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Association Between Pulse Pressure and Mortality in Patients Undergoing Maintenance Hemodialysis

Preston S. Klassen, MD, MHS

Edmund G. Lowrie, MD

Donal N. Reddan, MB, MRCPI, MHS

Elizabeth R. DeLong, PhD

Joseph A. Coladonato, MD

Lynda A. Szczech, MD

J. Michael Lazarus, MD

William F. Owen, Jr, MD

HYPERTENSION IS AN IMPORTANT predictor of subsequent adverse clinical outcomes in the general population.¹⁻³ Information from cross-sectional and longitudinal cohort studies as well as interventional trials has been used to identify normal and optimal levels of blood pressure for healthy adults and specific at-risk populations, including patients with chronic kidney disease.^{1,3-7} Application of such outcome-derived management criteria to patients with end-stage renal disease (ESRD) treated by maintenance dialysis is hindered by counterintuitive epidemiological relationships between blood pressure and clinical events. A number of observational cohort studies have reported U-shaped or reverse-J relationships between conventional blood pressure measures (systolic, diastolic, and mean arterial) and mortality in patients undergoing hemodialysis.⁸⁻¹¹ These investigations report that patients receiving dialysis with systolic blood pressures between 140 and 175 mm Hg have improved survival com-

Context Although increased blood pressure is associated with adverse outcomes in the general population, elevated blood pressure is associated with decreased mortality in patients with end-stage renal disease undergoing maintenance hemodialysis. Recent investigations in the general population have demonstrated the predictive utility of pulse pressure (systolic minus diastolic blood pressure), a measure reflecting the pulsatile nature of the cardiac cycle.

Objectives To estimate the relationship between pulse pressure and mortality in patients undergoing maintenance hemodialysis and to test our hypothesis that an increasing pulse pressure would be associated with increased risk of death up to 1 year despite the inverse relationship between conventional blood pressure measures and mortality in patients with end-stage renal disease.

Design, Setting, and Patients Retrospective cohort investigation of patients with end-stage renal disease undergoing maintenance hemodialysis at 782 hemodialysis facilities throughout the United States. Of 44 069 eligible patients as of January 1, 1998, 37 069 with complete demographic data were included in the analyses of clinical and laboratory data collected from October 1 through December 31, 1997. Patients were followed up through December 31, 1998.

Main Outcome Measures The primary study outcome was death at 1 year. A secondary outcome was the magnitude of the pulse pressure.

Results The final patient cohort was similar to national averages with respect to age, sex, race, and diabetic status. Mean (SD) pulse pressures before dialysis were 75.0 (15.0) mm Hg and 66.9 (13.9) mm Hg after dialysis. By the end of the 1-year follow-up, 5731 patients (18.4%) died. After adjusting for level of systolic blood pressure, multivariable Cox proportional hazards modeling showed a direct and consistent relationship between increasing pulse pressure and increasing death risk. Each incremental elevation of 10 mm Hg in postdialysis pulse pressure was associated with a 12% increase in the hazard for death (hazard ratio, 1.12; 95% confidence interval, 1.06-1.18). Postdialysis systolic blood pressure was inversely related to mortality with a 13% decreased hazard for death for each incremental elevation of 10 mm Hg (hazard ratio, 0.87; 95% confidence interval, 0.84-0.90). In a multivariable linear regression model, important variables directly associated with elevated pulse pressure included age, diabetes, white race, female sex, and number of years receiving dialysis (all $P < .001$).

Conclusions Pulse pressure is associated with risk of death in a large, nationally representative sample of patients undergoing maintenance hemodialysis. The recognition of pulse pressure as an important correlate of mortality in patients receiving dialysis highlights the need to investigate the relationship between potential therapeutic implications of conduit vessel function and clinical outcomes in patients with end-stage renal disease.

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Author Affiliations are listed at the end of this article.
Corresponding Author and Reprints: Preston S. Klassen, MD, MHS, Duke Institute of Renal Outcomes

Research and Health Policy, Box 3646, Duke University Medical Center, Durham, NC 27710 (e-mail: klass001@mc.duke.edu).

pared with those whose systolic pressures are lower than 140 mm Hg.

