

Pharmacotherapy of Hypertension in Chronic Dialysis Patients

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Abstract

Among patients on dialysis, hypertension is highly prevalent and contributes to the high burden of cardiovascular morbidity and mortality. Strict volume control *via* sodium restriction and probing of dry weight are first-line approaches for the treatment of hypertension in this population; however, antihypertensive drug therapy is often needed to control BP. Few trials compare head-to-head the superiority of one antihypertensive drug class over another with respect to improving BP control or altering cardiovascular outcomes; accordingly, selection of the appropriate antihypertensive regimen should be individualized. To individualize therapy, consideration should be given to intra- and interdialytic pharmacokinetics, effect on cardiovascular reflexes, ability to treat comorbid illnesses, and adverse effect profile. β -Blockers followed by dihydropyridine calcium-channel blockers are our first- and second-line choices for antihypertensive drug use. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers seem to be reasonable third-line choices, because the evidence base to support their use in patients on dialysis is sparse. Add-on therapy with mineralocorticoid receptor antagonists in specific subgroups of patients on dialysis (*i.e.*, those with severe congestive heart failure) seems to be another promising option in anticipation of the ongoing trials evaluating their efficacy and safety. Adequately powered, multicenter, randomized trials evaluating hard cardiovascular end points are urgently warranted to elucidate the comparative effectiveness of antihypertensive drug classes in patients on dialysis. In this review, we provide an overview of the randomized evidence on pharmacotherapy of hypertension in patients on dialysis, and we conclude with suggestions for future research to address critical gaps in this important area.

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Introduction

Hypertension in people with ESRD on chronic dialysis is often poorly controlled, highly prevalent, and difficult to diagnose (1,2). Elevated BP, particularly when recorded outside of dialysis with home or ambulatory BP monitoring, is clearly associated with increased risk of cardiovascular morbidity and mortality (3). Sodium and volume overload are the most important causes of hypertension in patients on dialysis; therefore, nonpharmacologic interventions, such as dietary sodium restriction, enhanced sodium removal with dialysis, and probing of dry weight, should be the initial therapies for achievement of adequate BP control (4,5). This therapeutic approach is challenging, because several factors, such as short delivered dialysis (6), missed dialysis sessions, patient nonadherence to the dietary recommendations for sodium restriction, and intradialytic sodium gain through high dialysate sodium prescription, may be barriers to the achievement of dry weight (7). Even after aggressive volume management, hypertension remains poorly controlled; in these patients, pharmacologic therapy is necessary to control BP. Most classes of antihypertensive drugs are useful for pharmacotherapy of hypertension in patients on dialysis, and a combination therapy is often required (4,5).

In this article, we discuss the choice of the appropriate antihypertensive regimen in the era of the currently available evidence from randomized studies evaluating

the BP-lowering efficacy, safety, and cardioprotective and pharmacokinetic properties of antihypertensive agents in the dialysis population. In the absence of properly designed randomized trials, several aspects of pharmacologic and nonpharmacologic management of hypertension in patients on dialysis remain obscure. We conclude with critical gaps in the existing knowledge, provide directions for future research, and call for randomized trials among patients on dialysis.

Research Challenges in Designing Interventional Studies

Compared with the nondialysis population, BP among patients on dialysis is highly variable from pre- to postdialysis and from one day to the other (8). Peridialytic BP recordings cannot accurately reflect the actual BP burden over the entire interdialytic period and can easily miss the magnitude of treatment-induced reduction in BP (9). In addition, out-of-dialysis unit BP recordings were shown to be strongly associated with all-cause and cardiovascular mortality, contrary to the limited or no prognostic significance of BP recordings obtained within the dialysis unit (3,10,11). The use of out-of-dialysis BP recordings (home or ideally, interdialytic ambulatory BP) as outcome measures of the efficacy of antihypertensive drugs is critical. However, state of art out-of-dialysis BP recording to evaluate BP outcomes are

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Table 1. Magnitude of change in ambulatory BP in response to pharmacologic and nonpharmacologic interventions in patients on dialysis

Author	Year	n	Modality	Characteristics	Design	Intervention	Follow-Up	BP Assessment	Baseline BP, mmHg	CFB in BP, mmHg
Agarwal (59)	1999	8	HD	Untreated hypertension	Single-arm interventional	Atenolol (25 mg TIW postdialysis)	3 wk	44-h ABPM	144/80	–17/–11
Agarwal et al. (60)	2001	11	HD	Uncontrolled hypertension with ≤ 2 antihypertensive drugs	Single-arm interventional	Lisinopril (10–40 mg TIW postdialysis) plus dry weight reduction	4 wk	44-h ABPM	149/84	–22/–11
Vlassopoulos et al. (62)	2002	10	HD	Hypertension	Single-arm interventional	Atenolol (12.5–100 mg TIW postdialysis)	5 wk	44-h ABPM	MBP: 104 $\pm$ 11.5	MBP: –8.4
Shimada et al. (63)	2005	13	HD	Hypertension	Single-arm interventional	Telmisartan (40 mg/d)	8 wk	24-h ABPM (dialysis off day)	Daytime: 151/77; nighttime: 154/75	Daytime: –21/–9; nighttime: –21/–9
Zheng et al. (64)	2007	10	HD	Treated hypertension	Single-arm interventional	Switching daily medications to trandolapril (2–8 mg), atenolol (25–100 mg), and/or amlodipine (5–10 mg) TIW	2–10 wk	44-h ABPM	122.3/75.3	–5.9/–4.9
Agarwal et al. (14)	2009	50	HD	Hypertension	Control group of the DRIP trial	No BP-lowering intervention	8 wk	44-h ABPM	146.4/83.4	Week 4: –3.8/–3.0; week 8: –6.9/–3.9
Agarwal et al. (14)	2009	100			Intervention group of the DRIP Trial	Probing of dry weight			145.8/82.9	Week 4: –10.7/–6.1; week 8: –13.5/–7.2
Agarwal et al. (15)	2014	100	HD	Hypertension with LVH	Atenolol group of the HDPAL trial	Atenolol (25–100 mg TIW postdialysis) plus dry weight reduction plus dialysate sodium reduction plus add-on antihypertensive therapy	12 mo	44-h ABPM	151.5/87.1	Month 6: –21.8/–13.3; month 12: –21.4/–12.5
Agarwal et al. (15)	2014	100			Lisinopril group of the HDPAL trial	Lisinopril (10–40 mg TIW postdialysis) plus dry weight reduction plus dialysate sodium reduction plus add-on antihypertensive therapy			151.9/87.2	Month 6: –16.8/–9.7; month 12: –17.9/–9.6

