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Antihypertensive Agents in Hemodialysis Patients: A Current Perspective

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Abstract

Hypertension affects most hemodialysis patients and is often poorly controlled. Adequate control of blood pressure is difficult with conventional hemodialysis alone but is important to improve cardiovascular outcomes. Nonpharmacologic interventions to improve blood pressure include educating patients about limiting sodium intake, ensuring adequate sodium solute removal during hemodialysis, and achieving target “dry weight.” However, most patients require a number of antihypertensive medications to achieve an appropriate blood pressure. First-line antihypertensive agents include angiotensin converting enzyme inhibitors and angiotensin receptor blockers given their safety profile and demonstrated benefit on cardiovascular outcomes in clinical trials. β -blockers and combined α - and β -blockers should also be used in patients with cardiovascular disease or congestive heart failure and may improve outcomes in these populations. Calcium channel blockers and direct vasodilators are also effective for controlling blood pressure. Many blood pressure agents can be dosed once daily and should preferentially be administered at night to control nocturnal blood pressure and minimize intradialytic hypotension. In patients who are noncompliant with therapy, renally eliminated agents (such as lisinopril and atenolol) can be given thrice weekly following hemodialysis. Older antihypertensive agents which require thrice daily dosing ought to be avoided given the high pill burden with these regimens and the concern for noncompliance resulting in rebound hypertension. Newer antihypertensive agents, such as direct renin inhibitors, may provide alternative options to improve blood pressure but require testing for efficacy and safety in hemodialysis patients.

Hypertension affects up to 90% of maintenance hemodialysis patients and is a risk factor for adverse cardiovascular outcomes, including the development of left ventricular hypertrophy, left ventricular dilation, heart failure, and death (1–5). Further, recent studies demonstrate control of blood pressure in hemodialysis patients contributes to regression of left ventricular hypertrophy and improved cardiovascular morbidity and mortality (6–8). In a meta-analysis of randomized controlled trials of antihypertensive therapy in hemodialysis patients, blood pressure lowering treatment was associated with a 29% lower relative risk of cardiovascular events, a 29% lower relative risk of cardiovascular mortality and a 20% lower relative risk of all-cause mortality (8).

While blood pressure control may improve cardiovascular outcomes in hemodialysis patients, the management of blood pressure in this population is challenging. Considering extracellular fluid volume is a key determinant of blood pressure in hemodialysis patients (9), nonpharmacologic interventions such as minimizing sodium intake, ensuring adequate sodium solute removal during HD, and achievement of “dry weight” should be the initial

treatments for blood pressure control (10). Despite these interventions, pharmacologic therapy is usually required to control blood pressure in hemodialysis patients. Most classes of agents are appropriate for use in hemodialysis patients and a combination of agents is typically required to control blood pressure. Thus, this article will review the choice of antihypertensive agents in hemodialysis patients, the effectiveness and safety of select antihypertensive agents, the available clinical trials investigating outcomes with antihypertensive agent class, and newer antihypertensive agents on the horizon for use in hemodialysis patients.

Antihypertensive Agents

Renin Angiotensin Aldosterone System Inhibitors

Inhibitors of the renin angiotensin aldosterone system (RAAS) ought to be considered as first line agents for blood pressure control in hemodialysis patients because of their documented safety, their tolerability, and their beneficial effect on left ventricular hypertrophy, arterial stiffness, endothelial cell function, and oxidative stress (11–14). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines also suggest RAAS inhibitors to be the preferred antihypertensive agents in hemodialysis patients, particularly those with diabetes mellitus or a history of heart failure (15).