Investigations of hypertension generally focus on the steady components of blood pressure, such as mean arterial pressure (MAP), which is determined by cardiac output and peripheral vascular resistance.¹²⁻¹⁴ However, there is increasing evidence that the oscillating pulsatile nature of the cardiac cycle can also provide important information about the cardiovascular risk conferred by hypertension, particularly in middle-aged and elderly populations.¹⁵⁻¹⁹ This pulsatile component of blood pressure is governed by the relationship between ventricular ejection and viscoelastic properties of large arteries (arterial stiffness), as well as the indirect effect of arterial wave reflection from the periphery back to central conduit arteries. Pulse pressure (systolic minus diastolic blood pressures) is an index of the pulsatile component of the cardiac cycle.¹⁴ Data from large prospective cohort and interventional trials have been used to investigate relationships between pulse pressure and clinical events in non-ESRD populations. These studies have correlated increased pulse pressure with heart failure, myocardial infarction, and all-cause and cardiovascular death.^{15,17,18,20,21}

Patients with ESRD exhibit vascular abnormalities that contribute to elevated pulse pressure, including increased arterial stiffness, pulse-wave velocity, and early wave reflection.^{22,23} These vascular abnormalities have been associated with all-cause and cardiovascular mortality in small studies using noninvasive vascular imaging and continuous ambulatory blood pressure monitoring.^{24,25} Pulse pressure has been related to all-cause and cardiovascular mortality in nondiabetic Japanese patients receiving dialysis.²⁶ The relatively small population in that study did not exhibit the inverse relationship between systolic blood pressure and death that is typically seen in large dialysis cohorts in the United States. Given that epidemiological associations of conventional blood pressure measures with clinical events appear to be different between ESRD

patients in the United States and the general population, this study was conducted to examine the relationship between pulse pressure and mortality in a large, national sample of patients undergoing maintenance hemodialysis.

METHODS

Patients and Measurements

The study population included 44 069 patients undergoing maintenance hemodialysis during 1998 at 782 facilities operated by Fresenius Medical Care, North America, based in Lexington, Mass.²⁷ Patients with complete data for sex, race, diabetic status, and body size measures (height and weight) were included (n=37 069).

Demographic, clinical, and laboratory data were collected on all patients during the months of October, November, and December 1997. Repeated measures, including blood pressure, dialysis dose, and laboratory measurements were averaged over the entire 3 months of data collection. Patients were followed up until December 31, 1998. Patients who left the facilities or received a kidney transplantation were censored. Date of death or censoring was recorded for time-to-event analysis of all-cause mortality.

Demographic and clinical parameters recorded included age, sex, race, diabetic status (defined either as a comorbid condition or as the etiology of ESRD), years receiving dialysis prior to entry into the study, height, and weight before and after dialysis treatment initiation. Dose of hemodialysis was quantified as the fractional decline in blood urea nitrogen concentration during a single dialysis treatment (urea reduction ratio). The volume of fluid removed during dialysis was expressed as a percentage of postdialysis weight (intradialytic volume change). Systolic and diastolic blood pressures were recorded both before and after dialysis sessions and were measured, by trained health care professionals or automated monitors, with patients in a sitting position. Pulse pressure was quantified as the difference between average systolic and average diastolic pressures over the

data collection period. Laboratory data included predialysis hematocrit, albumin, creatinine, calcium, phosphorous, parathyroid hormone (PTH), and ferritin concentrations. All measurements were determined in a single laboratory (Spectra Laboratories, Rockleigh, NJ).

Statistical Analysis

The clinical and demographic characteristics including measures of systolic, diastolic, and pulse pressure were described for the cohort overall. Univariate analyses estimated the associations between pulse pressure and demographic, clinical, and laboratory parameters, using the *t* test and linear regression for categorical and continuous parameters, respectively. To determine independent associations, multivariable linear regression estimated the relationship between pulse pressure and the parameters described above.

Associations with mortality to 1 year were estimated using Cox proportional hazards regression. To confirm that this cohort exhibited the anticipated inverse relationship between conventional blood pressure measures and mortality, the association between systolic blood pressure and death was estimated in an unadjusted model. Pulse pressure was subsequently examined in both unadjusted and adjusted models built using stepwise methods. Models were also created to examine other single-blood pressure components and dual-blood pressure component pairs. Interactions between pulse pressure and age, sex, race, diabetic status, and level of systolic blood pressure were tested. Finally, individual subjects were categorized according to level of both systolic blood pressure and pulse pressure. The percentage of subjects dead at 1 year was calculated for each category, and the results were graphically displayed.

All *P* values are 2-sided. Analyses were performed using SAS software (version 8.1, SAS Institute, Cary, NC).

RESULTS

Of the 37 069 patients included in the analyses, 31 176 completed 1 year of fol-

low-up: 5893 subjects were censored during follow-up because of either kidney transplantation, transfer to a non-FMC dialysis unit, or loss to follow-up. Censored patients were more likely to be younger, white, nondiabetic, and to have been receiving dialysis for fewer years. Demographic and clinical characteristics of patients in the study population and excluded subjects are described in TABLE 1. During the follow-up year, 5731 patients (18.4%) died. The baseline characteristics and death rate of the study population are similar to those for the US hemodialysis population as reported by the United States Renal Data Service and the Centers for Medicare and Medicaid Services.^{28,29}

The study population had mean (SD) systolic blood pressures of 154.3 (20.4) mm Hg before and 139.6 (19.1) mm Hg

after dialysis treatment. Diastolic blood pressures were 79.3 (11.2) mm Hg before and 72.7 (10.1) mm Hg after dialysis treatment. Predialysis pulse pressure was 75.0 (15.0) mm Hg and the postdialysis pulse pressure was 66.9 (13.9) mm Hg.