CFB, change from baseline; HD, hemodialysis; TIW, three times per week; ABPM, ambulatory BP monitoring; MBP, mean BP; DRIP, Dry-Weight Reduction in Hemodialysis Patients; LVH, left ventricular hypertrophy; HDPAL, Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril.

available only in a few of the studies conducted so far (Table 1). Notably, use of ambulatory BP monitoring also has the advantage of recording BP during nighttime, providing additional information on the efficacy of drugs to restore the nondipping BP pattern and improve nocturnal hypertension. The blunted nocturnal BP fall is common in patients on dialysis and associated with acceleration of target organ damage (12) and increased mortality risk (13).

Nonpharmacologic interventions (*i.e.*, changes in dry weight or dialysate sodium) can easily confound the BP-lowering efficacy of antihypertensive drug therapy. The Dry-Weight Reduction in Hemodialysis Patients (DRIP) trial showed the net BP-lowering effect of probing of dry weight in patients on hemodialysis who are hypertensive (14). A reduction in postdialysis weight of 0.9 kg provoked a significant decrease of 6.9/3.1 mmHg in interdialytic ambulatory BP at 4 weeks. Because background antihypertensive therapy was not modified, BP lowering seen in the DRIP trial is solely attributable to dry weight reduction. In contrast, it is rather difficult to distinguish the BP-lowering effect of drug therapy from the BP reduction caused by dry weight adjustment in studies combining pharmacologic and nonpharmacologic BP-lowering interventions. In the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial (15), changes in interdialytic ambulatory BP during follow-up were no different between the atenolol and the lisinopril groups. However, lisinopril-treated patients required greater dry weight reduction and administration of higher numbers of antihypertensive drugs as add-on therapy (15). This suggests that the BP-lowering efficacy of atenolol is superior to that of lisinopril.

Pharmacologic Management of Hypertension in Patients on Dialysis

Meta-analyses of randomized trials showed that BP lowering with the use of antihypertensive agents reduces cardiovascular morbidity and mortality in patients on dialysis (16,17), particularly when they are hypertensive (16). All antihypertensive drug classes can be used for pharmacotherapy of hypertension (4,5). The exception may be diuretics, which are generally ineffective in patients with low GFR. Echocardiographic studies showed that, among anuric patients, intravenous administration of high-dose loop diuretics causes minimal alterations in central hemodynamic parameters (18). Given the risk of ototoxicity, use of diuretics in anuric patients on dialysis is not recommended (4,5). These compounds may have a role in those with preserved residual renal function as a maneuver to limit interdialytic weight gain (19); whether such an approach is useful or detrimental has not been adequately examined.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Blockade of the renin-angiotensin-aldosterone system (RAAS) is often recommended as first-line antihypertensive therapy for patients on dialysis by extrapolation of cardiovascular benefits of RAAS inhibitors in the general population (5). However, extrapolation of outcomes from the general population or those with CKD not on

dialysis to those on dialysis is hazardous. For example, in the Fosinopril in Dialysis trial 397 patients on hemodialysis were randomly assigned to the angiotensin-converting enzyme inhibitor (ACEI) fosinopril (titrated up to 20 mg/d) or placebo for 48 months (20). This study enrolled patients with left ventricular hypertrophy (LVH), but hypertension was not an inclusion criterion. Although fosinopril significantly lowered predialysis BP relative to placebo in the subgroup of hypertensive participants, incidence of fatal and nonfatal cardiovascular events was no different between the active treatment and placebo groups (relative risk [RR], 0.93; 95% confidence interval [95% CI], 0.68 to 1.26) (20). In contrast, in a much smaller Japanese study that included only 80 patients on hemodialysis without overt cardiovascular disease, the angiotensin receptor blocker (ARB) candesartan improved cardiovascular event-free survival versus placebo (21). Similarly, Suzuki *et al.* (22) showed that, among 360 patients with hypertension on hemodialysis, ARB therapy (valsartan, candesartan, or losartan) reduced by 49% the risk of cardiovascular death, nonfatal myocardial infarction (MI), stroke, coronary revascularization, and hospitalized congestive heart failure (CHF) in comparison with control therapy not including ARBs or ACEIs (hazard ratio [HR], 0.51; 95% CI, 0.33 to 0.79). A meta-analysis of these three studies showed that ACEI and ARB use was not associated with significant reduction in the risk of future cardiovascular events (pooled RR, 0.66; 95% CI, 0.35 to 1.25), indicating the necessity for larger high-quality studies (23). The subsequent Olmesartan Clinical Trial in Okinawa Patients under Okinawa Dialysis Study Trial compared the effect of olmesartan (10–40 mg/d) versus control therapy not including RAAS inhibitors in 469 patients with hypertension on hemodialysis. Over a mean follow-up of 3.5 years, incidence of all-cause death, nonfatal stroke, MI, and coronary revascularization was identical in the ARB and control arms (HR, 1.00; 95% CI, 0.71 to 1.40) (24).