Angiotensin Converting Enzyme Inhibitors—A number of clinical trials have demonstrated angiotensin converting enzyme inhibitors (ACE-I) are safe and effective in hemodialysis patients. In a small study of 11 hemodialysis patients, the observed administration of lisinopril thrice weekly following hemodialysis effectively lowered ambulatory systolic blood pressure by 22 mmHg (from 149 / 84 to 127 / 73 mmHg) and was not associated with an increase in intradialytic hypotension (16). Other trials which measured hemodialysis unit blood pressures demonstrated a 5–12 mmHg reduction in systolic blood pressure with ACE-I (11,17). Clinical trials have also shown ACE-I therapy to be relatively safe in hemodialysis with no significant effect on serum potassium and <3% incidence of symptomatic hypotension (17,18). Other studies suggest RAAS inhibitors are associated with an increased risk of hyperkalemia in hemodialysis cohorts, potentially due to inhibiting extrarenal potassium loss (19,20). Thus, considering the effects of RAAS inhibitors on potassium handling in HD patients is uncertain, monitoring of serum potassium following initiation of RAAS inhibitors is suggested. ACE-I are well-tolerated overall and one of the most common reasons for discontinuation is cough (21). Cough can occur in 5–20% of patients and typically resolves within 2–6 weeks of discontinuing therapy. ACE-I have also been associated with higher requirements for erythropoietin stimulating agents (ESA) and have been associated with an anaphylactoid reaction with AN69 dialyzers (22,23).

Retrospective analyses and small clinical trials suggest ACE-I may help preserve residual renal function and improve outcomes in hemodialysis patients. Moist et al., in a secondary analysis of 1842 incident dialysis patients followed in the USRDS Wave 2 Study, identified the use of an ACE-I at baseline to be associated with an ~30% lower relative risk of loss of residual renal function at 1-year (24). Efrati et al., in a retrospective analysis of 126 hemodialysis patients (60 prescribed ACE-I and 66 not prescribed ACE-I) identified the use of ACE-I to be associated with improved survival (25). Two retrospective analyses of hemodialysis patients with acute coronary syndromes suggest the use of ACE-I following MI to be associated with lower mortality (26,27). Another secondary analysis suggested the use of ACE-I may be associated with improved survival following cardiac arrest (28). Ichihara et al. demonstrated, in a 12-month randomized controlled trial of ACE-I vs. angiotensin receptor blocker (ARB) vs. placebo in 64 hemodialysis patients, that low dose

ACE-I (and ARB) improved pulse wave velocity (11). Another small randomized trial of daily ACE-I vs. placebo in 30 hemodialysis patients demonstrated regression of left ventricular hypertrophy with ACE-I (12).

The largest randomized controlled study testing the effect of ACE-I on cardiovascular outcomes in hemodialysis patients was the FOSIDIAL (Fosinopril in Dialysis) trial (Table 1). In this study, 397 patients on maintenance hemodialysis for ≥ 6 months and with left ventricular hypertrophy were randomized 1:1 to fosinopril 20 mg/day vs. placebo and followed for 2 years. The primary outcome was a combined endpoint of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, cardiovascular revascularization, hospitalization for heart failure, and resuscitated cardiac arrest. Of note, hypertension was not an entry criteria for the study but the administration of fosinopril in hypertensive patients lowered systolic blood pressure ~ 6 mmHg greater than placebo (with an absolute change in systolic BP of 11.7 mmHg). While there was no significant difference in the primary endpoint between fosinopril and placebo, there was a nonsignificant 10–20% reduction in the primary endpoint with fosinopril (17).

While ACE-I are a good first-line antihypertensive agent, most ACE-I (with the exception of fosinopril) are removed with hemodialysis (Table 2). Hemodialysis removal of ACE-I is not problematic in most hypertensive patient and may help avoid intradialytic hypotension. However, in patients who experience intradialytic hypertension, dialyzable ACE-I ought to be changed to either an ARB or a nondialyzable ACE-I (i.e., fosinopril) (29,30). Dosing of most ACE-I should be daily; however, as a result of its longer half life because of its predominant renal excretion, lisinopril has demonstrated good blood pressure control with thrice weekly administration following hemodialysis (16). For noncompliant patients, directly observed lisinopril administration immediately following hemodialysis may be a good therapeutic option.

Nocturnal dosing of once daily antihypertensive medications is preferred to try to minimize the nocturnal surge of blood pressure observed in many dialysis patients and to minimize the occurrence of intradialytic hypotension (2,15).