Results of univariate and multivariable analyses were similar for pulse pressure before and after dialysis. Univariate analysis showed that postdialysis pulse pressure rose with increasing age, from 61.7 mm Hg in the lowest quartile of age to 70.2 mm Hg in the highest quartile; pulse pressure increased by 2.2 mm Hg for every 10-year increase in age ($P < .001$). The mean pulse pressure for women was higher than for men (68.7 vs 64.7 mm Hg, $P < .001$). Although whites had lower mean systolic blood pressure than blacks (138.1 vs 141.5 mm Hg, $P < .001$), whites also had lower

mean diastolic blood pressure (70.7 vs 75.1 mm Hg, $P < .001$), resulting in a slightly higher mean pulse pressure in whites than blacks (67.4 vs 66.4 mm Hg, $P < .001$). A higher pulse pressure was seen among patients with diabetes mellitus compared with patients without (70.0 vs 64.0 mm Hg, $P < .001$). There was an inverse relationship between duration of dialytic therapy and pulse pressure, with a drop of 2.7 mm Hg for every 5 years a patient was receiving dialysis prior to entry into the study ($P < .001$). Hematocrit levels were also inversely associated with pulse pressure, with an increase of 1.7 mm Hg for every 3% drop in hematocrit levels ($P < .001$). Other univariate associations (body weight; height; intradialytic volume change; and albumin, calcium, phosphorous and parathyroid hormone levels) were statistically significant but each contributed less than 1% to the variability in pulse pressure. Serum ferritin levels did not correlate significantly with pulse pressure. Variability in pulse pressure between patients was driven primarily by variations in systolic pressure, evidenced by a large correlation coefficient for the relationship between systolic and pulse pressure ($r^2 = 0.73$, $P < .001$) compared with the relationship between diastolic and pulse pressure ($r^2 = 0.06$, $P < .001$).

Because systolic blood pressure correlates highly with pulse pressure in univariate analysis, the level of systolic blood pressure may influence the associations between pulse pressure and other parameters. Systolic blood pressure was therefore included as a covariate in a multivariable regression analysis of pulse pressure (TABLE 2). After adjustment for level of postdialysis systolic blood pressure, important demographic and clinical variables directly associated with elevated pulse pressure were age (2.1 mm Hg per 10-year increase), the presence of diabetes mellitus (2.6 mm Hg), white race (2.2 mm Hg), female sex (1.8 mm Hg), and duration of dialysis prior to entry into the study (0.5 mm Hg per 5-year increase) (all $P < .001$). Pulse pressure was also directly associated with increasing phosphorous ($P < .001$) and

Table 1. Description of Clinical Cohort*

Variable	Study Population			
	All	Complete Follow-up	Partial Follow-up	Excluded
Total number of patients	37 069	31 176	5893	7000
Sex, %				
Men	51.3	51.0	52.8	51.9
Women	48.7	49.0	47.2	48.1
Age, y	60.1 (15.1)	60.5 (14.8)	58.0 (16.3)	60.3 (15.6)
Race, %				
White	49.9	48.5	56.9	53.2
Black	43.4	44.6	36.9	38.4
Asian	1.1	1.3	1.5	1.1
Native American	0.7	0.7	0.7	0.5
Other	4.9	4.7	4.0	6.8
Diabetes mellitus, %				
Present	47.9	48.1	46.9	46.6
Absent	52.1	51.9	53.1	53.4
Duration of dialysis prior to study entry, y	3.4 (3.6)	3.5 (3.7)	2.8 (3.2)	3.7 (3.9)
Laboratory measurements				
Creatinine, mg/dL†	9.6 (3.3)	9.6 (3.2)	9.5 (3.5)	9.4 (3.4)
Albumin, g/dL	3.9 (0.4)	3.9 (0.4)	3.8 (0.4)	3.8 (0.4)
Hematocrit, %	33.3 (3.3)	33.3 (3.3)	33.1 (3.4)	33.0 (3.4)
Urea reduction ratio, %	68.7 (7.4)	68.8 (7.3)	67.8 (7.9)	68.1 (7.8)
Predialysis pressure, mm Hg				
Systolic	154.3 (20.4)	154.4 (20.4)	153.9 (20.4)	152.7 (19.8)
Diastolic	79.3 (11.2)	79.2 (11.1)	79.8 (11.3)	79.5 (10.9)
Pulse	75.0 (15.0)	75.2 (15.0)	74.1 (15.0)	73.2 (14.4)
Postdialysis pressure, mm Hg				
Systolic	139.6 (19.1)	139.5 (19.0)	140.2 (19.3)	140.0 (18.4)
Diastolic	72.7 (10.1)	72.6 (10.1)	73.5 (10.3)	73.9 (10.1)
Pulse	66.9 (13.9)	66.9 (13.8)	66.8 (14.2)	66.1 (13.4)

*Data are presented as mean (SD) unless otherwise indicated.