RAAS blockade is suggested to exert beneficial actions on LVH and large artery stiffness, both of which are strong cardiovascular risk predictors in patients on dialysis (25,26). This notion is supported by small randomized studies showing that, compared with placebo or other therapies, ACEIs and ARBs caused greater reductions in left ventricular mass index (LVMI) and pulse wave velocity (PWV) (Table 2) (27,28). A previous meta-analysis of five randomized studies showed that ACEI or ARB use resulted in a significant reduction in LVMI, with a weighted mean difference of 15.4 g/m² (95% CI, 7.4 to 23.3) relative to control therapy (23). Improvement in LVMI with ARB therapy was evident in another meta-analysis of six randomized studies (29). However, these benefits were not consistent in all relevant studies. In the recent Saving Residual Renal Function among Hemodialysis Patients Receiving Irbesartan Study, 12-month treatment with irbesartan was not superior to placebo in reducing LVMI and aortic PWV; notably, ARB-induced reductions in LVMI and PWV went in parallel with the changes in predialysis BP (30). Therefore, it remains unclear whether these beneficial actions on cardiac remodeling and arterial stiffness are BP mediated or BP independent (31).

Dual RAAS blockade may offer additive cardiovascular protection in specific subgroups of patients on dialysis (*i.e.*,

Table 2. Randomized studies evaluating the effects of angiotensin–converting enzyme inhibitors and angiotensin receptor blockers in patients on dialysis

Author	Year	n	Modality	Characteristics	Design	Control Group	Intervention	Follow-Up, mo	Outcome	Overall Effect	Details
Zannad <i>et al.</i> (20)	2006	397	HD	Hypertension (not all patients) and LVH	Double blind	Placebo	Fosinopril (titrated up to 20 mg/d)	24	CV death, resuscitated death, nonfatal stroke, MI, hospitalized CHF, and coronary revascularization	Neutral	Incidence of fatal and nonfatal CV events was no different between the fosinopril and placebo groups (RR, 0.93; 95% CI, 0.68 to 1.26)
Takahashi <i>et al.</i> (21)	2006	80	HD	Without overt CV disease	Open label	Nothing	Candesartan (4–8 mg/d)	36	SCD, fatal or nonfatal MI, unstable angina, hospitalized CHF, serious arrhythmia	Better	Candesartan therapy improved CV event–free survival (OR, 0.23; 95% CI, 0.08 to 0.67)
Suzuki <i>et al.</i> (22)	2008	360	HD	Hypertension	Open label	Other therapy not ACEIs or ARBs	Losartan (50–100 mg/d), valsartan (80–160 mg/d), or candesartan (up to 12 mg/d)	36	Composite of CV death, nonfatal MI, stroke, coronary revascularization, and CHF	Better	ARB treatment reduced the occurrence of fatal and nonfatal CV events (HR, 0.51; 95% CI, 0.33 to 0.79)
Cice <i>et al.</i> (32)	2010	332	HD	LVEF <40% on ACEIs	Double blind	Placebo	Telmisartan (titrated up to 80 mg/d)	36	All-cause mortality; CV mortality, hospitalization for CHF	Better	Add-on telmisartan therapy reduced all-cause (HR, 0.51; 95% CI, 0.32 to 0.82) and CV mortality (HR, 0.42; 95% CI, 0.38 to 0.61)
Iseki <i>et al.</i> (24)	2013	469	HD	Hypertension	Open label	Other therapy not ACEIs or ARBs	Olmesartan (titrated up to 40 mg/d)	42	All-cause death, nonfatal stroke, MI, and coronary revascularization	Neutral	Occurrence of the primary outcome during follow-up was identical in the olmesartan and control groups (HR, 1.00; 95% CI, 0.71 to 1.40)
London <i>et al.</i> (65)	1994	24	HD	Hypertension and LVH	Open label	Nitrendipine (20–40 mg TID postdialysis)	Perindopril (2–4 mg TID postdialysis)	12	Change in LVMI and aortic PWV	Better	Perindopril but not nitrendipine regressed LVMI and PWV, despite the similar decrease in BP in both groups

Table 2. (Continued)

Author	Year	n	Modality	Characteristics	Design	Control Group	Intervention	Follow-Up, mo	Outcome	Overall Effect	Details
Shibasaki <i>et al.</i> (66)	2002	30	HD	Hypertension	Open label	Enalapril (10 mg/d) or amlodipine (10 mg/d)	Losartan (100 mg/d)	6	Change in LVMI	Better	Losartan was superior to amlodipine and enalapril in causing regression of LVMI ($-24.7 \pm 3.2\%$ versus $-10.5 \pm 5.2\%$ versus $-11.2 \pm 4.1\%$), despite the similar decrease in mean BP with all drugs
Suzuki <i>et al.</i> (67)	2003	24	PD	LVH	Double blind	Placebo	Valsartan (160 mg/d)	12	Change in LVMI	Better	Improvement in LVMI with valsartan therapy (145 ± 5 versus 121 ± 4 g/m ² ; $P < 0.05$) but not with placebo
Suzuki <i>et al.</i> (68)	2004	33	HD	Incident patients with diabetes and LVH	Open label	Monotherapy with losartan or enalapril	Dual RAAS blockade with losartan (100 mg/d) and enalapril (10 mg/d)	12	Change in LVMI	Better	Dual RAAS blockade was associated with 28% greater reduction in LVMI compared with each monotherapy
Kanno <i>et al.</i> (69)	2004	24	HD	Incident patients with diabetes and LVH	Open label	Placebo	Losartan (100 mg/d)	12	Change in LVMI	Better	Despite the similar BP reduction, improvement in LVMI was evident only in the losartan group
Ichihara <i>et al.</i> (70)	2005	64	HD	Never previously treated with ACEIs or ARBs	Open label	Placebo	Losartan (25 mg/d) andtrandolapril (1 mg/d)	12	Change in baPWV	Better	Both losartan andtrandolapril reduced the rate of change in baPWV during follow-up relative to placebo
Matsumoto <i>et al.</i> (71)	2006	30	HD	LVH	Open label	Placebo	Imidapril (2.5 mg/d)	6	Change in LVMI	Better	LVMI was reduced in the imidapril (132 ± 10 versus 109 ± 6 g/m ² ; $P < 0.05$) but not in the placebo group
Yu <i>et al.</i> (28)	2006	56	HD	Normotensive	Open label	Placebo	Ramipril (2.5 mg TIW)	12	Change in LVMI	Neutral	Ramipril did not improve LV sizing and functional parameters relative to placebo
Shigenaga <i>et al.</i> (72)	2009	45	PD	Hypertension	Open label	Other therapy not ACEIs or ARBs	Candesartan (16 mg/d) and valsartan (160 mg/d)	6	Change in BP variability, LVMI, baPWV	Better	Both ARBs improved short-term BP variability, LVMI, baPWV compared with control therapy