Angiotensin Receptor Blockers—Clinical trials have also demonstrated ARB to be safe and well-tolerated in hemodialysis patients. In two small trials, the use of an ARB (vs. placebo or usual care) was not associated with hyperkalemia or with higher ESA requirements (13,14). The effects of ARB on blood pressure seem to vary in different studies and this is likely because of differences in how blood pressure was measured (whether via dialysis unit blood pressure or the gold standard of ambulatory blood pressure). In a study by Takahashi et al., the use of candesartan (4–8 mg/day) had no effect on dialysis unit blood pressure during 3 years of follow-up (blood pressure at baseline was 153 / 82 and was 153 / 83 mmHg during follow-up); however, home blood pressure recordings were not obtained (13). In a trial by Suzuki et al., patients prescribed an ARB exhibited a ~ 14 -mmHg decrease in systolic blood pressure during 3 years of follow-up (from 154 / 81 to 140 / 80 mmHg) which was similar to the placebo arm (14). In a separate small study of valsartan or candesartan in 11 hemodialysis patients, systolic blood pressure was significantly lowered ~ 30 mmHg with the use of either ARB at 8 months (31). Thus, ARB are relatively effective at lowering blood pressure and are well-tolerated.

Small trials with surrogate endpoints have suggested ARB may improve cardiovascular outcomes by improving pulse wave velocity and reducing left ventricular hypertrophy (Table 1). Two larger studies also suggest ARB may improve hard endpoints such as cardiovascular events. In a study by Takahashi et al., 80 maintenance hemodialysis patients were randomized to candesartan 4–8 mg vs. usual care and followed for 3 years for the

combined primary endpoint of fatal or nonfatal myocardial infarction, unstable angina, hospitalized heart failure, ventricular tachycardia or fibrillation, or sudden death. The study was stopped early by the data safety monitoring board and the final analysis demonstrated candesartan therapy significantly reduced cardiovascular events and mortality rates in this trial (13). In a study by Suzuki et al., 366 hypertensive hemodialysis patients were randomized in an open label fashion to either valsartan, candesartan, or losartan once daily vs. placebo and followed for 36 months until the primary endpoint of fatal and nonfatal cardiovascular events [defined as the composite of cardiovascular disease (CVD) death, myocardial infarction, stroke, congestive heart failure, coronary artery bypass grafting, or percutaneous coronary intervention]. In this study, the use of an ARB reduced nonfatal CVD events in patients undergoing long-term hemodialysis but there was no difference in all-cause mortality (14).

Of importance to note, none of the ARB are removed by hemodialysis (Table 2). Further, the simplicity of dosing of ARB (being once daily) make them an attractive option for blood pressure control when cost is not a significant consideration.

Combination Therapy of ACE-I and ARB—In support of the use of more than one inhibitor of RAAS, one small study of 33 incident hemodialysis patients suggested a benefit from combining an ACE-I and ARB. This preliminary study randomized incident diabetic hemodialysis patients to an ACE-I vs. ARB vs. combination of ACE-I / ARB and achieved good blood pressure control (to <140 mmHg systolic) in all groups and regression of left ventricular mass index (LVMI) at 1-year in all arms. However, the patients treated with a combination of an ACE-I / ARB exhibited an additional 28% reduction in LVMI when compared with those treated with RAAS inhibitor monotherapy (32). While this small study suggests potential benefit with combination therapy, trials in non ESRD populations at high cardiovascular risk have failed to demonstrate improved cardiovascular outcomes with a combination of RAAS inhibitors (33). Thus, while adding an ARB to an ACE-I may improve blood pressure control and may further reduce LVH beyond monotherapy, larger studies are required to determine whether this therapeutic combination can improve CV outcomes in hemodialysis patients.

Aldosterone Antagonists—While aldosterone antagonists are an attractive option for improving cardiovascular outcomes, particularly in patients with heart failure (34), the use of aldosterone antagonists in hemodialysis patients has not been fully investigated to date. Further, the clinical use of these agents may be limited because of concern about the risk of hyperkalemia. As most dialysis patients are anuric, hyperkalemia resulting from aldosterone blockade could occur because of its effects on extrarenal potassium handling (such as inhibiting the intestinal elimination of potassium).