†To convert creatinine from mg/dL to $\mu\text{mol/L}$ multiply by 88.4.

calcium ($P=.04$). Pulse pressure was inversely associated with height, hematocrit, and albumin levels ($P<.001$). Body weight, percentage of intradialytic volume change, and ferritin and serum phosphorous levels did not significantly correlate with pulse pressure in the multivariable model. Multivariable analysis of predialysis pulse pressure showed similar results.

The results of an unadjusted Cox proportional hazards model relating systolic blood pressure before and after dialysis to 1-year mortality are shown in FIGURE 1. Subjects with systolic pressures lower than the reference range of 135 to 144 mm Hg had greater mortality risk; those with systolic pressures higher than the reference range had lower mortality risk. Similar to a previous report⁸ of another hemodialysis population, postdialysis systolic blood pressure exhibited more of a U-shape or Reverse-J curve than predialysis systolic pressure. The unadjusted Cox model relating pulse pressure before and after dialysis to 1-year mortality is shown in FIGURE 1B. The curves for unadjusted pulse pressure were similar to the systolic blood pressure curves; postdialysis pulse pressure exhibited a more pronounced U-shape. Compared with subjects in the reference category of 50 to 59 mm Hg, patients with higher postdialysis pulse pressures experienced increasing mortality. Because pulse pressure has a high correlation with systolic blood pressure, examining the indepen-

dent association between pulse pressure and mortality requires an adjustment for level of systolic pressure. After controlling for the level of systolic blood pressure, a direct and consistent association is seen between increasing pulse pressure and increasing risk for mortality (FIGURE 2A). In this model pulse pressure is a function solely of diastolic blood pressure. For any given level of systolic pressure, lower diastolic blood pressure is associated with increased risk of death (Figure 2B).

The results of a full mortality model adjusting for other variables known to influence either pulse pressure or death are shown in TABLE 3. After adjustment for systolic blood pressure and 14 other demographic and clinical parameters, postdialysis pulse pressure remained significantly associated with mortality to 1 year; each incremental elevation of 10

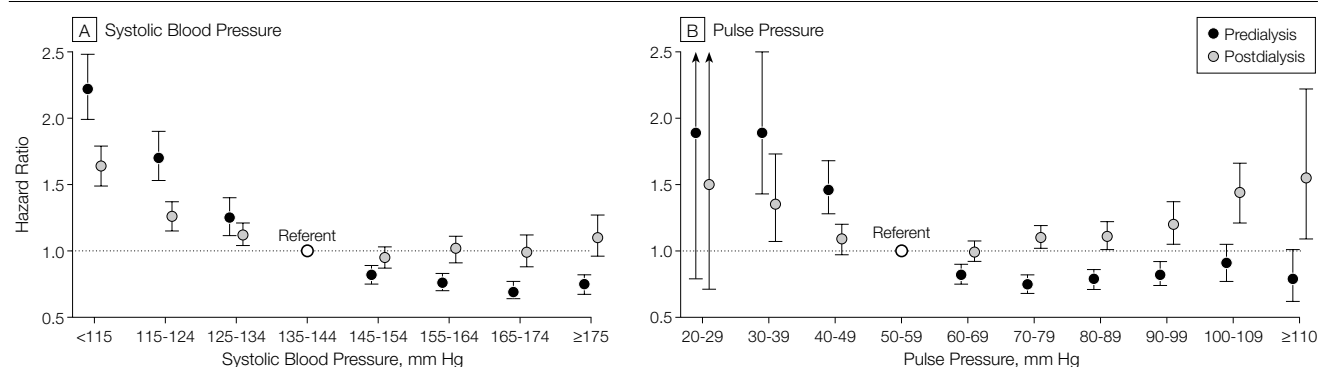
mm Hg in pulse pressure was associated with a 12% increased hazard of death (95% CI, 1.06-1.18; $P<.001$). Systolic blood pressure was inversely related to mortality (13% decreased death hazard for each elevation of 10 mm Hg in systolic pressure; 95% CI, 0.84-0.91; $P<.001$). Mortality risk increased with age (hazard ratio [HR], 1.30; 95% CI, 1.26-1.33), years receiving dialysis (HR, 1.04; 95% CI, 1.02-1.06), and the presence of diabetes mellitus (HR, 1.42; 95% CI, 1.32-1.51) (all $P<.001$). Mortality decreased with higher albumin levels (HR, 0.33; 95% CI, 0.31-0.36), weight (HR, 0.92; 95% CI, 0.91-0.93), and hematocrit levels (HR, 0.93; 95% CI, 0.90-0.96) (all $P<.001$). Female sex (HR, 0.80; 95% CI, 0.74-0.85), and black race (HR, 0.82; 95% CI, 0.77-0.88) were also associated with lower mortality (both $P<.001$). Multivariable analysis of pre-

