Original Article

Predictive Significance of Blood Pressure Values for the Incidence of Cardiovascular Events in Chronic Hemodialysis Patients

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We conducted a prospective study investigating the relationship between blood pressure values and the risk of cardiovascular disease in patients with end-stage renal diseases. Five hundred fifty-three patients on chronic hemodialysis were followed for 5 years, and the relationship between systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and pulse pressure (PP) and the incidence of death and cardiovascular events were evaluated. There were 85 cardiovascular and 88 non-cardiovascular deaths during the 5 years. Fatal and nonfatal cardiovascular events occurred in 205 patients. Factors such as old age, diabetes and electrocardiographic findings of left ventricular hypertrophy and arrhythmia were associated with a high incidence of cardiovascular events as well as the incidence of death. With regard to blood pressure values, only PP was significantly associated with the risk of death ($p=0.003$). Both SBP and PP showed a significant association with the incidence of cardiovascular events ($p=0.004$ and $p<0.001$). In other words, an increase in PP by 10 mmHg corresponded to a 22% increase in cardiovascular events, and a 10 mmHg SBP increase corresponded to a 10% increase in cardiovascular events. In conclusion, PP is a better predictor of death and cardiovascular events than other blood pressure values in chronic hemodialysis patients. (*Hypertens Res* 2008; 31: 1703–1709)

***Key Words*: hemodialysis, blood pressure, pulse pressure, cardiovascular events, prognosis**

Introduction

Because the incidence of end-stage renal disease (ESRD) is increasing in Japan as well as in Western countries, the improvement of prognoses for dialysis patients is becoming an important issue. Patients undergoing dialysis therapy are at more than 10 times higher risk for developing cardiovascular diseases than the general population; these cardiovascular complications often limit the life expectancy of dialysis patients (*1*). Therefore, the intensive management of cardiovascular risk factors is necessary for the prevention of cardiovascular diseases and the improvement of prognoses in dialysis patients. Among the cardiovascular risk factors, hypertension has a pivotal impact on the development of cardiovascular diseases such as stroke, coronary heart disease and heart failure in various populations.

A large-scale meta-analysis of the middle- and old-aged general population showed a linear relationship between blood pressure and mortality due to cardiovascular diseases that can be extended to the normotensive population (*2*). However, such a linear relationship was not necessarily observed in earlier studies investigating the influence of blood pressure on mortality and cardiovascular morbidity in hemodialysis patients (*3*). Moreover, it has been reported that low diastolic blood pressure (DBP) was instead associated

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Table 1. Background Characteristics of the Study Subjects

Parameter	Value
Age, years	57±12
Sex, men/women	331/222
Cause of renal failure, *n* (%)	
Chronic glomerulonephritis	347 (62.7)
Diabetic nephropathy	150 (27.1)
Others	56 (10.1)
Duration of hemodialysis, years	7.4±6.0
Preexistence of cardiovascular diseases, *n* (%)	185 (33.5)
Habitual alcohol intake, +/–	122/431
Habitual smoking, +/–	189/364
Body mass index, kg/m^2	20.7±2.8
Systolic blood pressure, mmHg	155±19
Diastolic blood pressure, mmHg	81±9
Mean blood pressure, mmHg	106±11
Pulse pressure, mmHg	74±15
Pulse rate, bpm	76±8
Cardiothoracic ratio, %	50.4±5.4
Left ventricular hypertrophy, +/–	154/399
Antihypertensive medication	
Diuretic	196
β-Blocker	63
Calcium channel blocker	340
ACE inhibitor	152
α-Blocker	111
Other	43

Mean±SD. ACE, angiotensin converitng enzyme.

