Appendix continued...	*"Elimination, Metabolism"*	*Dosing*	*"Supplement required with dialysis"*	*Miscellaneous*
ACE inhibitors				*Anemia, anaphylactoid reactions*
Benazepril	R(H)	50 %	NO	Non-renal clearance of benazeprilate
Captopril	R	25-50%	YES	Active metabolite accumulation
Cilazapril	R(H)	25 %	YES	
Enalapril	R(H)	50 %	YES	Patent drug accumulation
Fosinopril	R and H	Unchanged	NO	50% hepatic elimination
Lisinopril	R	25 %	YES	
Perindopril	R(H)	25-50%	YES	
Quinapril	R(H)	25-50%	NO	
Ramipril	R(H)	25-50%	YES	
Trandolapril	R(H)	50 %	YES	Trandolaprilate is further metabolized prior to excretion
Angiotensin II receptor antagonists				
Candesartan	R (H)	AVOID		
Eprosartan	H	AVOID		
Irbesartan	H	Unchanged	NO	
Losartan	R (H)	Unchanged	NO	
Olmesartan	R H	Unchanged	NO	
Telmisartan	H	Unchanged	NO	
Valsartan	H	Unchanged	NO	
Calcium channel blockers				
Amlodipine	H	Unchanged	NO	
Diltiazem	H	Unchanged	NO	Risk of conduction disturbance
Felodipine	H	Unchanged	NO	
Isradipine	H	Unchanged	NO	
Lacidipine	H	Unchanged	NO	
Nicardipine	H	Unchanged	NO	
Nifedipine	H	Unchanged	NO	
Nitrendipine	H	Unchanged	NO	
Verapamil	H	"50-75% Active metabolites accumulation"	NO	Negative inotropic and dromotropic effects
Vasodilators				
Diazoxide	R (H)	Unchanged	YES	Smaller doses or slow inf. To avoid decreasing of BP and of protein binding
Hydralazine	H (NR)	Dosing interval prolonged	NO	Induction of lupus-like syndrome. Prolonged activity in slow acetylators
Minoxidil	H	Unchanged	YES	Active metabolites accumulation
Nitroprusside	NR	Titrate by blood pressure	YES	"Accumulation of thyocyanate. Thyocyanate is dialysable"

R=renal elimination, H=hepatic elimination, NR=non-renal elimination

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European Society of Hypertension Scientific Newsletter:
Update on Hypertension Management

2004; 5: No. 21

TREATMENT OF HYPERTENSION IN DIALYSED PATIENTS

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Introduction

Hypertension is common in dialysed patients (>80% at pre-dialysis state, >60% in patients with hemodialysis, >30 percent in those with peritoneal dialysis) (1). The leading cause of death in dialysed patients is cardiovascular.

The relationship between hypertension and cardiovascular mortality/morbidity is apparently controversial in dialysed patients because of the high prevalence of co-morbid conditions, by the underlying vascular pathology and by the effects of dialysis on blood pressure. The effects of age, left ventricular hypertrophy/dysfunction (also more prevalent in patients with hypertension) and poor nutrition may mask the true relationship between blood pressure and mortality in dialysed patients (2). Hypertension has been associated with stroke, ventricular arrhythmias and progression of atherosclerosis in patients on hemodialysis. Improved survival due to adequate blood pressure control of dialysed patients has been clearly demonstrated, stressing the importance of adequate antihypertensive treatment (3).

The etiology of hypertension in dialysis patients is multi-factorial (Table 1).

Table 1. **Etiology of hypertension in dialysed patients** (from ref. 4)

- sodium and volume excess due to diminished sodium excretory capacity of kidney
- activation of the renin-angiotensin-aldosteron system
- increased activity of the sympathetic nervous system
- increased endogenous vasoconstrictor (endothelin-1, Na-K-ATPase inhibitors, adrenomedullin), and decreased vasodilator (nitric oxide, prostaglandins) compounds
- frequent administration of erythropoietin
- increased intracellular calcium content, induced by parathyroid hormone excess
- calcification of arterial tree, arterial stiffness
- pre-existent hypertension
- nocturnal hypoxemia, frequent sleep apnea

Blood pressure measurement in dialysis patients

Pre- or post-dialysis blood pressure measurements in patients with hemodialysis may be misleading for the diagnosis of hypertension. The pre-dialysis systolic blood pressure may overestimate while the post-dialysis systolic blood pressure may underestimate the mean inter-dialytic systolic blood pressure by 10 mmHg; the mean systolic blood pressure by 7 mmHg (5).

