Effect of Lisinopril and Atenolol on Aortic Stiffness in Patients on Hemodialysis

Panagiotis I. Georgianos and Rajiv Agarwal

Abstract

Background and objectives Whether improvements in arterial compliance with BP lowering are because of BP reduction alone or if pleiotropic effects of antihypertensive agents contribute remains unclear. It was hypothesized that, among patients on hemodialysis, compared with a β-blocker (atenolol), a lisinopril-based therapy will better reduce arterial stiffness.

Design, setting, participants, & measurements Among 200 participants of the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril Trial, 179 patients with valid assessment of aortic pulse wave velocity at baseline (89 patients randomly assigned to open-label lisinopril and 90 patients randomly assigned to atenolol three times a week after dialysis) were included in the secondary analysis. Among them, 109 patients had a valid pulse wave velocity measurement at 6 months. Monthly measured home BP was targeted to <140/90 mmHg by addition of antihypertensive drugs and dry weight adjustment. The difference between drugs in percentage change of aortic pulse wave velocity from baseline to 6 months was analyzed.

Results Contrary to the hypothesis, atenolol-based treatment induced greater reduction in aortic pulse wave velocity relative to lisinopril (between drug difference, 14.8%; 95% confidence interval, 1.5% to 28.5%; P=0.03). Reduction in 44-hour ambulatory systolic and diastolic BP was no different between groups (median [25th, 75th percentile]; atenolol: −21.5 [−37.7, −7.6] versus lisinopril: −15.8 [−28.8, −1.5] mmHg; P=0.27 for systolic BP; −14.1 [−22.6, −5.3] versus −10.9 [−18.4, −0.9] mmHg, respectively; P=0.30 for diastolic BP). Between-drug difference in change of aortic pulse wave velocity persisted after adjustments for age, sex, race, other cardiovascular risk factors, and baseline ambulatory systolic BP but disappeared after adjustment for change in ambulatory systolic BP (11.8%; 95% confidence interval, −2.3% to 25.9%; P=0.10).

Conclusions Among patients on dialysis, atenolol was superior in improving arterial stiffness. However, differences between atenolol and lisinopril in improving aortic stiffness among patients on hemodialysis may be explained by BP-lowering effects of drugs.

Clin J Am Soc Nephrol 10: 639–645, 2015. doi: 10.2215/CJN.09981014

Department of Medicine, Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, Indianapolis, Indiana

Correspondence: Prof. Rajiv Agarwal, Department of Medicine, Indiana University School of Medicine and Richard L. Roudebush Veterans Administration Medical Center, 1481 West 10th Street, Indianapolis, IN 46202. Email: ragarwal@iu.edu

Introduction

Among populations with elevated cardiovascular risk, people with ESRD have one of the highest rates of cardiovascular mortality. Unlike the general population, where atherosclerotic events make the bulk of the burden of cardiovascular disease, among patients with ESRD, arteriosclerosis seems to be a more important cause. Among these patients, arterial stiffening culminates in premature vascular ageing (1,2). This process is believed to be caused by long-term structural alterations of the intrinsic elastic properties of the aortic wall that culminate in profound alterations in large-artery function (1,2). Such alterations accelerate cardiovascular disease through multiple pathways, such as isolated systolic hypertension, left ventricular hypertrophy (LVH), and subendocardial hypoperfusion. It is, therefore, unsurprising that arterial stiffness represents a strong predictor of cardiovascular mortality, especially among patients with ESRD (3,4).

No medications are available that directly improve aortic compliance without altering BP. However, antihypertensive drugs improve arterial compliance and are associated with survival benefits in patients on hemodialysis, providing evidence that increased arterial rigidity is not simply a risk marker but a novel therapeutic target as well (5). Although angiotensin-converting enzyme inhibitor (ACEI) use is associated with improvement in arterial compliance, the evidence in ESRD remains from nonrandomized trials (5). Accordingly, it remains unclear whether improvement in arterial compliance is independent of BP lowering or whether it is BP mediated. To exclude a BP-mediated effect, accurate measurement of BP load is necessary. Among patients on hemodialysis in particular, interdialytic ambulatory BP is required to accurately assess the pressure burden. No previous study has used this method to establish the BP independent of drug effects. However, pleiotropic effect on vasculature may be particularly relevant for

agents blocking the renin-angiotensin-aldosterone system (RAAS); these agents inhibit the proliferative action of angiotensin II, downregulate arterial wall fibrosis and collagen synthesis, and rearrange arterial wall biomaterials in a BP-independent manner (6). These effects may be of particular benefit in delaying progression of arteriosclerosis in ESRD, where vascular aging is more pronounced than the typical age-related arterial stiffening observed in nonrenal populations (7).