Table 2. Laboratory Data of the Study Subjects

Parameter	Value
Blood hemoglobin, g/dL	9.4±1.3
Hematocrit, %	28.8±4.0
Blood chemistry	
Aspartate aminotransferase, U/L	18±12
Alanine aminotransferase, U/L	14±12
Total protein, g/dL	6.6±0.5
Albumin, g/dL	4.0±0.4
Urea nitrogen, mg/dL	79±20
Creatinine, mg/dL	11.3±2.7
Na, mEq/L	139±3
K, mEq/dL	5.2±0.8
Ca, mg/dL	9.4±1.0
Inorganic phosphrus, mg/dL	5.8±1.6
Total cholesterol, mg/dL	159±37
Triglycerides, mg/dL	125±74
β_2-Microglobulin, mg/L	32.3±10.0

Mean±SD.

with poor life prognoses for hemodialysis patients that were followed for 5 years (*4*). In clinical practice, systolic blood pressure (SBP) and DBP are generally evaluated for the management of hypertension. In addition, several clinical studies have indicated the significance of pulse pressure (PP) as an independent predictor of future cardiovascular events in patients with hypertension (*5*).

In this prospective study, we followed a cohort of hemodialysis patients and assessed the relationship between blood pressure values and the incidence of cardiovascular diseases and survival.

Methods

We enrolled a total of 553 patients with ESRD who were undergoing stable maintenance hemodialysis as an outpatient for more than three months on January 1, 1998 at the hemodialysis unit of Dokkyo Medical University Hospital (Tochigi, Japan) and eight nearby hemodialysis hospitals and clinics. Patients with uncured cancer were excluded; however, all eligible subjects participated in the study. Baseline data were collected, including medical history, physical examination, habits of cigarette smoking and alcohol consumption, cardiothoracic ratio on chest roentgenogram and electrocardiographic findings. Blood pressure was measured before each dialysis session on the arm without blood access using a sphygmomanometer with the patient in a supine position after having rested for at least 10 min. The average blood pressure values over 2 weeks were used for the evaluation (*6*, *7*). PP was calculated by subtracting the DBP from the SBP. Mean blood pressure (MBP) was defined as (SBP+2×DBP)/3. Routine hematological and chemical analyses were performed using blood taken before the dialysis session.

After their registration in January 1998, the patients were followed up until January 2003. The primary endpoint was the occurrence of cardiovascular events that required hospitalization or caused death. Cardiovascular events were classified into the following categories: stroke, coronary heart disease, heart failure, arrhythmia (including sudden death) and other vascular diseases. Cerebral stroke was diagnosed by means of neurological signs and symptoms together with computed tomography, if available. Coronary heart disease was diagnosed by means of chest symptoms and electrocardiogram. Elevation of serum cardiac enzyme was ascertained in diagnosing myocardial infarction. Clinical symptoms and chest roentgenogram were evaluated for the diagnosis of heart failure. Arrhythmia was diagnosed based on a standard 12-lead electrocardiogram. Other vascular diseases include arteriosclerotic obliteration, dissecting aneurysm of the aorta and pulmonary embolism. Stenosis or occlusion of the arteriovenous fistula used for blood access was not included in the cardiovascular events category. The secondary endpoint in this study was death due to any cause. The cause of each death was reviewed by a panel of four physicians. In the review process, all available information was collected, including medical records and interviews with the attending medical staff and family members that witnessed the event.

Table 3. Incidence of Fatal and Nonfatal Cardiovascular Events during the 5 Years of the Study

Cardiovascular disease	Number	Percentage (%)
Stroke	50	9.0
Coronary heart disease	40	7.2
Heart failure	40	7.2
Arrhythmia, sudden death	48	8.7
Other vascular disease	27	4.9
Total	205	37.1

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects (Somerset West version, 1996) and was approved by the institutional review board. Informed consent was obtained from all subjects.

Values are expressed as means±SD. Univariate and multivariate Cox proportional hazards analyses were performed to evaluate the influence of variables on the incidence of cardiovascular events and death. The χ^2 test and the Steel test were used for the analyses of categorical data. A p value less than 0.05 was considered to indicate statistical significance.