In two small open label studies of low dose spironolactone, there was no significant increase in serum potassium in 14 patients with 6 weeks of thrice weekly spironolactone (25 mg) but 1 / 15 patients with daily spironolactone (25 mg) were withdrawn from the drug because of hyperkalemia (potassium of 7.6 mEq/l after 20 days of therapy) (35,36). In one small prospective randomized double-blinded placebo-controlled cross-over study of eight hemodialysis patients, the administration of 50 mg of spironolactone twice daily in oligoanuric hemodialysis patients was effective at decreasing predialysis systolic blood pressure by 11 mmHg and had no significant effect on pre or post dialysis plasma potassium at 2 weeks (37). In a larger open label study of low dose spironolactone (25 mg/day) administered to 61 oligoanuric hemodialysis patients for 8 months, 11 patients discontinued use because of side effects (other than hyperkalemia) and potassium levels increased overall (4.6 to 5.0 mEq/l) with treatment; however no patients had a potassium > 6.8 mEq/l or required ion exchange resin therapy (38). While these studies suggest in controlled observed

settings, aldosterone antagonists maybe relatively safe, further research demonstrating their efficacy and safety are required prior to their use in hemodialysis patients.

Renin Inhibitors—Aliskiren is in a new class of antihypertensive drugs and inhibits the conversion of angiotensinogen to angiotensin I (and therefore decreases the formation of angiotensin II) by directly inhibiting renin. Thus, renin inhibitors block the deleterious effects of angiotensin II without increasing renin levels. This drug has shown promise for improving renal outcomes in patients with chronic kidney disease and diabetes (39). The clearance of aliskiren is via hepatic metabolism with renal elimination. This drug has not been tested in hemodialysis populations and its removal with hemodialysis is unknown. Therefore, the role of this new agent in hemodialysis patients is yet to be determined as studies evaluating its efficacy and safety have not been performed to date.

β-Adrenergic Blockers

β-blockers continue to be important agents for blood pressure control in hemodialysis patients and should to be the preferred antihypertensive agent in patients with recent acute coronary syndrome (15). In addition, β-blockers ought to be considered, in conjunction with RAAS inhibitors, as preferred agents in patients with heart failure. In a small study of eight hypertensive hemodialysis patients, atenolol following hemodialysis (directly observed therapy 3×/week) lowered ambulatory systolic blood pressure ~17 mmHg (from 144 / 80 to 127 / 69 mmHg) and did not significantly increase the incidence of intradialytic hypotension or hyperkalemia (40). Notable adverse effects associated with β-blockers include bradycardia, erectile dysfunction, fatigue, and lipid and glucose abnormalities. In hemodialysis patients, nonselective β-adrenergic blockers (such as propranolol and nadolol) may increase the risk of exercise-induced or fasting induced hyperkalemia, however this does not occur with selective β-adrenergic blockers (such as metoprolol) (41,42). Overall, β-blockers are effective and fairly well-tolerated in hemodialysis populations.

Observational studies suggest the use of β-blockers may improve CV outcomes in hemodialysis patients. In a secondary analysis of 2,550 incident hemodialysis patients, the use of β-blockers in patients without a history of heart failure was associated with a lower risk of de novo heart failure, cardiac death, and all-cause mortality. However, in this cohort only 20% of patients were administered this drug (43). Foley et al. in a secondary analysis of 11,142 prevalent hemodialysis patient in United States Renal Database Systems Wave 3 and 4 Study identified only 8.5% of the population were prescribed β-blockers but their use was associated with a 16% lower adjusted hazard of death (44). Further, two secondary analysis suggest the use of β-blockers are associated with improved survival following cardiac arrest and acute myocardial infarction (26,28).