Table 2. Multivariable Linear Regression Analysis of Blood Pressure After Receiving Dialysis*

Variable	Parameter Estimate (SE)	F Value	P Value
Age, 10-year increase	2.12 (0.02)	6536	<.001
Diabetes	2.57 (0.07)	1161	<.001
White race	2.18 (0.07)	859	<.001
Women	1.81 (0.07)	498	<.001
Years on dialysis, 5-y increase	0.52 (0.05)	102	<.001
Albumin, 1-g/dL increase	-0.69 (0.10)	47	<.001
Hematocrit, 3% increase	-0.17 (0.03)	26	<.001
Height, 10-cm increase	-0.13 (0.03)	19	<.001
Phosphorus, 1-mg/dL increase	0.08 (0.02)	10	<.001
Calcium, 1-g/dL increase	0.10 (0.05)	4	.04

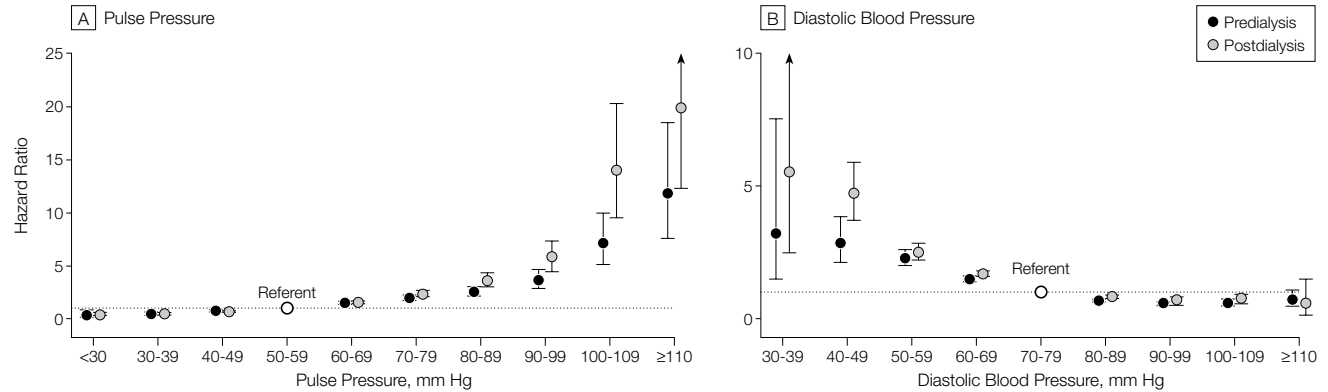
*Model also adjusted for systolic blood pressure. All F tests were 1 *df* tests, with 27 976 denominator *df*. Similar associations were seen for predialysis pulse pressure.

Figure 1. Unadjusted Hazard Ratios for 1-Year Mortality Associated With Systolic Blood Pressure and Pulse Pressure



Error bars indicate 95% confidence interval.

Figure 2. Hazard Ratios for 1-Year Mortality Associated With Pulse Pressure and Diastolic Blood Pressure After Adjustment for Systolic Blood Pressure



Error bars indicate 95% confidence intervals.

Table 3. Multivariable Cox Proportional Hazards Model of 1-Year Mortality*

Variable Increase	Parameter Estimate (SD)	Hazard Ratio (95% CI)	Wald χ^2	P Value
Pulse pressure by 10 mm Hg	0.12 (0.02)	1.12 (1.06-1.18)	20	<.001
Albumin by 1 g/dL	-1.10 (0.04)	0.33 (0.31-0.36)	807	<.001
Age by 10 y	0.26 (0.01)	1.30 (1.26-1.33)	369	<.001
Weight by 5 kg	-0.08 (0.01)	0.92 (0.91-0.93)	252	<.001
Diabetes mellitus	0.36 (0.03)	1.42 (1.32-1.51)	118	<.001
Urea reduction ratio by 5%	-0.10 (0.03)	0.90 (0.88-0.92)	104	<.001
Ferritin by 100 mg/dL	0.02 (0.003)	1.02 (1.01-1.02)	70	<.001
Calcium by 1 mg/dL	0.16 (0.02)	1.16 (1.12-1.22)	64	<.001
Women	-0.24 (0.03)	0.80 (0.74-0.85)	57	<.001
Systolic blood pressure by 10 mm Hg	-0.14 (0.02)	0.87 (0.84-0.91)	56	<.001
Phosphorus by 1 mg/dL†	0.078 (0.01)	1.08 (1.06-1.10)	56	<.001
Black race	-0.18 (0.03)	0.82 (0.77-0.88)	34	<.001
Years receiving dialysis by 2 y	0.04 (0.01)	1.04 (1.02-1.06)	23	<.001
Hematocrit by 3%	-0.07 (0.02)	0.93 (0.90-0.96)	22	<.001
Parathyroid hormone by 100 mg/dL	0.02 (0.01)	1.02 (1.01-1.03)	20	<.001
Intradialytic volume change by 5%	0.16 (0.01)	1.17 (1.05-1.30)	8	.003

*CI indicates confidence interval.