Therefore, in this study, we hypothesized that an ACEI-based antihypertensive regimen will be more effective in inducing regression of aortic stiffness than the nonvasodilating β-blocker atenolol in patients with hypertension on hemodialysis over and above BP reduction measured by interdialytic ambulatory BP monitoring (ABPM).

Materials and Methods

Study Population

The design of the Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) Trial was published (8). Briefly, the HDPAL Trial was an open-label, randomized, parallel-group, active-treatment controlled trial that evaluated the effect of lisinopril versus atenolol on left ventricular mass index (LVMI) in 200 patients on hemodialysis who had hypertension confirmed by interdialytic ABPM and echocardiographic LVH. Exclusion criteria consisted of (*1*) chronic atrial fibrillation, (*2*) body mass index $\geq$40 kg/m^2, (*3*) history of nonadherence to the weekly dialysis schedule in the previous month, (*4*) severe chronic obstructive pulmonary disease, (*5*) history of stroke or myocardial infarction during the previous 6 months, (*6*) known contraindication to atenolol or lisinopril, or (*7*) known drug abuse. The primary outcome of the HDPAL Trial was the difference between the atenolol and lisinopril groups in change of LVMI from baseline to 12 months; study results on the primary end point were previously published (8).

The study was carried out from August of 2005 to September of 2013 in four dialysis centers affiliated with Indiana University. Protocol procedures were conducted in accordance with the Declaration of Helsinki (2000 Amendment), and all patients provided informed written consent before study enrollment. The study was approved by the Institutional Review Board of Indiana University and the Research and Development Committee of the Roudebush Veterans Affairs Medical Center.

Study Design

Run-In Washout Period. Before randomized drug assignment, patients were inserted in a 3-week run-in period, during which previous antihypertensive medications, if any, were tapered; patients were asked to monitor their home BP during 4 consecutive days of each week up to a maximum of 3 weeks to determine their hypertension status. Withdrawal of antihypertensive medications was stopped in case of a rise in home BP >160/100 mmHg, and then, 44-hour interdialytic ABPM was performed. Diagnosis of hypertension was confirmed when mean 44-hour ambulatory BP was $\geq$135/85 mmHg. However, after an episode of stroke shortly after washout, the protocol was amended, and drug removal was performed only when treated home BP was $\leq$150/90 mmHg or ambulatory BP remained normal after tapering antihypertensive drugs. To confirm diagnosis of LVH, two-dimensional guided M-mode echocardiograms were performed immediately postdialysis with a digital cardiac ultrasound device (Cypress Acuson; Siemens Medical). LVMI$\geq$104 g/m^2 in women and $\geq$116 g/m^2 in men were considered diagnostic of LVH according to standard criteria of the American Society of Echocardiography (9).

Drug Assignment. Eligible patients were randomized in a 1:1 ratio to receive open-label atenolol or lisinopril three times a week (TIW) postdialysis for 12 months with the aim of reaching home BP $\leq$140/90 mmHg. Randomization was performed using a random permuted block design, and computer-generated random sequence was used for allocation concealment. Initial drug doses were selected according to baseline ABPM. If 44-hour ambulatory BP was ranging from 135 to 154 mmHg for systolic BP (SBP) and from 85 to 94 mmHg for diastolic BP (DBP), patients were administered atenolol at 25 mg or lisinopril at 10 mg TIW. Initial doses were doubled every 2–4 weeks up to a maximum dose of 100 mg TIW for atenolol and 40 mg TIW for lisinopril. In case of uncontrolled home BP during the monthly follow-up visits, felodipine or amlodipine at 10 mg one time daily was added followed by other antihypertensive medications in the following order: doxazosin, minoxidil, and guanfacine. If baseline ambulatory BP was $\geq$155/95 mmHg, atenolol and lisinopril were started at maximal doses. Off-study administration of RAAS inhibitors and β-blockers was prohibited. Assessment of dry weight during follow-up was on the basis of the clinical judgment of the investigator.

Outcome. This paper is a secondary analysis of the HDPAL Trial aiming to explore the difference between the atenolol and lisinopril groups in change of aortic pulse wave velocity (PWV) from baseline to 6 months. The outcome was evaluated at 6 months because of the early termination of the trial that resulted in insufficient PWV data at the 12-month visit. Among 179 patients included in analysis, 109 participants at the 6-month visit had valid PWV measurements; of these, PWV data were available only for 79 patients at 12 months.