Water-soluble β-blockers such as atenolol and metoprolol are dialyzable and require supplementation to avoid exacerbation of arrhythmias following dialysis (Table 2). Metoprolol is mainly metabolized by the liver and therefore does not require dose adjustment while atenolol is excreted mainly by the kidneys and thus its half-life is prolonged in hemodialysis patients. However, patients who are noncompliant with medications can be given atenolol (directly observed therapy) following hemodialysis to effectively control interdialytic blood pressure (40).

While atenolol may be effective in noncompliant patients, other selective β-1 adrenergic blockers such as metoprolol and combination α- and β-blockers such as carvedilol should be generally favored because of studies demonstrating cardiovascular protection with these agents, particularly in patients with heart failure (45–47).

Combined α - and β -Blockers

Combined α - and β -blockers are becoming increasingly popular for use in hemodialysis patients because of their effectiveness, reduced cost, and demonstrated benefit in patients with dilated cardiomyopathy. In one small trial of patients randomized to carvedilol vs. placebo, carvedilol lowered systolic blood pressure ~11 mmHg (from 134 / 75 to 123 / 67 mmHg at 12 months). One caveat was that there was a fairly high rate of drop-out because of drug intolerance (20% with carvedilol vs. 13% with placebo) which included hypotension, bronchospasm, and bradycardia. In addition, both carvedilol and labetalol are nonselective inhibitors of β -adrenergic receptors and, theoretically, may increase the risk of predialysis, fasting hyperkalemia, as has been demonstrated with propranolol and nadolol. However, a small cross-over study of carvedilol vs. placebo in 17 anuric hemodialysis patients found that carvedilol had no effect on exercise induced hyperkalemia, providing some reassurance (48). Therefore, combined α - and β -blockers are an effective therapeutic option to control blood pressure in hemodialysis patients although a potential effect on serum potassium must be kept in mind.

In one small trial in hemodialysis patients with heart failure, carvedilol was demonstrated to improve cardiovascular outcomes. In this study, 132 hemodialysis patients with New York Heart Association class II or III were randomized to carvedilol vs. placebo and followed for 12 months with a primary outcome of change in left ventricular (LV) volume (Table 1). At 12 months, carvedilol reduced LV volume and resulted in improved LV function and clinical status when compared with placebo (49). On additional follow-up of patients following completion of the study, patients assigned to carvedilol exhibited reduced all-cause mortality as well as fatal and nonfatal cardiovascular events (46).

Combined α - and β -blockers (labetalol, carvedilol) are not significantly cleared by hemodialysis and thus provide the added benefit of not requiring additional dosing following hemodialysis. Dosing of combined α - and β -blockers are typically twice a day, however newer once a day formulations are now available (i.e., Coreg CR) and should preferentially be used in patients who are noncompliant with more frequent dosing.

Calcium Channel Blockers

Calcium channel blockers (CCB) can effectively lower blood pressure in hemodialysis patients and are often effective in patients with volume overload (50). A recent randomized controlled trial found amlodipine (a dihydropyridine CCB) lowered systolic blood pressure ~10 mmHg without an increased risk of intradialytic hypotension when compared with placebo (7% vs. 13%, respectively) (52). Dihydropyridine CCB (examples include amlodipine, felodipine, and nifedipine) are highly selective inhibitors of vascular smooth muscle calcium channels and are thus effective at reducing systemic vascular resistance. The nondihydropyridine CCB (diltiazem and verapamil) are more myocardial selective and their combined use with β -blockers requires caution because of augmented suppression of cardiac contractility and increasing the risk of bradycardia and electrical conduction defects.

Two retrospective analyses suggest CCB are associated with a lower risk of mortality in hemodialysis patients (52,53). However, one small clinical trial comparing a CCB (nitrendipine) to ACE-I (perindopril) failed to demonstrate a reduction in LVH with the use of a CCB despite effectively lowering blood pressure to similar levels (Table 1) (54). Tepel et al. recently published results from a randomized controlled trial comparing amlodipine to placebo in 251 hypertensive hemodialysis patients. The primary endpoint was all-cause mortality with a secondary combined endpoint of all-cause mortality or cardiovascular events. While there was no difference in all-cause mortality at 30 months between arms,

amlodipine significantly reduced the post hoc secondary combined endpoint of all-cause mortality and cardiovascular events (51).