The ambulatory pressure monitoring (ABPM) appears to be reproducible and it has shown that blood pressure is frequently high pre-dialysis state, it falls immediately after dialysis, and then it gradually increases during the inter-dialytic period. ABPM may be useful in determining "systolic blood pressure load" which is an important factor in the development of left ventricular hypertrophy. Pre-dialysis blood pressure correlates better with left ventricular hypertrophy than post-dialysis blood pressure measurement (6). The dialyzed patients usually lose the diurnal variation in blood pressure and consequently these patients develop nocturnal hypertension.

Home blood pressure measurement, an increasingly popular method, may be useful to estimate the blood pressure control also in dialysed patients (7).

Target blood pressure of hypertensive dialysed patients

For most patients on dialysis (mainly in older age), the goal blood pressure is less than an average value below 150/90 mmHg on no medication. The reasonable target goal of a mean ambulatory blood pressure is less than 135/85 mmHg during the day and is less than 120/80 mmHg by night (4). Very low systolic blood pressure (<110 mm Hg) may be associated with enhanced cardiovascular mortality ("J" or "U" shaped curve). An algorithm for blood pressure control is given in Table 2.

Table 2. **Algorithm for blood pressure control in dialysis patients** (modified from ref. 8)

1. Estimate dry weight
2. Determine Hypertension Severity Index
3. Initiate non-pharmacological treatment
4. Attain dry weight
5. Start or increase the dose of antihypertensives to maintain BP below 150/90 mmHg
6. If BP is not controlled or dry weight not attained in 30 days, consider:
   - 24-48 hours ABPM
   - increasing time of dialysis to facilitate removal of fluid and attainment of dry weight
   - discontinuing sodium modelling
   - increasing the dose or number of antihypertensives
7. If BP remains uncontrolled, consider:
   - evaluating for secondary forms of hypertension
   - peritoneal dialysis
   - bilateral nephrectomy (exceptional)

Non-pharmacological treatment of hypertension in dialysed patients (Table 3)

Control of plasma volume can either normalize the blood pressure or help normalize blood pressure in dialysed patients. Multiple clinical definitions of stable "dry weight" have been advanced:

- either the blood pressure has normalized or symptoms of hypervolemia disappear (not merely the absence of edema);
- after dialysis seated blood pressure is optimal, and symptomatic orthostatic hypotension and clinical signs of fluid overload are not present;
- at the end of dialysis patients remains normotensive until the next dialysis without antihypertensive medication.

Some factors may limit fluid removal by predisposing to episodes of hypotension during hemodialysis treatment, as hypotension is one of the important cardiovascular risk factors. Limiting control of volume overload in dialysis patients has been denoted as lag phenomenon.

To avoid large inter-dialytic weight gains, patients should restrict salt intake (750 to 1000 mg of sodium/day). This also decreases thirst (an important factor of patient compliance). A fixed low dialysate sodium concentration with combination of dietary salt restriction, or a programmed decrease in sodium dialysate concentration (from 155 to 135 meq/L) may result in smaller doses of antihypertensive drugs to control blood pressure.

The long, slow hemodialysis treatment (eight hours, and three times a week) is associated with the maintenance of normotension without medications in almost all patients, as this decreases afferent renal nerve activity and efferent sympathetic activation. Nocturnal hemodialysis treatment (six or seven nights a week during sleep hours) can also normalize blood pressure without medications in most of the patients.

More frequent hemodialysis treatment (two hours six times

per week) may also be associated with normotension without medications and with regression of left ventricular hypertrophy.

Bilateral nephrectomy may be considered in the rare non-compliant individuals with life-threatening hypertension, whose blood pressure cannot be controlled with any of the above detailed dialysis modality.