Table 2. (Continued)

Author	Year	n	Modality	Characteristics	Design	Control Group	Intervention	Follow-Up, mo	Outcome	Overall Effect	Details
Mitsuhashi et al. (27)	2009	40	HD	Hypertension	Open label	Other therapy not ACEIs or ARBs	Losartan (50–100 mg/d)	12	Change in BP variability, LVMI, baPWV	Better	Losartan significantly improved BP variability, LVMI, and baPWV relative to control therapy
Peters et al. (30)	2014	82	HD	Incident patients with residual function	Double blind	Placebo	Irbesartan (titrated up to 300 mg/d)	12	Change in LVMI and aortic PWV	Neutral	Irbesartan was not superior to placebo in reducing LVMI (Δ placebo versus Δ ARB = -1.3 g/m ² ; $P=0.90$) and PWV (Δ placebo versus Δ ARB = 0.4 m/s; $P=0.49$)

HD, hemodialysis; LVH, left ventricular hypertrophy; CV, cardiovascular; MI, myocardial infarction; CHF, congestive heart failure; RR, relative risk; 95% CI, 95% confidence interval; SCD, sudden cardiac death; OR, odds ratio; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio; LVEF, left ventricular ejection fraction; TIW, three times per week; LVMI, left ventricular mass index; PWV, pulse wave velocity; PD, peritoneal dialysis; RAAS; renin-angiotensin-aldosterone system; baPWV, brachial-ankle pulse wave velocity; LV, left ventricular.

in patients with severe CHF). In a double-blind trial, 332 patients on hemodialysis with left ventricular ejection fraction (LVEF) <40% already treated with ACEIs were randomized to add-on telmisartan (40–80 mg/d) or placebo (32). After a mean follow-up of 35.5 months, telmisartan reduced cardiovascular mortality (HR, 0.42; 95% CI, 0.38 to 0.61) and hospitalizations for worsening CHF (HR, 0.38; 95% CI, 0.18 to 0.51). Incidence of hyperkalemia was similar in the telmisartan and placebo groups (32). Whether dual RAAS blockade is generalizable to the overall dialysis population requires additional research; this trial included patients with particular clinical characteristics (*i.e.*, patients with CHF and reduced LVEF). Additionally, it could be argued that the low incidence of hyperkalemia with dual RAAS blockade in this trial could be partially attributed to the fact that study participants were receiving intensive RRT with four dialysis session per week and that most of them had a well functioning arteriovenous fistula as vascular access for dialysis (32).

The intradialytic kinetics of various ACEIs differ substantially from each other. With the exception of the non-dialyzable fosinopril, most of the other ACEIs are removed during dialysis. In contrast, ARBs are nondialyzable, and no supplement doses are required (5,33).

In summary, the evidence base to support the use of ACEIs or ARBs among patients on dialysis for either cardioprotection or regression of LVH is thin. Thus, in our practice, we use them as third-line agents after blockers and dihydropyridine calcium-channel blockers (CCBs).

Mineralocorticoid Receptor Antagonists

Among patients not on dialysis with CHF and reduced LVEF, add-on therapy with mineralocorticoid receptor antagonists (MRAs) on top of background treatment with ACEIs, ARBs, and/or β -blockers effectively reduced cardiovascular morbidity and mortality (34). Efficacy of spironolactone and eplerenone among patients on dialysis is less well studied, mainly because of the concerns that any benefit from their use may be counteracted by excessive risk of life-threatening hyperkalemia. MRAs could theoretically reduce potassium removal through the intestine, which represents an important route of excretion, particularly in anuric patients on hemodialysis. A recent randomized study compared the safety profile of eplerenone (25–50 mg/d) versus that of placebo in 146 patients on hemodialysis. Over a 13-week follow-up, incidence of hyperkalemia (defined as predialysis serum potassium >6.5 mmol/L) was higher in eplerenone-treated patients (RR, 4.50; 95% CI, 1.0 to 20.2) (35). However, eplerenone was not associated with excess need for permanent drug discontinuation because of hyperkalemia or hypotension, which was the primary study end point (35). Whether potassium-binding resins could be helpful in maintaining the potassium balance in patients with dialysis-requiring CKD treated with spironolactone or eplerenone requires randomized trials to evaluate efficacy and safety of this strategy (36).

The cardioprotective properties of MRAs among patients on dialysis are supported by a number of randomized studies showing that these drugs culminate in sustained reduction of interdialytic BP and improvement in LVMI,

Table 3. Randomized studies evaluating the effects of mineralocorticoid receptor antagonists in patients on dialysis