Calcium channel blockers are not removed by hemodialysis and thus do not require additional postdialysis dosing (Table 2). In addition, once daily dosing of most CCB make them attractive for use in hemodialysis patients.

α -Adrenergic Blocking Agents

α -Adrenergic blocking agents, such as doxazosin, prazosin, and terazosin, are used less frequently for blood pressure control following the results of the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) (55). In high-risk hypertensive patients randomized to doxazosin vs. diuretic in ALLHAT, there was a higher rate of CV events in patients randomized to doxazosin. However, in hemodialysis patients requiring multiple antihypertensive agents to control blood pressure, these agents can be safely used and do not require additional dosing with hemodialysis. For longer acting formulations, nocturnal dosing is preferred to try to minimize the occurrence of postural hypotension. These agents should be avoided in patients with intradialytic hypotension and should not be used in combination with midodrine because of its counteracting effects on alpha adrenergic stimulation.

Centrally Acting Sympathetic Agonists

The central nervous system sympathetic agonists, such as methyl dopa, guanabenz, guanfacine, and clonidine, are used less frequently for blood pressure control because of their higher rates of adverse side effects. These adverse effects include dry mouth, erectile dysfunction, fatigue, and rebound hypertension. Clonidine is the main sympathetic agonist still in use in hemodialysis populations, particularly in those with difficult to control hypertension and those with significant hypertension during hemodialysis. Some nephrologists have found clonidine patches to be effective and well tolerated while avoiding the frequent dosing requirements of oral formulations (56). While clonidine patches are preferred by some patients, they are not universally effective and some patients find them difficult to keep in place during strenuous activity and with showering.

Direct Vasodilators

Hydralazine and isosorbide dinitrate are potent vasodilators and are effective at lowering blood pressure in patients with resistant or refractory hypertension. Hydralazine plus nitrates in addition to standard therapy (including an ACE-I and β -blocker) have been demonstrated to improve outcomes in African Americans with heart failure (57). However, this drug combination has not been tested in hemodialysis patients. While this drug combination maybe effective, the major limitation is compliance because of thrice daily dosing and a pill burden of at least six pills. Thus, in hemodialysis patients already prescribed other antihypertensive agents and phosphorus binders, this drug regimen is a less practical option. Hydralazine is not removed by hemodialysis, but isosorbide dinitrate is removed by hemodialysis and requires extra dosing around dialysis (Table 2). Because of reflex stimulation of the sympathetic nervous system with vasodilators, these drugs should be administered simultaneously with a β -blocker to offset tachycardia. The major side effects of hydralazine are fluid retention (managed by dialysis) and less commonly a drug-induced lupus-like syndrome including arthralgias, myalgias, joint swelling, pericarditis / pleuritis, rash, or fever.

Minoxidil is a more potent vasodilator than hydralazine and can be reserved for patients who remain hypertensive despite other drug therapies. The benefit to minoxidil over hydralazine / nitrates is the ease of dosing which is once or twice a day (Table 2). While minoxidil is quite

effective and is not extensively removed by hemodialysis, significant fluid retention including pleural and pericardial effusions can occur during therapy and may require discontinuation if not controlled with hemodialysis.

Diuretics

Diuretics are used infrequently in hemodialysis patients. One study identified up to 32% of hemodialysis patients to be prescribed a diuretic during the first 30 days of hemodialysis initiation which declined to ~10% at 2 years (58). In a secondary analysis of 16,420 hemodialysis patients from Dialysis Outcomes and Practice Patterns Study, diuretic use was associated with lower interdialytic weight gain and a lower relative risk of cardiac death which may have been because of confounding by indication with higher residual renal function in patients prescribed diuretics. However, this study supports the clinical experience that in select patients, such as those with residual renal function and urine output, diuretics can be helpful at controlling interdialytic weight gain and blood pressure and should not necessarily be stopped upon initiation of hemodialysis.