The clinician must define the dry weight and goal blood pressure for each dialyzed patients based upon his or her best judgment.

Table 3. **Non-pharmacological treatment of hypertension in dialysis patients**

Aerobic exercise
Control of salt and fluid intake
Cessation of smoking
Weight reduction
Avoidance of alcohol
Long, slow and more frequent hemodialysis treatment

Pharmacological treatment of hypertension in dialyzed patients

Antihypertensive drug therapy is necessary in 25-30 % of patients. The type of drug or antihypertensive combination depends on severity of hypertension (Table 4) and co-morbidities.

Table 4. **Hypertension Severity Index (HSI)**

HSI score	Systolic BP (mmHg)	Diastolic BP (mmHg)
0	< 150	< 90
1	150-159	90-99
2	160-179	100-109
3	> 179	> 109

To calculate for an individual dialysis treatment sum the pre-dialysis systolic and diastolicand post-dialysis systolic and diastolic blood pressure scores. The HSI can range from 0 to 12.

Table 5 shows the compelling indications of antihypertensive drugs, and their specific side effects and special important precautions.

Table 5. **Use of antihypertensive drugs in hemodialysis patients**

Drugs	***Compelling indication***	***Specific side-effects***	***Special precautions***
ACE inhibitors	"Left ventricular hypertrophy Heart failure Diabetes mellitus "	Anaphylactoid reactions with AN69 dialyzator	
Dihydropyridin calcium channel blockers	Associated coronary heart disease		
Non-dihydropyridin calcium channel blockers	Associated coronary heart disease		Avoid combination with beta-blockers
Beta-blockers	Associated coronary heart disease	Excessive bradycardia with liposoluble compounds	Avoid combination with non-dihydropyridin calcium channel blockers
Centrally acting anti-adrenergic drugs	None	Post hemodialysis hypertensive rebound with methyldopa	Avoid
Alpha-adrenergic receptor blockers	"Hyperlipidemia, Insulin resistance"		Beware severe hypotension
Direct vasodilators	Hypertensive crisis		Use only in well-equipped hospital setting

Antihypertensive drugs

Calcium channel blockers are very effective and well tolerated in dialysis patients, even in those who are volume expanded. They are useful in patients with left ventricular hypertrophy, diastolic dysfunction and stabile angina pectoris. Calcium channel blockers do not require supplementary post dialysis dosing. Calcium channel blockers have a unique feature among dialysis patients since a prospective cohort study from USRDS showed a significant 26 % reduction in cardiovascular mortality.

Angiotensin converting enzyme (ACE) inhibitors are effective and well tolerated in dialysis patients. They are useful in patients with left ventricular hypertrophy, and in those with heart failure due to systolic dysfunction. ACE inhibitors reduce mortality in hypertensive patients undergoing maintenance dialysis. Significantly lower mortality was observed among the ACE inhibitor-treated dialysis patients (<65 years of age). This survival benefit was independent from antihypertensive effect. These drugs can reduce the synthesis/secretion of erythropoietin, and trigger an anaphylactoid reaction in patients dialyzed with AN69 dialyzer.

Angiotensin II receptor blockers (ARBs) There is only limited experience with these drugs in end-stage renal disease. Losartan does not enhance the risk of anaphylactoid dialyzator-reactions with the ACE inhibitors. No dose adjustment is necessary in renal failure in the absence of volume depletion.

Beta-blockers are indicated in dialysis patients after myocardial infarction. Potential side effects include central nervous system depression (mainly lipid-soluble drugs), bradycardia, and heart failure. Preferable beta-blocker may be labetalol or carvedilol, which has a lower incidence of bronchospasm and has neutral effect on plasma lipid levels. Atenolol administered three times a week post-dialysis, may be effective.

Peripheral alpha-1 adrenergic receptor blocker (prazosin, doxazosin) would help to counteract the increase in sympathetic nerve activity. On long-term treatment the favourably metabolic effects (on lipids and insulin resistance) might be advantageous. These drugs are preferred in antihypertensive combinations.