Author	Year	n	Modality	Characteristics	Design	Control Group	Intervention	Follow-Up	Primary Outcome	Overall Effect	Details
Matsumoto <i>et al.</i> (40)	2014	309	HD	Oligoanuric	Open label	Nothing	Spironolactone (25 mg/d)	36 mo	Death or hospitalization for CCV event	Better	Spironolactone reduced the occurrence of the primary outcome by 62% (HR, 0.38; 95% CI, 0.17 to 0.83)
Lin <i>et al.</i> (41)	2015	253	HD or PD	Non-CHF patients	Open label	Placebo	Spironolactone (25 mg/d)	24 mo	Death from CCV events, absorbed arrest, and SCD	Better	Spironolactone reduced the occurrence of the primary outcome by 58% relative to placebo (HR, 0.42; 95% CI, 0.26 to 0.78)
Gross <i>et al.</i> (73)	2005	8	HD	Oligoanuric	Double blind, crossover	Placebo	Spironolactone (50 mg twice daily)	2 wk	Change in predialysis SBP	Better	Reduction of 10.6 mmHg in predialysis SBP with spironolactone therapy
Taheri <i>et al.</i> (74)	2009	16	HD	CHF with LVEF<45%	Double blind	Placebo	Spironolactone (25 mg TIW postdialysis)	6 mo	Change in LVEF	Better	Improvement in LVEF with spironolactone therapy (CFB of 6.2±1.64 in the spironolactone group versus 0.83±4.9 in the placebo group)
Vukusich <i>et al.</i> (39)	2010	53	HD	Absence of residual renal function	Open label	Placebo	Spironolactone (50 mg TIW postdialysis)	24 mo	Change in carotid IMT	Better	Spironolactone significantly reduced carotid IMT over time relative to placebo
Taheri <i>et al.</i> (75)	2012	18	PD	NYHA 3–4 CHF	Double blind	Placebo	Spironolactone (25 mg TIW)	6 mo	Change in LVEF	Better	Improvement in LVEF with spironolactone therapy (25.7±7.3% versus 33.3±7.8%; P=0.002)
Ni <i>et al.</i> (38)	2014	82	HD	Refractory hypertension	Double blind	Placebo	Add-on spironolactone (25 mg/d)	3 mo	Change in 24-h BP	Better	Spironolactone caused an average reduction of 10.9/5.8 mmHg in 24-h BP relative to placebo
Ito <i>et al.</i> (37)	2014	158	PD	Concurrent treatment with ACEIs or ARBs	Open label	Nothing	Spironolactone (25 mg/d)	24 mo	Change in LVMI	Better	Improvement in LVMI at 6, 18, and 24 mo of follow-up with spironolactone therapy
Feniman-De-Stefano <i>et al.</i> (76)	2015	17	HD	LVH	Double blind	Placebo	Spironolactone (titrated up to 25 mg/d)	6 mo	Change in LVMI	Better	LVMI was reduced from 77±14.6 to 69±10.5 g/m ² (P<0.04 versus baseline) in the spironolactone group
Walsh <i>et al.</i> (35)	2015	154	HD	RRT for at least 3 mo	Open label	Placebo	Eplerenone (titrated up to 50 mg/d)	3 mo	Drug discontinuation because of hyperkalemia or hypotension	Neutral	Eplerenone was noninferior to placebo with respect to the primary outcome (absolute between-group risk difference: 1.2 percentage points; 95% CI, -4.7 to 7.1)

HD, hemodialysis; CCV, cerebrovascular; HR, hazard ratio; 95% CI, 95% confidence interval; PD, peritoneal dialysis; CHF, congestive heart failure; SCD, sudden cardiac death; SBP, systolic BP; LVEF, left ventricular ejection fraction; TIW, three times per week; CFB, change from baseline; IMT, intima-media thickness; NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy.

LVEF, and carotid intima-media thickness (Table 3) (37–39). Two larger studies provided evidence that these beneficial effects on surrogate cardiovascular risk factors may be translated into survival benefits. In the Dialysis Outcomes Heart Failure Aldactone Study, 309 oligoanuric patients on hemodialysis were randomized to spironolactone (25 mg/d) or no add-on therapy for a mean follow-up of 3 years. Spironolactone lowered by 62% the risk of cardiovascular death or cardiovascular-related hospitalization (HR, 0.38; 95% CI, 0.17 to 0.83) (40). Incidence of serious hyperkalemia leading to drug discontinuation was as low as 1.9%. In the second study, 253 nonheart failure patients receiving hemodialysis or peritoneal dialysis were randomized to 2-year add-on therapy with spironolactone (25 mg/d) or placebo. Spironolactone reduced by 58% the occurrence of the composite primary outcome of cardiocerebrovascular death, observed cardiac arrest, and sudden death (HR, 0.42; 95% CI, 0.26 to 0.78) (41). These promising results need to be confirmed in larger, properly designed studies. A trial named the Aldosterone Antagonist Hemodialysis Survival Trial (42) that plans to recruit 825 patients on hemodialysis is underway and anticipated to shed more light on the potential harms and benefits of MRAs in patients on dialysis.

β -Blockers

Vulnerability of patients on dialysis to serious arrhythmias and sudden death together with excessive sympathetic overactivity make β -blockade an attractive therapeutic option for cardiovascular protection in this population (Tables 4–6) (43). In a double-blind fashion, 114 patients on hemodialysis with dilated cardiomyopathy (not necessarily hypertensive) were randomized to carvedilol (titrated up to 25 mg twice daily) or placebo. Over a mean follow-up of 2 years, carvedilol improved left ventricular systolic performance and reduced the risk of all-cause hospitalization (HR, 0.44; 95% CI, 0.25 to 0.77) and mortality (HR, 0.51; 95% CI, 0.32 to 0.82) (44). Cardioprotective properties of β -blockers are supported by the HDPAL trial which performed a head-to-head comparison between the β -blocker atenolol and the ACEI lisinopril (both administered thrice weekly postdialysis) in 200 patients with hypertension on hemodialysis with LVH (15). The HDPAL Trial was neutral with respect to the primary outcome; improvement in LVMI over the 12-month follow-up was similar in both arms. However, lisinopril-treated patients required more aggressive volume management and administration of higher numbers of antihypertensive drugs to achieve the prespecified home BP target of <140/90 mmHg. The HDPAL Trial was prematurely terminated because of excess risk of serious cardiovascular adverse events in the lisinopril group. Incidence of the combined end point of MI, stroke, hospitalized heart failure, and cardiovascular death was 2.29 times higher in lisinopril-treated patients than in atenolol-treated patients (incidence rate ratio, 2.29; 95% CI, 1.07 to 5.21) (15). In a secondary analysis of the HDPAL Trial, atenolol was shown to be superior to lisinopril in improving aortic PWV (45). The recently reported Beta-Blocker to Lower Cardiovascular Dialysis Events Trial failed to advance our knowledge on the cardioprotective role of β -blockade because of the low recruitment rate that resulted in a small