Study Evaluations

Aortic PWV. Arterial stiffness was assessed by measuring aortic PWV through direct visualization of the central aorta with an echo-Doppler technique (10). Flow pulse was recorded by continuous Doppler from the root of the left subclavian artery and just proximal to the bifurcation of the abdominal aorta with simultaneous electrocardiographic recording. The distance (D) from the suprasternal notch to the recording site of aortic signal was used to estimate the length of the descending aorta. Time elapsed (t) from the peak of the R wave to the foot of the systolic impulse was recorded over six beats (10). Aortic PWV was calculated as PWV=D/t by dividing the length of central aorta by the transit time. Measurements were performed over six consecutive cardiac cycles, and the average of these six recordings was used to maintain the quality of PWV assessment at baseline and 6-month visits.

Ambulatory BP Monitoring. ABPM was performed with a Spacelab 90207 monitor (SpaceLabs Medical, Redmond, Washington) for 44 hours, including a whole interdialytic

period after the midweek dialysis. The monitor was set to obtain recordings three times hourly from 06:00 to 21:59 (daytime) and two times hourly from 22:00 to 05:59 (nighttime). Measurements were used in analysis only if >80% of recordings were valid with ≤2 nonconsecutive day hours with fewer than two valid measurements and ≤1 night hour without valid recording according to standard recommendations for ABPM (11). Ambulatory BP was recorded at baseline evaluation and repeated at 6 months.

Statistical Analyses

Continuous variables were expressed as means±SDs, and categorical variables were expressed as absolutes frequencies and percentages. Comparison of demographic, clinical, and hemodynamic parameters between the atenolol and lisinopril groups was performed with regression analyses for continuous data and chi-squared tests for categorical data.

The primary statistical method was mixed linear modeling using fixed and random effects. In the initial unadjusted model, the outcome variable was aortic PWV (natural log transformed to approximate a normal distribution). Independent fixed predictors were visit (as indicator variable), treatment arm (atenolol or lisinopril), and the interaction of the two terms. The random intercept component was the subject, and random slopes were the visits; maximal likelihood estimates were used for estimation of marginal means. Because of skewed distribution, aortic PWV is expressed as the geometric mean (95% confidence interval [95% CI]) in mixed models, and treatment-induced changes in PWV are expressed as proportional (%) changes from baseline to 6 months.

To explore whether the difference between drugs in change of PWV would persist after controlling for potential confounders, we built additional adjusted models in a stepwise manner. First, we performed adjustments for age, sex, and race (black or nonblack; model 1); second, we adjusted for smoking, diabetes, and history of preexisting cardiovascular disease (defined as stroke, myocardial infarction, coronary revascularization, and hospitalized heart failure; model 2). In subsequent models, we controlled for the effect of ambulatory SBP at baseline (model 3) and the treatment-induced change in ambulatory SBP during follow-up (model 4) to examine whether regression of aortic stiffness was attributable to BP lowering. Subsequently, each of these models was further adjusted for baseline 44-hour heart rate and treatment-induced reduction in 44-hour heart rate to explore whether long-term heart rate control with β-blockade was a mediator of improvement in aortic PWV.

Statistical analysis was performed with Stata, version 11.2 (Stata Corp., College Station, Texas). A two-sided P value of <0.05 was considered statistically significant.

Results

Baseline Characteristics of Study Participants

The trial flow was previously described (8). Among 200 randomized enrolled participants in the HDPAL Trial from August of 2005 to September of 2013, 17 participants did not have their PWV assessed, and four participants had technically inadequate measurement at baseline; thus, 179 patients with hypertension on hemodialysis with a complete dataset on baseline aortic PWV were included in the analysis. Among them, 109 patients had measurements of PWV at 6 months, of whom 60 participants were in the atenolol group and 49 participants were in the lisinopril group. The remaining 70 patients were withdrawn from the analysis for the following reasons: (*1*) 20 patients withdrew consent, (*2*) 11 patients did not have PWV measurements at the 6-month visit, (*3*) seven patients died, (*4*) six patients moved out, (*5*) four patients were removed by the investigator, (*6*) one patient was switched to peritoneal dialysis, (*7*) one patient was transplanted, and (*8*) 20 patients were not assessed because of early trial termination. Patients without PWV measurement at the 6-month visit did not differ from study completers in the atenolol and lisinopril groups in terms of demographic and clinical characteristics (data not shown).