†To convert phosphorous from mg/dL to mmol/L multiply by 0.323.

dialysis pulse pressure showed similar relationships (pulse pressure HR, 1.07; 95% CI, 1.02-1.13).

To further examine the relationships between postdialysis blood pressure components and mortality, each was entered into the adjusted mortality model as single and paired covariates (TABLE 4). When examined as isolated variables, systolic, diastolic, and pulse pressure are each inversely associated with mortality (models 1-3). Adjusting for systolic blood pressure changes the association between pulse pressure and death to a direct relationship (model 4). Adjust-

ing for diastolic blood pressure causes both pulse pressure (model 5) and systolic pressure (model 6) to become non-significant contributors to the mortality models (Table 4).

The risk attributed to pulse pressure in the full mortality model differed among individuals with elevated and nonelevated blood pressure ($P < .001$ for the interaction term between systolic pressure and pulse pressure). Subjects were then divided into 5 categories of systolic blood pressure: <120, 120 to 139, 140 to 159, 160 to 179, and ≥ 180 mm Hg. The full mortality model was

tested for each blood pressure category and the results are shown in TABLE 5. Pulse pressure was significantly associated with mortality only in subjects with systolic pressures less than or equal to 140 mm Hg. The relationship between systolic blood pressure, pulse pressure, and death is graphically demonstrated in FIGURE 3. As pulse pressure increased within each category of systolic blood pressure, the percentage of subjects who died at 1 year also increased. As systolic blood pressure increased within each category of pulse pressure, the death percentages decreased until pressures higher than 165 mm Hg, at which point some groups displayed an increase in death (reverse-J curve).

The interaction between pulse pressure and age was significant ($P < .001$). The risk associated with pulse pressure in the younger half of the cohort (age <62 years) was approximately 2 times the risk associated with pulse pressure in the older half (HR, 1.24 vs 1.12). Similar interactions for race, diabetes mellitus, and sex were tested but did not meet statistical significance.

COMMENT

To our knowledge, these analyses are the first to demonstrate the association between pulse pressure and an increased death risk in a large, Western national, representative sample of patients receiving hemodialysis. In an adjusted model,

an incremental increase of 10 mm Hg in postdialysis pulse pressure was associated with a 12% increase in the hazard for death. The amount of variability in mortality accounted for by pulse pressure was similar to that seen for race, hematocrit level, years receiving dialysis, or parathyroid hormone level. The association between pulse pressure and mortality was examined both with and without adjustment for level of systolic blood pressure. Since variability of pulse pressure in the study population is largely accounted for by variation in systolic blood pressure, a model examining mortality and pulse pressure alone could be confounded by the independent relationship between mortality and systolic pressure. By adjusting for systolic pressure in the final model, the question effectively posed is, for a given level of systolic blood pressure, does the magnitude of the pulse pressure matter? These results suggest that it does. Moreover, although pulse pressure is more likely to be elevated in patients with elevated systolic blood pressure, the risk attributed to pulse pressure is actually driven by patients with systolic pressures below 140 mm Hg.

As Figure 2B illustrates, when adjusting for level of systolic blood pressure the magnitude of the pulse pressure is determined solely by the diastolic blood pressure. In essence, this indicates that for any given level of systolic blood pressure, the lower the diastolic pressure, the greater the risk of death. When systolic and diastolic blood pressure are jointly entered into a mortality model, it is diastolic blood pressure, and not systolic, that is significantly associated with death (model 6 in Table 5).

Pathophysiology of Pulse Pressure

Pulse pressure is a simple mathematical combination of systolic and diastolic blood pressure and is therefore an easily measured correlate of pulsatile hemodynamic load during the cardiac cycle. It reflects dynamic stress that is caused by large-artery stiffness and early, reflected arterial pressure waves from the periphery back to central, conduit vessels. Early return of reflected arte-

rial waves increases afterload at end-systole and decreases coronary perfusion pressure during diastole.³⁰ This may be particularly important when underlying cardiac dysfunction is present,³¹ as is often the case in ESRD.^{32,33} Studies in non-ESRD populations have shown that

death and cardiac disease may be related more to pulsatile stress than to the steady-state stress that is associated with small-vessel resistance and reflected in static measures of blood pressure, such as systolic, diastolic, or mean arterial pressure.^{19,21}

Table 4. Mortality Risk Associated With Postdialysis Single and Dual Blood Pressure Components in Multivariable Cox Proportional Hazards Models of 1-Year Mortality*