Centrally acting drugs (methyldopa, clonidine, guanfacine) have more side effects that those described above. Newer imidazoline receptor agonists (moxonidine, rilmenidine) are felt to be safe and effective, but only limited experience is available.

Pharmacokinetics of frequently used antihypertensive drugs in dialysis patients is given in the Appendix.

Special situations

Treatment of refractory hypertension in hypertensive dialysis patients: Use of minoxidil – the strongest direct vasodilator - may be effective in reducing blood pressure. Dialysed patients who are noncompliant and in whom volume status and hypertension cannot be adequately controlled may benefit from switching to continuous ambulant peritoneal dialysis (CAPD).

Treatment of erythropoietin-induced hypertension (9):
- Try to decrease the actual dry weight
- decrease the dose (if possible) or interrupt treatment, and reintroduce later at lower dosage
- introduce or increase antihypertensive medication with preference of calcium channel blockers

Treatment of hypertension in the diabetic dialysis patients: The number of dialysis patients with type-2 diabetes mellitus is rapidly increasing, and these patients are generally hypertensive. Exchangeable sodium is increased in diabetic patients, and orthostatic hypotension due to autonomic neuropathy, and dialysis hypotension with severe symptoms, coronary artery disease, and vascular atherosclerosis are frequent. Longer dialysis, slow ultrafiltration rate, hemofiltration and glucose-containing dialysate can be used to avoid the risk of severe hypotension. ACE inhibitors and ARBs decrease blood pressure, may prevent end-organ vascular diseases. Calcium channel blockers are effective in reducing blood pressure but may result in severe hypotensive episodes. Benefit from beta blockade is particularly significant in patients with type-2 diabetes mellitus and coronary heart disease.

Conclusions

The progress of dialysis technology leads to better tolerated dialysis treatment and more adequate removal of sodium-water overload. Treatment of hypertension in dialysis patients still remains a careful clinical judgment: adequate evaluation of the dry weight, choice of adequate treatment time and frequency. In those patients in whom ultra-filtration and maintenance of dry weight do not adequately control hypertension, antihypertensive medications are indicated (10-16).

Appendix. **Features of frequently used antihypertensive drugs in hemodialysis patients**

	"Elimination, Metabolism"	*Dosing*	*"Supplement required with dialysis"*	*Miscellaneous*
Diuretics				
Thiazides/chlorthalidone	R	AVOID		
K+ sparing	R	AVOID		
Acetazolamide	R	AVOID		
Loop agents				
Furosemide	R (H)	Useful in high doses	NO	Ototoxicity and augment aminoglycoside toxicity
Bumetadine	R (H)	Useful in high doses		
Etacrynic acid	R (H)	AVOID		
Beta-blockers				
Acebutolol	H (R)	25-50%	NO	Active metabolites accumulation
Atenolol	R	25-50%	YES	Removed by dialysis
Bisoprolol		25 %	YES	
Betaxolol		50 %	YES	
Carvedilol		Unchanged	NO	
Labetalol	H	Unchanged	NO	
Metoprolol	H	Unchanged	NO	
Nadolol	R	50 %	YES	Removed by dialysis
Pindolol	H (R)	Unchanged	NO	
Propranolol	H	Unchanged	NO	Active metabolites accumulation interfere with bilirubin dosage
Sotalol	R	30 %	YES	Class 3 antiarrhythmic properties
Tertatolol	R	Unchanged	NO	Active metabolites accumulation
Timolol	H	Unchanged	NO	Inactive metabolites accumulation
Centrally acting				
Methyldopa	R (H)	Interval extension of dose adjustment	YES	Active metabolites accumulation risk of prolonged hypotension
Clonidine	R	50 %	NO	Risk of rebound hypertension
Guanfacine		Unchanged	NO	
Moxonidine, rilmenidine		?	?	Beneficial effects on insulin resistance
Alpha-1-adrenergic blockers				
Prazosin	H(R)	Unchanged	NO	First dose effect
Doxazosin		Unchanged	NO	Beneficial effects on insulin resistance and on plasma lipids
Urapidil	H(R)	Unchanged	NO	Inactive metabolites may accumulate