Results

Table 1 lists physical and background characteristics of the study subjects. The leading cause of renal failure was chronic glomerulonephritis followed by diabetic nephropathy. These statistics are consistent with the overall major causes of renal failure in Japan in 1998. Of the 553 patients, 185 had a past or present history of such cardiovascular diseases as cerebrovascular disease (n=44), coronary heart disease (n=58), valvular heart disease (n=31), arrhythmia (n=51), heart failure (n=44) and peripheral vascular disease (n=19). Thirty-three patients had two or more cardiovascular diseases. Habitual drinkers and smokers included 22.1% and 34.2% of the patients, respectively. Only 36 (6.5%) had body mass indices greater than 25 kg/m^2. With regard to blood pressure values, the average SBP measured before each dialysis session was in the hypertensive range. As many as 441 patients (79.7%) were taking antihypertensive drugs; calcium channel blockers were the most frequently used drugs. One hundred and sixty-seven patients were taking one antihypertensive drug, 142 patients were taking two drugs and 132 patients were taking three or more drugs. Laboratory findings were shown in Table 2. In addition to renal anemia, increases in serum urea nitrogen, creatinine, potassium, inorganic phosphorus and β_2-microglobulin were naturally observed in the chronic hemodialysis patients enrolled in this study.

During the 5 years, three patients successfully underwent renal transplantation at 33, 37 and 40 months, and their follow-ups were discontinued thereafter. Except for these three patients, all other patients were followed up until their death or when the 5 years of the study had passed. As indicated in Table 3, fatal and nonfatal cardiovascular events occurred in 205 patients. Table 4 shows the relationship between the background characteristics (including blood pressure values) and the incidence of these cardiovascular events as evaluated by univariate Cox proportional hazard analysis. Among the baseline characteristics of the patients, age, diabetes, preexistence of cardiovascular diseases, PP, cardiothoracic ratio on chest roentgenogram and left ventricular hypertrophy on electrocardiogram were the most highly significant factors related to the risk of cardiovascular events. SBP, in addition to PP, was significantly related to the incidence of cardiovascular events in the univariate Cox proportional hazards analysis. Increases in SBP and PP by 10 mmHg correspond to a 10.4% and 21.9% higher risk of developing cardiovascular diseases, respectively.

Table 4. Relationship between Background Parameters and the Incidence of Cardiovascular Events as Evaluated by Univariate Cox Proportional Hazards Analysis

Parameter	Hazard ratio (95% confidence interval)	p value
Age	1.032 (1.020–1.045)	<0.001
Sex	1.082 (0.818–1.431)	0.578
Diabetes	2.209 (1.669–2.923)	<0.001
Duration of hemodialysis	0.966 (0.943–0.990)	0.005
Preexistence of cardiovascular diseases	2.479 (1.883–3.263)	<0.001
Habitual alcohol intake	1.048 (0.785–1.399)	0.749
Habitual smoking	0.960 (0.688–1.340)	0.809
Body mass index	1.004 (0.995–1.028)	0.891
Systolic blood pressure	1.010 (1.003–1.017)	0.004
Diastolic blood pressure	0.993 (0.978–1.007)	0.310
Mean blood pressure	1.006 (0.995–1.108)	0.282
Pulse pressure	1.020 (1.011–1.030)	<0.001
Pulse rate	1.011 (0.995–1.028)	0.182
Cardiothoracic ratio	1.057 (1.032–1.083)	<0.001
Left ventricular hypertrophy	2.002 (1.511–2.652)	<0.001
Number of antihypertensive drugs	1.081 (0.965–1.212)	0.179

Figure 1 presents the incidence of total cardiovascular events in the study subjects divided into quintiles according to blood pressure values. The incidence of cardiovascular events increased with increasing SBP and PP. Such a linear relation was not apparent for MBP. On the other hand, the relationship between cardiovascular event incidence and DBP was a U-shaped curve; the incidence of cardiovascular events in the lowest DBP quintile was significantly higher than that of the middle quintile (p=0.036).

Table 5 presents the relationship between blood pressure values and the risk of each cardiovascular disease category, as analyzed by the univariate Cox proportional hazards model. PP showed a significant association with the risk of stroke,