Model	Blood Pressure Variable per 10 mm Hg Increase	HR (95% CI)	P Value
1	Pulse	0.94 (0.92-0.97)	<.001
2	Systolic	0.94 (0.92-0.95)	<.001
3	Diastolic	0.86 (0.83-0.89)	<.001
4	Pulse	1.12 (1.06-1.18)	<.001
	Systolic	0.87 (0.84-0.91)	<.001
5	Pulse	0.97 (0.95-1.00)	.06
	Diastolic	0.87 (0.84-0.91)	<.001
6	Systolic	0.97 (0.95-1.00)	.06
	Diastolic	0.89 (0.85-0.94)	<.001

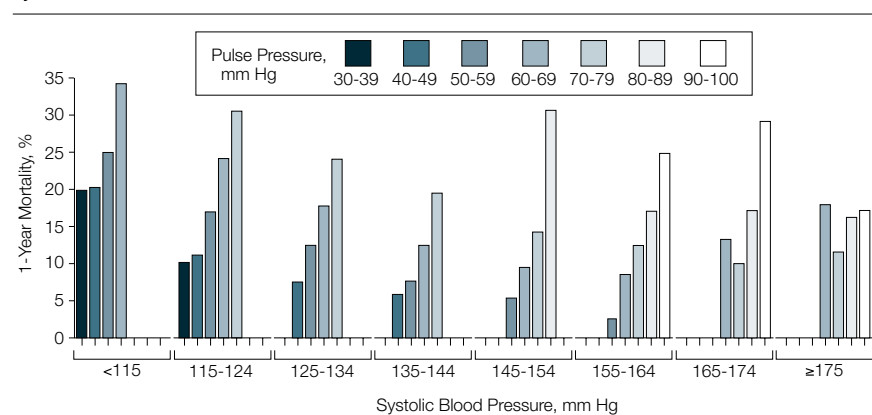
*Each model is also adjusted for age; sex; race; diabetes; years receiving dialysis; dialysis dose; body weight; percentage intradialytic volume change; and albumin, hematocrit, calcium, phosphorous, ferritin, and parathyroid hormone levels. HR indicates hazard ratio; CI, confidence interval.

Table 5. Hazard Ratio for Death Associated With Postdialysis Pulse Pressure Stratified by Level of Systolic Blood Pressure*

Systolic Blood Pressure Category, mm Hg	No. of Patients	Pulse Pressure, HR (95% CI)	P Value
<120	5309	1.17 (1.07-1.29)	.01
120-139	15 756	1.22 (1.10-1.33)	<.001
140-159	13 612	1.04 (0.93-1.14)	.56
160-179	4910	1.05 (0.90-1.22)	.53
≥180	959	0.98 (0.73-1.33)	.91

*Each model is also adjusted for age; sex; race; diabetes; years receiving dialysis; dialysis dose; body weight; percentage intradialytic volume change; systolic blood pressure; and albumin, hematocrit, calcium, phosphorous, ferritin, and parathyroid hormone levels. HR indicates hazard ratio; CI, confidence interval.

Figure 3. Percentage of Patients Who Died at 1 Year Within Categories of Postdialysis Systolic Blood Pressure and Pulse Pressure



Categories with fewer than 10 patients are not shown. Within each category of systolic blood pressure, the grouped columns indicate death percentage as pulse pressure increases. Within each pulse pressure category, the death percentage can be followed across categories of increasing systolic blood pressure.

End-stage renal disease is associated with elevated arterial stiffness, pulse-wave velocity, and early wave reflections compared with age- and blood pressure-matched controls with normal renal function.^{22,23} The mechanisms underlying these changes are incompletely described but may be a reflection of abnormal vascular biology seen in chronic kidney disease. The atherogenic environment of chronic kidney disease includes contributions from hypertension, hypervolemia, qualitative and quantitative lipid abnormalities, divalent ion changes, aberrant inflammatory responses, and hyperhomocysteinemia, among other putative disturbances.³⁴ Pulse pressure was extremely high in the majority of patients undergoing hemodialysis in this current cohort, with fewer than 10% of subjects having pulse pressures lower than 50 mm Hg, the mean value found in population-based samples.³⁵ The pathobiologic correlate of this finding is that the preponderance of patients undergoing hemodialysis may experience a substantial burden of increased afterload and decreased coronary perfusion pressure. It is conceivable that this may contribute to the high prevalence of left ventricular hypertrophy and cardiovascular death seen in the ESRD population.

Clinical Implications

Static measures of blood pressure in patients with ESRD have relationships with mortality that appear to be quite different than in the general population. Epidemiologic investigations have reported that higher blood pressures are associated with improved survival compared with lower pressures.⁸⁻¹¹ A potential explanation for this phenomenon is that cardiac dysfunction in the ESRD population confers an increased risk of death and is reflected by normal or reduced blood pressures. This may partially explain the finding that the risk associated with pulse pressure is significant and of greatest magnitude in subjects with blood pressure in the normal range, lower than 140 mm Hg. In its simplest form, pulse pressure may serve as an ad-

ditional risk-stratification tool to identify patients with ESRD at high risk for death in a more clinically comprehensible form than what systolic or diastolic blood pressure measurements alone would indicate. Further studies are required to determine the efficacy of using pulse pressure and other measures of conduit vessel function as predictors of risk and as targets for primary and secondary preventive efforts.