Baseline characteristics of study participants in the atenolol and lisinopril groups are depicted in Table 1. The study population consisted of 119 men and 60 women who were predominantly black in race (87.2%) with mean age of 52.1±12.4 years old receiving hemodialysis for a median period of 2.5 years. Study groups were balanced at baseline in terms of age, race, body mass index, dialysis vintage, smoking, and diabetic status, although the lisinopril group had more women and higher proportions of hospitalized heart failure and coronary revascularization (Table 1).

Background Antihypertensive Treatment and Ambulatory BP at Baseline and over Time

The number and type of previous antihypertensive medications of study participants are presented in Table 2. Before any washout, most patients (96.4%) were treated for hypertension. RAAS inhibitors and β-blockers were the most commonly prescribed antihypertensive drug classes. The number and nature of background antihypertensive medications were evenly distributed in both study groups.

Mean 44-hour ambulatory SBP, DBP, pulse pressure, and 44-hour heart rate at baseline did not significantly differ between the two groups (Table 2). Changes from baseline to 6 months in ambulatory SBP and DBP were no different in the atenolol group relative to the lisinopril group. As expected, atenolol induced a significantly greater decrease in 44-hour heart rate at 6 months relative to lisinopril (−7.6±11.8 versus +3.±10.3 bpm; $P<0.001$) (Table 2).

Drug Effects on Aortic PWV

Table 3 shows the results of the atenolol- and lisinopril-based therapies on PWV. In unadjusted analysis, among patients treated with atenolol, aortic PWV was significantly reduced from baseline to 6 months by 9.3%; in contrast, no significant change was evident during follow-up within the lisinopril group. Between-group difference of 14.8% (95% CI, 1.5% to 28.5%; $P=0.03$) was evident. When this model was adjusted for baseline 44-hour heart rate and treatment-induced change of 44-hour heart rate, between-drug difference in percentage change of aortic PWV was even higher (20.7%; 95% CI, 5.4% to 36.1%; $P<0.01$) (Table 3).

This significant aortic PWV reduction in favor of the atenolol-based regimen persisted after adjustment for age,

Table 1. Baseline characteristics of study participants

Clinical Characteristic	Atenolol	Lisinopril	Overall	*P* Value
n	90	89	179	
Pulse wave velocity (m/s)	7.7±2.6	7.5±2.8	7.6±2.7	0.72
Age (yr)	51.7±11.6	52.6±13.3	52.1±12.4	0.60
Men, *n* (%)	67 (74.4)	52 (58.4)	119 (66.5)	0.02
Black race, *n* (%)	76 (84.4)	80 (89.9)	156 (87.2)	0.28
Hispanic race, *n* (%)	1 (1.1)	0 (0)	1 (0.6)	0.32
Dialysis vintage (yr)	3 (1, 6)	2 (1, 6)	2.5 (1, 6)	0.55
Anuric, *n* (%)	60 (66.7)	59 (66.3)	119 (66.5)	0.96
Diabetes mellitus, *n* (%)	39 (43.3)	36 (40.4)	75 (41.9)	0.70
Hospitalized heart failure, *n* (%)	19 (21.1)	33 (37.1)	52 (29.1)	0.02
Coronary artery disease, *n* (%)	18 (20)	26 (29.2)	44 (24.6)	0.15
Coronary revascularization, *n* (%)	2 (2.2)	11 (12.4)	13 (7.3)	<0.01
Cerebrovascular disease, *n* (%)	11 (12.2)	18 (20.2)	29 (16.2)	0.15
Peripheral vascular disease, *n* (%)	8 (8.9)	9 (10.1)	17 (9.5)	0.78
Smoking, *n* (%)	39 (43.3)	41 (46.1)	80 (44.7)	0.71
Height (in)	68.4±4.1	67.6±3.6	68±3.9	0.20
Weight (kg)	85±22.5	79.6±24.3	82.3±23.5	0.13
Body mass index (kg/m^2)	28.2±7.2	27.1±8.5	27.7±7.9	0.34
Access type, *n* (%)				0.76
Fistula	53 (58.9)	52 (58.4)	105 (58.7)	0.95
Graft	14 (15.6)	11 (12.4)	25 (14)	0.54
Catheter	23 (25.6)	26 (29.2)	49 (27.4)	0.58
Delivered dialysis duration (min)	225.1±35.3	219.5±34.9	222.4±35.1	0.28
Albumin (g/dl)	3.6±0.5	3.6±0.5	3.6±0.5	0.53
Hemoglobin (g/dl)	11.3±1.2	11.4±1.4	11.3±1.3	0.63

Data are presented as mean±SD or *n* (%) with the exception of dialysis vintage, which is presented as median (25th, 75th percentile).

sex, and race (between-drug difference, 15%; 95% CI, 0.8% to 27.7%; *P*=0.03) and even additional adjustments for diabetic status, smoking, history of preexisting cardiovascular disease, and baseline 44-hour ambulatory SBP (14.1%; 95% CI, 0.6% to 27.6%; *P*=0.04). However, when change of 44-hour ambulatory SBP during follow-up was included in the multivariate model, between-drug difference in percentage change of aortic PWV disappeared (11.8%; 95% CI, −2.3% to 25.9%; *P*=0.10). Additional adjustment of these models for baseline 44-hour heart rate and its change over 6 months did not mitigate the between-drug difference in percentage change of aortic PWV (Table 3).