sample size (46). Particularly, among 1443 patients screened, only 354 were eligible, 91 consented, and 72 entered the 6-week active treatment run-in period. Of these, only 49 participants (68%; 95% CI, 57% to 79%) tolerated carvedilol therapy (6.25 mg twice daily) during the run in and progressed to randomization (46). Narrow inclusion criteria and insufficient washout of background β -blockade therapy led to exclusion of high-risk patients who were more likely to benefit from the cardioprotective actions of carvedilol.

β -Blockers represent a highly variable medication class with respect to their pharmacokinetic properties. Atenolol is easily removable during dialysis compared with lipophilic agents, such as propranolol (5,33). Intradialytic removal of β -blockers, apart from interfering with their efficacy, may also exacerbate the risk of serious arrhythmias and sudden death. In a propensity-matched retrospective cohort study of 6588 patients on hemodialysis, use of a high-dialyzable versus a low-dialyzable β -blocker was associated with 40% higher risk of all-cause death (47). Another concern around the use of β -blockers is the risk of exercise-induced or fasting hyperkalemia, an adverse effect that has been described for the nonselective β -blockers nadolol and labetalol and attributed to the role of β_2 -receptors in regulating potassium entry intracellularly (48). Finally, unfavorable metabolic effects of older versus newer β -blockers on serum lipid profile, insulin sensitivity, and risk of new-onset diabetes may have unintended cardiovascular consequences, which should be also taken into account (49).

CCBs

CCBs can effectively lower BP, even in the volume-expanded state (50), and are often used as combination therapy for management of hypertension in patients on dialysis. Tepel *et al.* (51) randomized 251 patients with hypertension on hemodialysis to receive amlodipine (5–10 mg/d) or placebo for 30 months. Amlodipine insignificantly improved survival relative to placebo but reduced by 47% the composite secondary end point of all-cause death, nonfatal stroke, MI, coronary revascularization, and angioplasty for peripheral vascular disease (HR, 0.53; 95% CI, 0.31 to 0.93) (51). Other studies suggested that dihydropyridine CCBs are as effective as ACEIs or ARBs in reducing oxidative stress and producing regression of both LVMI and carotid intima-media thickness (52,53). The pharmacokinetics of CCBs are unaltered among patients on dialysis, and these agents are generally nondialyzable (5,33).

Other Agents

The centrally acting α -agonist clonidine can effectively lower BP by reducing autonomic activation. Because of troublesome side effects, such as dry mouth, dizziness, and somnolence, this agent is reserved for patients with difficult to control hypertension (33). Guanfacine is also centrally acting but has less potential for causing sedation or dry mouth. Similarly, the direct vasodilators minoxidil and hydralazine are used as drugs of last resort in patients with multidrug-resistant hypertension. These agents cause reflex tachycardia, the control of which often requires the concomitant administration of β -blockers (33). A serious

Table 5. Randomized studies evaluating the effects of calcium-channel blockers in patients on dialysis

Author	Year	n	Modality	Characteristics	Design	Control Group	Intervention	Follow-Up	Outcome	Overall Effect	Details
Tepel <i>et al.</i> (51)	2008	251	HD	Hypertension	Double blind	Placebo	Amlodipine (10 mg/d)	19 mo	All-cause death, nonfatal stroke, MI, coronary revascularization, and angioplasty for PVD	Better	Amlodipine reduced the risk of all-cause mortality and future CV event relative to placebo (HR, 0.53; 95% CI, 0.31 to 0.93)
Kojima <i>et al.</i> (77)	2004	10	HD	Hypertension	Open label, crossover	Nifedipine CR (20–40 mg/d)	Binedipine (4–8 mg/d)	4 wk	Change in 24-h BP	Better	Binedipine was superior to nifedipine CR in improving 24-h BP
Aslam <i>et al.</i> (52)	2006	19	HD	Hypertension	Double blind, crossover	Valsartan (up to 320 mg/d)	Amlodipine (5–10 mg/d)	6 wk	Change in 44-h BP and biomarkers of oxidative stress	Neutral	Amlodipine was no different from valsartan in reducing 44-h BP and markers of oxidative stress
Yilmaz <i>et al.</i> (53)	2010	112	HD	Nondiabetic hypertensive	Open label	Ramipril	Amlodipine (5–10 mg/d)	12 mo	Change in LVMI and carotid IMT	Neutral	Amlodipine and ramipril reduced to a similar extent LVMI and carotid IMT

HD, hemodialysis; MI, myocardial infarction; PVD, peripheral vascular disease; CV, cardiovascular; HR, hazard ratio; 95% CI, 95% confidence interval; CR, continuous release; LVMI, left ventricular mass index; IMT = intima-media thickness.

and not so rare side effect of minoxidil is pericardial effusion. Hydralazine has been associated with a lupus-like syndrome. Lastly, use of α -adrenergic blockers in patients on dialysis is frequently associated with episodes of orthostatic and intradialytic hypotension. These side effects make their use problematic; when chosen, bedtime dosing of these compounds is preferred (33).