Endothelin-1 Antagonists

Increasing evidence suggests endothelin, a potent vasoconstrictor, may play a role in the pathogenesis of hypertension (59). Endothelin (ET) exerts its vasoconstrictor effect by binding to and activating the ETA receptor in vascular smooth muscle cells resulting in vasoconstriction (60). This vasoconstrictor effect is counterbalanced by binding of endothelin to the ETB receptor on endothelial cells which results in nitric oxide mediated vasodilation (61).

In recent years, several antagonists to endothelin receptors have been discovered and tested in clinical trials of essential hypertension. In a trial comparing the effectiveness of bosentan, a nonselective ETA/ETB receptor antagonist, to an ACE-I and placebo in patients with essential hypertension, bosentan was as effective as an ACE-I in lowering blood pressure (62). Selective ETA antagonist darusentan has been demonstrated to be effective at lowering blood pressure in two phase II clinical trials in patients with essential hypertension and resistant hypertension (63,64).

While ET receptor antagonists are generally well-tolerated in clinical trials, the major adverse effects are peripheral edema, a mild decrease in hemoglobin (thought to be related to hemodilution secondary to increased extracellular fluid), headache, and flushing. As these drugs are primarily metabolized and eliminated by the liver, one significant adverse effect is hepatic dysfunction, which is dose-dependent and reversible upon discontinuation of the drug.

The role of endothelin antagonists in controlling blood pressure in hemodialysis patients is yet to be determined as these drugs have not been tested in this patient population. One potential role for ET receptor antagonists are in ESA-induced hypertension. Selective ETA receptor antagonist darusentan (LU 135252), but not ETA/ETB receptor antagonist bosentan, prevented the aggravation of hypertension in renal failure rats treated with ESA (65).

Summary

Hypertension is common in hemodialysis patients and can often be difficult to control. Considering the high cardiovascular burden in hemodialysis patients, control of blood pressure is important to improve outcomes (8). First-line interventions for blood pressure control should focus on sodium restriction, adequate sodium removal during hemodialysis, and attaining an adequate “dry weight.” Despite these interventions, adequate blood pressure

control with thrice weekly hemodialysis typically requires the addition of pharmacologic agents. First-line pharmacologic agents for blood pressure control in hemodialysis patients should be RAAS inhibitors (either ACE-I or ARB) because of their documented benefit on left ventricular hypertrophy, pulse wave velocity, and potentially cardiovascular events. Second line agents include the addition of beta-blockers (particularly in patients with coronary artery disease), combined α - and β -blockers in patients with heart failure, CCBs, and alternative agents such as direct vasodilators. Most hemodialysis patients require a combination of antihypertensive agents to achieve adequate blood pressure control. Considering the high pill burden and high rates of noncompliance among hemodialysis patients, once daily (or thrice weekly) formulations should be used preferentially. Nocturnal dosing of once daily antihypertensive medications is favored to control the nocturnal increase in blood pressure observed in many hemodialysis patients and to minimize the risk of intradialytic hypotension. Newer antihypertensive agents, such as direct renin inhibitors, provide alternative choices for blood pressure control but need to be tested in hemodialysis patients to determine their safety and efficacy before being widely adopted.

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TABLE 1

Randomized trials of antihypertensive agents in hemodialysis patients

Reference	Patients	Intervention	Follow-up (months)	Results
<i>ACE-I trials</i>				
Zannad et al. (17)	397 HD patients with LVH	Fosinopril vs. placebo	24	No effect of fosinopril on CV event rate
<i>Combination trials (ACE-I and ARB and CCB)</i>				
Ichihara et al. (11)	64 HD patients	Losartan, trandolapril, or placebo	12	Reduction in PWV with losartan and trandolapril
Shibasaki et al. (66)	30 HD patients with hypertension	Losartan, enalapril, or amlodipine	6	Regression of LVH with losartan
London et al. (54)	24 HD patients with uncontrolled hypertension	Perindopril vs. nitredipine	12	Regression of LVH with perindopril
<i>ARB trials</i>				
Kanno et al. (67)	24 HD patients with diabetes and LVH	Losartan or placebo	12	Regression of LVH with losartan
Takahashi et al. (13)	80 HD patients	Candesartan vs. control	19	Reduction in CV event rate with candesartan
Suzuki et al. (14)	366 HD patients with hypertension	Either losartan, candesartan, or valsartan vs. placebo	36	Reduction in CV events with ARB
<i>Combined α- and β-blocker trials</i>				
Cice et al. (46,49)	132 HD patients with dilated cardiomyopathy	Carvedilol vs. placebo	12–24	Regression in cardiomyopathy and improved survival with carvedilol
<i>Calcium channel blocker trials</i>				
Tepel et al. (51)	251 HD patients with hypertension	Amlodipine vs. placebo	30	No effect on AC mortality but lower CV events with amlodipine