The therapeutic implications of this association between pulse pressure and mortality are difficult to define because of the observational nature of the study, which limits implications of causality. However, abnormalities in conduit vessel stiffness are modifiable by exercise and reduced sodium intake.^{36,37} Similarly, antihypertensive agents have differential effects on vascular compliance. In particular, angiotensin-converting enzyme inhibition and diuretics decrease arterial wave reflection and pulse-wave velocity and increase arterial compliance in certain populations.³⁸⁻⁴⁰ β -Blocker monotherapy may increase vessel stiffness and magnitude of arterial reflected waves.^{41,42} Calcium channel blockade produces varying results.^{43,44} Further studies are needed to determine (1) the effect of diet and/or pharmacotherapy on conduit vessel compliance and (2) whether targeted modification of vessel compliance produces improvements in clinical outcomes for patients with ESRD.

Study Strengths and Limitations

The principle strength of this investigation is that the study population is a large, contemporary, and representative sample of hemodialysis patients in the United States. Multiple blood pressures were collected to represent true blood pressure load and minimize outlying values. A large number of demographic, clinical, and laboratory parameters were available, allowing appropriate adjustments to isolate the relationships between blood pressure and mortality.

This investigation is limited by several design issues germane to observa-

tional registry research. First, this study was limited to data collected during routine provision of hemodialysis, and blood pressure measurements were not carried out using standardized protocols. This limitation is offset by the large number of observations recorded for each subject (approximately 36 measurements for times before and after dialysis). Moreover, the large number of participants minimizes bias introduced by a limited number of treatment centers or providers collecting blood pressure measurements. Second, in this analysis, we have assumed that pulse pressure is reflective of decreased vascular compliance. Because increased pulse pressure may be observed in other clinical conditions, such as aortic valve insufficiency, this assumption may not be true in some patients. Moreover, it is unclear what effect arteriovenous vascular anastomoses like autologous fistulae or prosthetic grafts, which are the principle form of hemodialysis access, have on pulse pressure. Third, pulse pressure is a crude measure of conduit vessel function compared with more direct measures such as pulse-wave velocity, proximal aortic compliance, characteristic impedance, and wave-form morphology. Although such measurements may better estimate the extent of the relationship between vessel characteristics and clinical outcomes, the feasibility of these investigations is often limited by their resource intensity, particularly in large study populations. Finally, this investigation was unable to precisely characterize the causes of mortality into cardiovascular vs non-cardiovascular etiologies. Despite this limitation, the size of this data set and the representative nature of the final patient cohort make it unlikely that the causes of death differ from US ESRD population. Based on national ESRD registry information, cardiovascular disease accounts for more than half the reported deaths in the American ESRD patients.²⁸

Pulse pressure is associated with mortality in patients undergoing maintenance hemodialysis. Considered indi-

vidually, both systolic and diastolic blood pressure have counterintuitive, inverse associations with mortality. This may be the result of widespread cardiac dysfunction in the ESRD population. It may also point to the need for careful consideration of what constitutes appropriate levels of blood pressure control. Addressing these questions will likely require prospective, interventional trials examining different levels of blood pressure control. Similarly, the recognition of pulse pressure as an important correlate of mor-

tality requires prospective confirmation and should be incorporated in future interventional trials to investigate the chain of causality between conduit vessel function and both cardiovascular events and all-cause death.

Author Affiliations: Duke Institute of Renal Outcomes Research and Health Policy, Department of Medicine, Duke University Medical Center (Drs Klassen, Lowrie, Reddan, Coladonato, Szczec, and Owen) and Duke Clinical Research Institute (Dr DeLong), Durham, NC; and Fresenius Medical Care, North America, Lexington, Mass (Drs Lowrie and Lazarus); Dr Owen now works at Baxter Healthcare International, Waukegan, Ill.

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Author Contributions: Study concept and design: Klassen, Lowrie, Reddan, Szczec, Owen.

Acquisition of data: Lowrie, Lazarus, Owen.

Analysis and interpretation of data: Klassen, Lowrie, Reddan, DeLong, Coladonato, Szczec, Owen.

Drafting of the manuscript: Klassen, Lowrie, Reddan, Owen.

Critical revision of the manuscript for important intellectual content: Klassen, Lowrie, Reddan, DeLong, Coladonato, Szczec, Lazarus, Owen.

Statistical expertise: Klassen, Lowrie, Reddan, DeLong, Coladonato, Szczec, Owen.

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