Discussion

This analysis aimed to compare the effect of lisinopril with that of atenolol on aortic PWV among patients with hypertension on hemodialysis and evaluate whether treatment-induced regression in aortic stiffness could be explained by the presence of cardiovascular risk factors and BP reduction. The main findings of this study were as follows. (*1*) Compared with lisinopril, atenolol treatment for 6 months was associated with an approximately 15% greater reduction in aortic PWV. (*2*) This difference between the two regimens persisted after controlling for age, sex, race, diabetes, smoking, history of previous cardiovascular disease, and baseline ambulatory SBP. (*3*) However, additional adjustments for the reduction in ambulatory SBP after treatment removed the between-group differences in change of PWV.

Contrary to our hypothesis that an ACEI-based regimen would confer benefits on structure and function of large arteries through pleiotropic actions on arterial wall remodeling, the findings of our study suggest that the major mediator of regression in arterial stiffness was the more effective BP lowering with atenolol treatment. Indeed, changes in BP over 6 months were, if anything, numerically higher in the atenolol group relative to the lisinopril group. Of note, we confirmed BP control with ABPM during the interdialytic period, which is considered the most reliable method of BP assessment in hemodialysis (12,13). Although ambulatory BP between groups was no different, superiority of atenolol over lisinopril in improving BP control is supported by the fact that patients treated with lisinopril in the HDPAL Trial required more aggressive volume management and higher numbers of antihypertensive drugs.

Another mechanistic pathway through which atenolol is proposed to reduce aortic PWV is the interaction of slowing heart rate with the viscoelastic behavior of the aortic wall (14). Several studies have shown that atrial pacing–induced increase in heart rate is accompanied by elevation in aortic PWV, mainly because of the arterial wall viscosity phenomenon (15,16). Unlike the acute interaction between heart rate and PWV and although long-term reduction in heart rate under β-blockade is suggested to promote remodeling of the aortic wall through reduction in mechanical wall stress, this analysis showed that additional adjustment of models for baseline 44-hour heart rate and its longitudinal change did not mitigate the between-drug

Table 2. Previous antihypertensive treatment and 44-hour ambulatory BP levels at baseline and their change over time in the atenolol and lisinopril groups

Parameter	Atenolol	Lisinopril	Overall	*P* Value
n	90	89	179	
Antihypertensive drugs, *n*	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.97
No antihypertensive drug, *n* (%)	5 (5.6)	1 (1.1)	6 (3.4)	0.10
ACEIs, *n* (%)	52 (57.8)	62 (69.7)	114 (63.7)	0.10
ARBs, *n* (%)	12 (13.3)	7 (7.9)	19 (10.6)	0.24
β-Blockers, *n* (%)	72 (80)	65 (73)	137 (76.5)	0.27
α-Blockers, *n* (%)	12 (13.3)	7 (7.9)	19 (10.6)	0.24
Centrally acting agents, *n* (%)	29 (32.2)	31 (34.8)	60 (33.5)	0.71
Nondihydropydine CCBs, *n* (%)	2 (2.2)	6 (6.7)	8 (4.5)	0.14
Dihydropydine CCBs, *n* (%)	44 (48.9)	45 (50.6)	89 (49.7)	0.82
Vasodilators, *n* (%)	22 (24.4)	22 (24.7)	44 (24.6)	0.97
Loop diuretics, *n* (%)	2 (2.2)	0 (0)	2 (1.1)	0.16
Baseline systolic BP (44 h; mmHg)	151.9±14.4	151.5±14.7	151.7±14.5	0.85
Baseline diastolic BP (44 h; mmHg)	87.7±11.1	87.9±12.6	87.8±11.8	0.91
Baseline pulse pressure (44 h; mmHg)	64.2±13.5	63.6±13.8	63.9±13.6	0.77
Heart rate (44 h; bpm)	81.4±11.9	79.9±12.1	80.6±12	0.42
Systolic BP change at 6 mo (44 h; mmHg)	−21.5 (−37.7, −7.6)	−15.8 (−28.8, −1.5)	−17.9 (−34.7, −4.2)	0.27
Diastolic BP change at 6 mo (44 h; mmHg)	−14.1 (−22.6, −5.3)	−10.9 (−18.4, −0.9)	−13.1 (−20.6, −1.4)	0.30
Pulse pressure change at 6 mo (44 h; mmHg)	−5.7 (−15.0, −1.1)	−5.8 (−11.2, 1.1)	−5.8 (−13.1, 0.7)	0.38
Heart rate change at 6 mo (44 h; bpm)	−7.6±11.8	3.6±10.3	−2.2±12.4	<0.001