AC, all cause; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; HD, hemodialysis; LVH, left ventricular hypertrophy; PWV, pulse wave velocity.

TABLE 2

Pharmacokinetics of select antihypertensive agents in hemodialysis (15,68,69)

Class	T ^{1/2} in ESRD	Range of dosing (initial to usual or maximum)	%Removal with hemodialysis
<i>Angiotensin converting enzyme inhibitors</i>			
Captopril	20–30 hours	12.5–50 mg q24 hours	Yes
Benazepril	?	5–40 mg q24 hours	20–50%
Enalapril	Prolonged	2.5–10 mg q24 to 48 hours	35%
Fosinopril	Prolonged	10–80 mg q24 hours	<10%
Lisinopril	54 hours	2.5–10 mg q24–48 hours	50%
Ramipril	prolonged	2.5–10 mg q24 hours	<30%
<i>Angiotensin receptor blockers</i>			
Losartan	4 hours	50–100 mg q24	None
Candesartan	5–9 hours	4–32 mg q24	None
Eprosartan	?	400–600 mg q24	None
Telmisartan	24 hours	40–80 mg q24	None
Valsartan	6 hours	80–160 mg q24	None
Irbesartan	11–15 hours	75–300 mg q24	None
<i>Aldosterone antagonists</i>			
Spironolactone ^a	?	25–50 mg qd	None
Eplerenone ^b	?	50–100 mg qd	None
<i>Renin inhibitor</i>			
Aliskiren	?	150–300 mg qd	?
<i>β-Blockers and combined α- and β-blockers</i>			
Atenolol	<120 hours	25–50 mg q48	75%
Metoprolol	3–8 hours	50–200 mg bid	High
Metoprolol XL	?	50–400 mg qd	High
Propranolol	3–6 hours	40–120 mg bid	<5%
Carvedilol	7–10 hours	6.25–25 mg bid	None
Carvedilol CR	?	20–80 mg qd	None
Labetalol	6–8 hours	100–1200 mg bid	<1%
<i>Calcium channel blockers</i>			
Amlodipine	?	2.5–10 mg qd	None
Diltiazem	Prolonged	Varies with formulation	<30%
Nifedipine	~5 hours	30–180 mg qd ^c	Low
Nicardipine	Prolonged	30–60 mg bid ^c	?
Felodipine	11–16	2.5–10 mg qd ^c	No
Verapamil	Prolonged	Varies with formulation	Low
<i>Alpha-adrenergic blockers</i>			
Doxazosin ^c	15–22 hours	1–8 mg qhs	None
Terazosin	9–12 hours	1–20 mg qhs	None
Prazosin	2–4 hours	1–5 mg bid to tid	?

Class	T ^{1/2} in ESRD	Range of dosing (initial to usual or maximum)	%Removal with hemodialysis
<i>Other</i>			
Clonidine	18–41 hours	0.1–0.4 mg bid-tid	<5%
Hydralazine	7–16 hours	10–100 mg q8 hour	None
Isosorbide dinitrate	?	5–40 mg tid	Yes
Minoxidil	?	5–100 mg qd	Partially

Qd, every day; bid, twice a day; tid, three times a day; qhs, at bedtime.

^aNot recommended with crcl < 30 ml/min and contraindicated in anuric patients.

^bContraindicated with crcl < 30 ml/min.

^cExtended release formulations.