Summary of Evidence and Clinical Practice Recommendations

Evidence to support the preferential administration of one antihypertensive drug class over another for pharmacologic management of hypertension in patients on dialysis is currently missing. Choice of the appropriate antihypertensive regimen should be individualized and on the basis of the BP-lowering efficacy of drugs, the BP-independent cardioprotective properties, the intra- and interdialytic pharmacokinetics, and the tolerability and side effect profile as well as the comorbidities of each patient. The use of β -blockers should be strongly considered on the basis of evidence suggesting that these agents likely offer the greatest cardioprotection (15,21,22,44), including their beneficial actions on regression of LVH and arterial stiffness (23,29,45). In the absence of randomized studies to compare the efficacy of different antihypertensive drug classes in patients with specific comorbidities or end organ damage conditions, any established indication of a certain drug class in the general population (*i.e.*, β -blockers for post-MI) should be extrapolated to patients on dialysis as long as firm evidence will become available in this specific population (5). We use dihydropyridine CCBs as second-line agents when BP remains uncontrolled despite nonpharmacologic measures and β -blockade. ACEIs and ARBs are our third choices. Recent studies suggest that, among patients on dialysis, add-on administration of MRAs may offer additive cardiovascular protection without excessive risk of serious hyperkalemia (54). Safety and efficacy of MRAs in patients on dialysis are under investigation in ongoing trials; in the meantime, wide use of spironolactone and eplerenone cannot be recommended. Because management of hypertension often requires combination therapy to achieve adequate BP control, long-acting dihydropyridine CCBs are useful as combination therapy. Other drug classes, such as centrally acting agonists, direct vasodilators, and α -adrenergic blockers, are frequently associated with serious side effects, and their use should be limited to patients with difficult to control hypertension.

Pharmacokinetic properties and dialyzability should be taken into account in the choice and dosing of antihypertensive drugs. The patterns and rhythms of BP during the intra- and interdialytic periods are additional factors that should be considered. In patients prone to intradialytic hypotension, short-acting agents, such as hydralazine, before dialysis should not be administered. There is little support to withhold antihypertensive therapy otherwise before dialysis. Patients experiencing paradoxical BP elevation during or immediately postdialysis also exhibit sustained background hypertension over the entire interdialytic period (55); accordingly, the target of therapy in these patients remains the achievement of adequate 44-hour BP

Table 6. Pharmacokinetics of selected antihypertensive agents in patients on dialysis (5,33)

Drug Class and Drug	Usual Dosage	Route of Excretion	Removal with Dialysis, %	Supplement Dose for Dialysis, mg
Angiotensin-converting enzyme inhibitors				
Benazepril	5–40 mg every day	K (L)	20–50	5–10
Captopril	12.5–50 mg three times per day	K	50	12.5–25
Enalapril	2.5–10 mg every 12 h	K (L)	50	2.5–5
Fosinopril	10 mg every day	K (L)	None	None
Lisinopril	2.5–10 mg every day ^a	K	50	2.5–5
Perindopril	2–8 mg every day	K (L)	50	2
Ramipril	5–10 mg every day	K (L)	20	2.5
Trandolapril	0.5–4 mg every day	K (L)	30	0.5
Angiotensin receptor blockers				
Candesartan	8–32 mg/d	K (L)	None	None
Eprosartan	600–1200 mg/d	L	None	None
Irbesartan	75–300 mg/d	L	None	None
Losartan	50–100 mg every day	K (L)	None	None
Olmesartan	10–40 mg/d	K (L)	None	None
Telmisartan	40–80 mg/d	L	None	None
Valsartan	80–320 mg every day	K (L)	None	None
Mineralocorticoid receptor antagonists				
Spironolactone	25–50 mg every day	K (L)	None	None
Eplerenone	50–100 mg every day	K (L)	None	None
β-Blockers				
Atenolol	25 mg every day ^b	K (L)	50	25–50
Bisoprostol	2.5–20 mg every day	L	None	None
Carvedilol	25 mg twice a day	L (K)	None	None
Labetalol	200–600 mg twice a day	K (L)	None	None
Metoprolol	50–100 mg twice a day	K (L)	None	None
Nadolol	80–100 mg twice a day	K	50	80
Propranolol	80–160 mg twice a day	K	None	None
Calcium-channel blockers				
Amlodipine	2.5–10 mg every day	L	None	None
Felodipine	5–10 mg every day	L	None	None
Nicardipine	20–40 mg three times a day	L	None	None
Nifedipine XL	30–90 mg every day	L	None	None
Lacidipine	2–6 mg/d	L (K)	None	None
Manidipine	10–20 mg/d	L	None	None
Diltiazem CD	180–360 mg	L (K)	None	None
Verapamil CD	180–360 mg every day	L (K)	None	None
α-Adrenergic blockers				
Doxazosin	1–16 mg every day	L	None	None
Prazosin	1–15 mg twice a day	L	None	None
Terazosin	1–20 mg every day	L	None	None
Others				
Clonidine	0.1–0.3 mg twice a day/three times a day	K (L)	5	None
Hydralazine	25–50 mg three times a day/twice a day	L	25–40	None

K, kidney; L, liver.

^aPreferred dosage for lisinopril is 10–40 mg three times weekly after dialysis. The maximum dose recommended in hemodialysis patients is 40 mg per day.

^bPreferred dosage for atenolol is 25 mg–100 mg three times weekly after dialysis to maximize the antihypertensive effect and convenience of dosing.

control and not simply the normalization of the intradialytic hemodynamic response (56). Therapeutic approach of intradialytic hypertension is not substantially differentiated from the overall treatment of hypertension in

patients on dialysis; dry weight should be probed (57), and if volume control alone is ineffective, antihypertensive drug therapy may be needed. Small studies seem to suggest that improvement in endothelial dysfunction

through newer vasodilating β -blockers may be of benefit in these individuals (58). Patients with sustained interdialytic hypertension should receive long-acting agents (56). A maneuver to reduce the high pill burden and enhance the patients' compliance is supervised thrice weekly administration of long-acting agents immediately postdialysis (59,60). This is strongly supported by the HDPAL Trial, in which administration of atenolol and lisinopril in a three times per week schedule culminated in sufficient home BP control over the course of the trial (15). Patients with a nondipping BP pattern during nighttime may benefit from bedtime dosing of at least one antihypertensive agent. Whether this strategy would reduce cardiovascular outcomes remains unknown.