Data are presented as mean±SD or *n* (%) with the exceptions of antihypertensive drugs, systolic BP, diastolic BP, and pulse pressure changes at 6 months, which are presented as median (25th, 75th percentile). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

difference in change of aortic PWV over 6 months. An alternative explanation could be downregulation of sympathetic vascular tone induced by atenolol treatment. Overactivation of the sympathetic nervous system is a typical feature and prominent player in the pathogenesis of hypertension and represents a well documented cardiovascular risk factor among patients on hemodialysis (17,18). Recent studies have shown a BP-independent association between muscular nerve sympathetic activity and aortic PWV (19,20), suggesting that suppression of sympathetic nervous system under β-blockade could be a functional regulator of regression in arterial stiffness.

In addition to the above, the results of this study are supported by several randomized studies conducted in the general hypertensive population, in which nonvasodilating β-blockers reduced PWV to a similar (21–23) or even higher (24,25) extent than vasodilating agents, especially when BP was lowered to the same degree in different treatment arms. In the Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study, Asmar *et al.* (21) randomized 471 patients with hypertension to the combination of the ACEI perindopril and a very low dose of indapamide or atenolol. After 12 months, both regimens caused equal reductions in aortic PWV (−0.79±1.91 versus −0.99±2.05; *P*=0.26), despite the more pronounced drop of mean BP in the group of perindopril/indapamide (21). Similarly, in a subgroup of 114 patients with hypertension participating in the Conduit Artery Function Evaluation Study, treatment for almost 5 years with the perindopril/amlodipine combination lowered aortic PWV to a similar extent as the atenolol/thiazide regimen (23). In a recent meta-analysis of nine randomized, controlled trials including 378 patients with hypertension, treatment with ACEIs did not significantly reduce PWV relative to other antihypertensive drug classes (pooled mean change difference between ACEI and non-ACEI groups: −0.19 m/s; 95% CI, −0.59 to 0.21; *P*=0.36) (26).

There are several strengths and limitations of our study. Strengths of this randomized, controlled study were the echocardiographic determination of PWV in the elastic part of the descending aorta in contrast to the tonometric method for estimating carotid-to-femoral PWV that also includes muscular-type arterial segments. Another notable advantage was the use of the most reliable technique of ABPM (12,13) to assess efficacy of randomized drugs in improving BP control. However, this study also had some limitations. First, this study did not include determination of central aortic pressures and wave reflection indices, which are also important components of arterial cushioning function. Whether an atenolol-induced decrease in aortic stiffness is also translated into a benefit on central hemodynamics cannot be answered by this trial. Second,

Table 3. Progressively adjusted models of change in aortic pulse wave velocity from baseline to 6 months (*n*=109)

