaou V, et al. Losartan versus losartan in the treatment of hypertension of renal transplant recipients. Hippokratia 2001; 5:156-164
89. Bakris G, Weir MR. Angiotensin – converting enzyme inhibitor-associated elevations in serum creatinine. Is this a cause for concern? Arch Int Med 2000; 160:685-693
90. Elmfeldt D, Olofsson B, Meredith P. The relationship between dose and antihypertensive effect of four AT1 – receptor blockers. Differences in potency and efficacy. Blood Pressure 2002; 11:292-301
91. Hansson L. The relationship between dose and antihypertensive effect for different AT1 – receptor blockers. Blood Pressure 2001; 10 (Suppl 30): 33-39
92. Meredith PA. Clinical comparative trials of angiotensin II type I (AT1) – receptor blockers. Blood Pressure 2001; 10 (Suppl 3): 11-17
93. Shihab PS, Bennet WM, Tanner AM, et al. Andiotensin II blockade decreases TGF-beta and matrix proteins in cyclosporine nephropathy. Kidney Int 1997; 52:660-673
94. Weir MR, Wei C. The role of angiotensin II and TGF-beta on the progression of chronic allograft nephropathy. JRAAS 2001; 2(Suppl 1):S88-S1190
95. Stigant CE, Cohen J, Vivera M, et al. ACE inhibitors and angiotensin II antagonists in renal transplantation: an analysis of safety and efficacy. Am J Kidney Dis 2000; 35:58-63
96. Urata H, Healy B, Stewart RW, Bumpus FM, Husain A. Angiotensin II-forming pathways in normal and failing human hearts. Cir Res 1990; 66:883-860
97. Ellis ML, Patterson JH. A new class of antihypertensive therpy: angiotensin II receptor antagonists. Pharmacotherapy 1996; 16:849-860
98. Balcells E, Meng QC, Johnson WH, Oparil S, Dell'Italia LJ. Angiotensin II formation from ACE and chymase in human and animal hearts: methods and species considerations. Am J Physiol 1997; 273:H1769-H1774
99. Hollemberg NK, Fisher ND, Price DA. Pathways for angiotensin II generation in intact human tissue: evidence from comparative pharmacological interruption of the rennin system. Hypertension 1998; 32:387-392
100. Siragy HM, de Gasparo M, Carey RM. Angiotensin type 2 receptor mediates valsartan – induced hypotension in conscious rats. Hypertension 2000; 35:1074-1077
101. Benz J, Oshrain C, Henry D, Avery C, Chiang YT, Gatlin M. Valsartan a new angiotensin II receptor antagonist: a double – blind study compring the incidence of cough with lisinopril and hydrochlorothiazide. J Clin Pharmacol 1997; 37:101-107
102. Conlin PR, Gerh WC, Fof J, Roehm JB, Boccuzzi SJ. Four year persistence patterns among patients initiating therapy with angiotensin II receptor antagonist losartan versus other antihypertensive drug classes. Clin Theraput 2001; 23:1999-2009
103. Lorenz M, Billensteiner E, Bodingbauer M, et al. The effect of ACE inhibitor and angiotensin II blocker therapy on early posttransplant kidney graft function. Am J Kidney Dis 2004; 43: 1065-1070
104. Klingbeil AU, Schneider M, Martus P, et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med 2003; 115:41-46
105. Suwelack B, Gerhard U, hausberg M, et al. Comparison of quinapril versus atenolol. Effects on blood pressure and cardiac mass after renal transplantation. Am J Cardiol 2000;86:583-585
106. Isobe N, Taniguchi K, Oshima S, et al. Candesartan cilexetil improves left ventricular function, left ventricular hypertrophy and endothelial function in patients with hypertensive heart disease. Circ J 2002; 66: 993-999
107. Huysman FT, van Heusden FH, Wetxels JF, et al. Antihypertensive effect of beta blockade in renal transplant recipients with or without host kidneys. Transplantation 1988;46:234-237
108. Hausberg M, Barenbrock M, Hohage H, et al. ACE inhibitor versus beta-blocker for the treatment of hypertension in renal allograft recipients. Hypertension 1999; 33:862-868
109. Chobanian AV, Bakris G, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. JAMA 2003; 289:2560-2572
110. Bell DS. Advantages of a third – generation beta blocker in patients with diabetes mellitus. Am J Cardiol 2004; 93:49-52).
111. Poole-Wilson PA, Cleland JG, Di Lenarda A, et al. Rational and design of the carvedilol or metoprolo European trial in patients with chronic heart failure: COMET. Eur J Heart Fail 2002; 4:321-329
112. Zezina L, Vessby B, Larsson E, Backman U, Fellstrom B. Carvedilol treatment of kidney graft recipients with chronic rejection. Clin Transplantation 1999; 13:484-490
113. Suter PM, Vetter W. Metabolic effects of antihypertensive drugs. J Hypertens 1995;13:S11-S17
114. Gress TW, Nieto FJ, Shahar WR, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factor for type 2 diabetes melltus. N Engl J Med 2000; 342:905-912