Perspectives and Directions for Future Research

One critical gap in our knowledge is whether BP control is associated with better outcomes in patients on dialysis. Randomizing patients to two different BP levels using out-of-office BP monitoring to assess cardiovascular outcomes would be a top research priority. It remains unclear whether one class of antihypertensive medications is superior to another in improving cardiovascular outcomes in patients on dialysis. Adequately powered, multicenter, randomized trials evaluating hard cardiovascular end points, ideally with identical BP targets in all treatment arms, are urgently warranted to elucidate the comparative effectiveness of major antihypertensive drug categories. Such types of studies may also clarify whether cardiovascular protection with antihypertensive therapy is BP mediated or whether specific drug categories offer cardioprotection beyond their BP-lowering properties. Another critical issue that remains unclear is the optimal levels at which BP should be targeted in patients on dialysis. Studies randomizing patients on dialysis to different BP goals, preferably with administration of similar BP-lowering agents in the randomized groups, are anticipated to elucidate whether a more aggressive BP-lowering strategy is associated with better or worse outcomes.

Given the high variability of BP among patients on dialysis (8), we need to know whether conventional peridialytic BP recordings are sufficient to guide the management of hypertension in this population. A small study randomized 60 patients on hemodialysis to home BP-guided versus predialysis BP-guided management of hypertension. Patients randomized to home BP-guided therapy achieved a significantly higher reduction in ambulatory systolic BP at study completion (61). Larger studies evaluating additional clinically relevant outcomes can clarify the value of home BP monitoring as a simple approach to optimize the management of hypertension in dialysis.

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See related commentary, “Commentary on Pharmacotherapy of Hypertension in Patients on Chronic Dialysis” on pages 2076–2077.

Commentary on Pharmacotherapy of Hypertension in Patients on Chronic Dialysis

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Introduction

This comprehensive review by Agarwal and Georgianos summarizes results of numerous clinical trials of antihypertensive medications in patients on chronic dialysis (1). The authors note the unique challenges of such studies in this patient population. For example, the effect of widely used, nonpharmacologic approaches to BP control, such as increased ultrafiltration and dietary sodium restriction, could easily outweigh the more modest effects on BP of pharmacologic treatments. Furthermore, there is enormous variability of BP across the interdialytic period, and uncertainty regarding the most appropriate or optimal timing of BP measurement on which to guide treatment. Acknowledging these challenges and limitations, upon their review the authors note the following key findings:

- Most clinical trials were open-label without blinding of treatment assignment.
- No trials in patients on maintenance dialysis compared different BP goals of antihypertensive pharmacologic treatment.
- Most trials utilized a placebo or “usual care” control comparator group; very few trials directly compared two or more classes of antihypertensive medications.
- Most prior trials involved small samples of patients and examined the effects on change in cardiac structure, vascular function, and/or BP. Only a few trials examined the effects of treatment on cardiovascular morbidity/mortality.
- In some trials of patients on hemodialysis with left ventricular hypertrophy or dilated cardiomyopathy, beta-blockers reduced the incidence of cardiovascular morbidity/mortality.
- Some trials demonstrated a reduction in adverse cardiovascular events with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, but other trials found no such reduction in risk with this class of antihypertensives.
- There is insufficient evidence to support the preferential use of one class of antihypertensive medications over another class.

Evaluating Clinical Trials

One useful systematic approach for evaluating clinical trials is to focus on three characteristics of study

design: the study population, the intervention, and the outcome. The study population in a clinical trial typically balances internal validity (the ability of a study to accurately answer a scientific question), with external validity (the extent to which study results can be applied to other individuals with the same general disease condition). For example, a clinical trial comparing calcium channel blockers to angiotensin-converting enzyme inhibitors might exclude dialysis patients who are obese, have obvious signs of volume overload, or are nonadherent. Such exclusions could improve internal validity by removing extraneous factors to enhance focus on the inherent biologic effects of the medications. However, excluding patients on dialysis who are obese, have clinical edema, or miss some dialysis sessions would preclude understanding of the risks and benefits of the study medications among these relatively common groups, diminishing clinical application. Because large randomized trial designs effectively balance participant characteristics across treatment groups, large pragmatic trials of BP treatments that employ broad entry criteria and simple monitoring strategies would maintain internal validity while providing the greatest impact on clinical care.

Clinical trials of medications must carefully consider the dosage and duration of the intervention to provide clear separation of treatment groups while maintaining patient safety. The numerous trials cited in this review provide ample preliminary data for choosing the correct dose and length of treatment for future large-scale clinical trials.

Ideally, trials assess the impact of a treatment on outcomes that are important to patients, such as the development of major diseases, mortality, symptoms, and quality of life. Surrogate end points are substitutes for direct measurements of how a patient feels, functions, or survives. To qualify as a surrogate end point, a characteristic or measurement must be shown to change in response to treatment in a manner that is consistent with clinical benefit. For example, in the general population, BP is an accepted surrogate end point for cardiovascular disease because antihypertensive medications lower BP while reducing the risks of stroke and heart failure. Simply demonstrating associations of a characteristic with disease risk is not sufficient to establish a surrogate

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end point for the purposes of clinical trials. For example, higher serum phosphate or hemoglobin levels are associated with greater risk of cardiovascular disease and death in patients with CKD; however, they would not be considered surrogate end points for studies of treatment of hyperphosphatemia or anemia with the intention of reducing morbidity/mortality. In fact, there are repeated examples of clinical trials in nephrology and other disciplines that demonstrated beneficial effects of an intervention on a biomarker, only to find null or harmful effects on clinical outcomes (2,3). Uncertainties regarding optimal BP targets and the most accurate methods to measure BP in patients on dialysis temper the use of BP as a surrogate end point in studies of ESRD. Future BP trials that directly assess clinical outcomes among patients on chronic dialysis would have the greatest impact on clinical care.

Disclosures

None.

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