Model	Geometric Mean (95% Confidence Interval)	Percentage Change from Baseline (95% Confidence Interval)	*P* Value of Change
Unadjusted			
Atenolol	7.23 (6.74 to 7.76)	−9.3 (−18.5 to −0.2)	0.04
Lisinopril	7.06 (6.57 to 7.58)	5.5 (−4.6 to 15.6)	0.28
Between-drug difference	−0.06 (−0.13 to 0.08)	14.8 (1.2 to 28.5)	0.03
Heart rate–adjusted between-drug difference	−0.02 (−0.12 to 0.08)	20.7 (5.4 to 36.1)	<0.01
Model 1: Age, sex, and race adjusted			
Atenolol	4.95 (3.89 to 6.29)	−9.3 (−18.4 to −0.2)	0.04
Lisinopril	4.83 (3.79 to 6.15)	5.7 (−4.3 to 15.7)	0.26
Between-drug difference	−0.02 (−0.12 to 0.07)	15 (1.5 to 28.5)	0.03
Heart rate–adjusted between–drug difference	−0.02 (−0.15 to 0.07)	18.5 (3.3 to 33.7)	0.02
Model 2: Plus diabetes, CVD, and smoking adjusted			
Atenolol	4.8 (3.75 to 6.14)	−8.7 (−17.7 to 0.4)	0.06
Lisinopril	4.75 (3.71 to 6.09)	5.6 (−4.3 to 15.5)	0.27
Between-drug difference	−0.01 (−0.10 to 0.08)	14.3 (0.8 to 27.7)	0.04
Heart rate–adjusted between-drug difference	−0.01 (−0.10 to 0.09)	17.2 (2.1 to 32.2)	0.03
Model 3: Plus baseline ambulatory SBP adjusted			
Atenolol	2.9 (1.74 to 4.85)	−8.5 (−17.5 to 0.6)	0.07
Lisinopril	2.88 (1.72 to 4.8)	5.6 (−4.3 to 15.6)	0.27
Between-drug difference	−0.01 (−0.10 to 0.08)	14.1 (0.6 to 27.6)	0.04
Heart rate–adjusted between-drug difference	−0.01 (−0.10 to 0.09)	16.9 (1.7 to 32.0)	0.03
Model 4: Plus change in ambulatory SBP adjusted			
Atenolol	2.6 (1.54 to 4.36)	0.1 (−11.4 to 11.6)	0.99
Lisinopril	2.57 (1.53 to 4.33)	11.8 (0.6 to 23)	0.04
Between-drug difference	−0.01 (−0.10 to 0.08)	11.8 (−2.3 to 25.9)	0.10
Heart rate–adjusted between-drug difference	−0.01 (−0.10 to 0.09)	14.6 (−0.3 to 29.5)	0.06

Heart rate adjusted between drug differences indicates additional adjustment of each of the models for (*1*) baseline 44-hour heart rate and (*2*) treatment-induced change in 44-hour heart rate from baseline to 6 months. CVD, cardiovascular disease; SBP, systolic BP.

change from baseline in aortic PWV was not the primary outcome of the HDPAL Trial; thus, no power estimation for this efficacy end point was performed before study initiation. However, we believe that the number of patients studied (179 participants in the HDPAL Trial) provided adequate power to detect a difference between drugs in change of aortic PWV over 6 months. Furthermore, premature termination of the HDPAL Trial did not allow evaluation of this efficacy end point at the prespecified 12-month follow-up period; thus, future studies with longer follow-up are needed to confirm these findings. Third, the study population consisted of patients predominantly black in race; whether these results can be extrapolated to patient populations with different racial and ethnic characteristics remains unknown.

In conclusion, among patients with hypertension on hemodialysis, treatment with atenolol for 6 months resulted in a greater reduction of aortic PWV relative to an ACEI-based regimen. This beneficial effect of atenolol was predominantly mediated through more effective BP lowering, suggesting that adequate BP control is the major therapeutic strategy toward delaying the progression of arteriosclerosis in hemodialysis. Future studies are warranted to elucidate whether this effect on arterial stiffness confers benefits in cardiovascular risk reduction.

Acknowledgments

This work was supported by National Institutes of Health Grant 2R01-DK062030-10 and funded by the National Institute of Diabetes and Digestive and Kidney Diseases.

Disclosures

None.

References

1. Briet M, Boutouyrie P, Laurent S, London GM: Arterial stiffness and pulse pressure in CKD and ESRD. *Kidney Int* 82: 388–400, 2012
2. Taal MW: Arterial stiffness in chronic kidney disease: An update. *Curr Opin Nephrol Hypertens* 23: 169–173, 2014
3. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 99: 2434–2439, 1999
4. Georgianos PI, Sarafidis PA, Lasaridis AN: Arterial stiffness: A novel cardiovascular risk factor in kidney disease patients [published online ahead of print Sebtember 3, 2013]. *Curr Vasc Pharmacol* 10.2174/15701611113119990147
5. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM: Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 103: 987–992, 2001
6. Safar ME: Can antihypertensive treatment reverse large-artery stiffening? *Curr Hypertens Rep* 12: 47–51, 2010
7. Agarwal R: Antihypertensive agents and arterial stiffness: Relevance to reducing cardiovascular risk in the chronic kidney disease patient. *Curr Opin Nephrol Hypertens* 16: 409–415, 2007

8. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG: Hypertension in hemodialysis patients treated with atenolol or lisinopril: A randomized controlled trial. *Nephrol Dial Transplant* 29: 672–681, 2014
9. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N: Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. *Am J Cardiol* 57: 450–458, 1986
10. Lehmann ED, Riley WA, Clarkson P, Gosling RG: Non-invasive assessment of cardiovascular disease in diabetes mellitus. *Lancet* 350[Suppl 1]: SI14–SI19, 1997
11. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, Clement D, de la Sierra A, de Leeuw P, Dolan E, Fagard R, Graves J, Head GA, Imai Y, Kario K, Lurbe E, Mallion JM, Mancia G, Mengden T, Myers M, Ogedegbe G, Ohkubo T, Omboni S, Palatini P, Redon J, Ruilope LM, Shennan A, Staessen JA, vanMontfrans G, Verdecchia P, Waeber B, Wang J, Zanchetti A, Zhang Y; European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability: European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. *J Hypertens* 32: 1359–1366, 2014
12. Agarwal R, Flynn J, Pogue V, Rahman M, Reisin E, Weir MR: Assessment and management of hypertension in patients on dialysis. *J Am Soc Nephrol* 25: 1630–1646, 2014
13. Sinha AD, Agarwal R: Peridialytic, intradialytic, and interdialytic blood pressure measurement in hemodialysis patients. *Am J Kidney Dis* 54: 788–791, 2009
14. Rhee MY, Kwon NY, Kim JD, Song SH, Yoon YW, Lee MY, Kim YK: Do acute changes in heart rate by isoproterenol affect aortic stiffness in patients with hypertension? *Korean J Intern Med* 19: 33–37, 2004
15. Tan I, Butlin M, Liu YY, Ng K, Avolio AP: Heart rate dependence of aortic pulse wave velocity at different arterial pressures in rats. *Hypertension* 60: 528–533, 2012
16. Wilkinson IB, Mohammad NH, Tyrrell S, Hall IR, Webb DJ, Paul VE, Levy T, Cockcroft JR: Heart rate dependency of pulse pressure amplification and arterial stiffness. *Am J Hypertens* 15: 24–30, 2002
17. Hausberg M, Kosch M, Harmelink P, Barenbrock M, Hohage H, Kisters K, Dietl KH, Rahn KH: Sympathetic nerve activity in end-stage renal disease. *Circulation* 106: 1974–1979, 2002
18. Zoccali C, Mallamaci F, Parlongo S, Cutrupi S, Benedetto FA, Tripepi G, Bonanno G, Rapisarda F, Fatuzzo P, Seminara G, Cataliotti A, Stancanelli B, Malatino LS: Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. *Circulation* 105: 1354–1359, 2002
19. Casey DP, Curry TB, Joyner MJ, Charkoudian N, Hart EC: Relationship between muscle sympathetic nerve activity and aortic wave reflection characteristics in young men and women. *Hypertension* 57: 421–427, 2011
20. Swierblewska E, Hering D, Kara T, Kunicka K, Kruszewski P, Bieniaszewski L, Boutouyrie P, Somers VK, Narkiewicz K: An independent relationship between muscle sympathetic nerve activity and pulse wave velocity in normal humans. *J Hypertens* 28: 979–984, 2010
21. Asmar RG, London GM, O'Rourke ME, Safar ME; REASON Project Coordinators and Investigators: Improvement in blood pressure, arterial stiffness and wave reflections with a very-low-dose perindopril/indapamide combination in hypertensive patient: A comparison with atenolol. *Hypertension* 38: 922–926, 2001
22. Boutouyrie P, Achouba A, Trunet P, Laurent S; EXPLOR Trialist Group: Amlodipine-valsartan combination decreases central systolic blood pressure more effectively than the amlodipine-atenolol combination: The EXPLOR study. *Hypertension* 55: 1314–1322, 2010
23. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M; CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee: Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: Principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 113: 1213–1225, 2006
24. Dhakam Z, McEniery CM, Yasmin, Cockcroft JR, Brown MJ, Wilkinson IB: Atenolol and eprosartan: Differential effects on central blood pressure and aortic pulse wave velocity. *Am J Hypertens* 19: 214–219, 2006
25. Pannier BM, Guerin AP, Marchais SJ, London GM: Different aortic reflection wave responses following long-term angiotensin-converting enzyme inhibition and beta-blocker in essential hypertension. *Clin Exp Pharmacol Physiol* 28: 1074–1077, 2001
26. Shahin Y, Khan JA, Chetter I: Angiotensin converting enzyme inhibitors effect on arterial stiffness and wave reflections: A meta-analysis and meta-regression of randomised controlled trials. *Atherosclerosis* 221: 18–33, 2012

Received: October 7, 2014 **Accepted:** January 5, 2015

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "Reducing Arterial Stiffness in CKD: Revising the Paradigms," on pages 547–550.