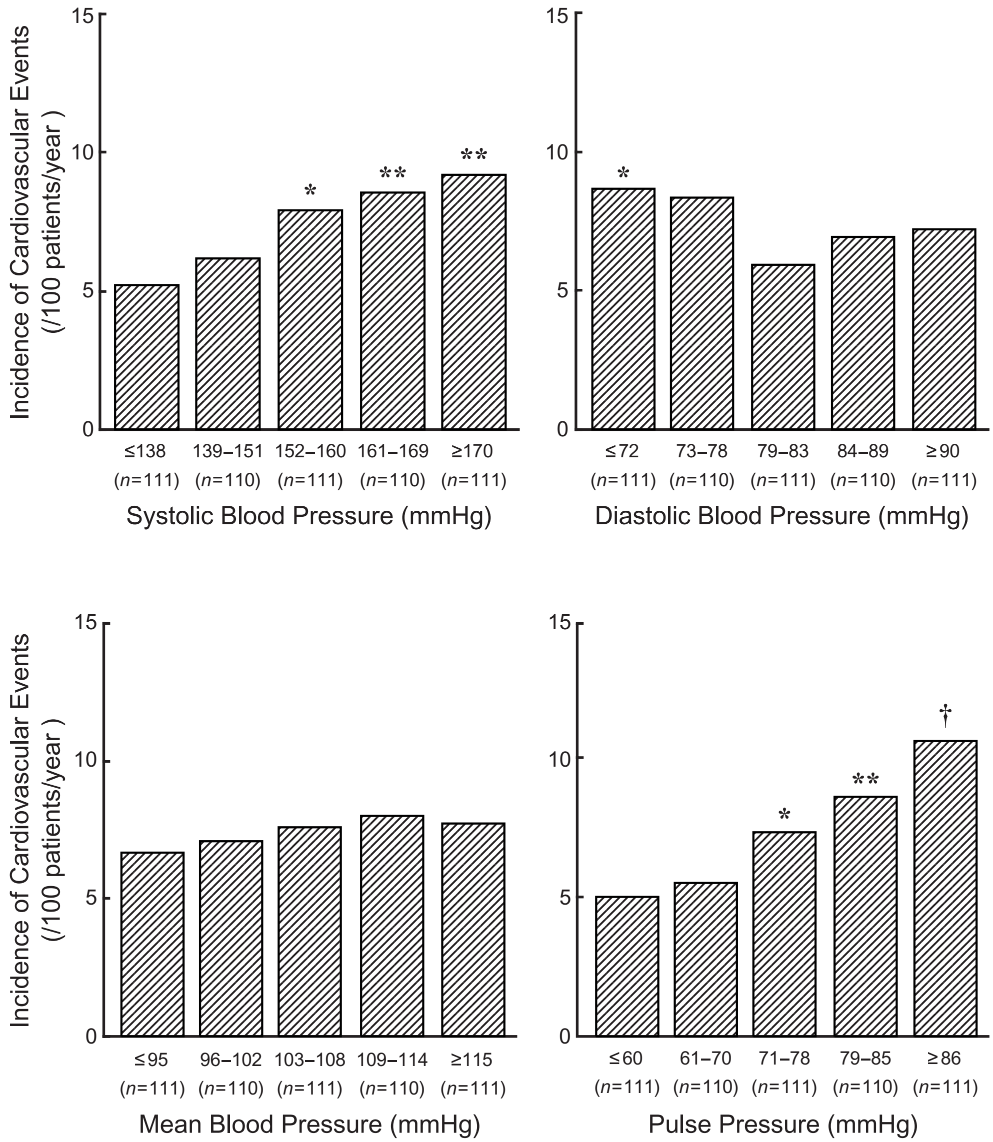

Fig. 1. *Incidence of cardiovascular events in chronic hemodialysis patients divided into quintiles by systolic and diastolic blood pressure values.* *$p<0.05$, **$p<0.01$, †$p<0.001$ *vs. the quintile with the lowest risk.*

coronary heart disease, heart failure and other vascular diseases, while only the incidence of stroke was significantly associated with SBP.

Including 85 patients who had developed fatal cardiovascular events, a total of 173 patients died during the 5 years. Table 6 shows the causes of these 173 deaths. Nearly half of them (49.4%) were due to cardiovascular diseases. Baseline characteristics such as male gender (hazard ratio of 1.426, $p=0.033$), age (hazard ratio of 1.068 for 1 year increase, $p<0.001$), diabetes (hazard ratio of 2.252, $p<0.001$), preexistence of cardiovascular diseases (hazard ratio of 1.731, $p<0.001$), habitual smoking (hazard ratio of 1.014, $p=0.045$), cardiothoracic ratio on chest roentgenogram (hazard ratio of 1.076 for 1% increase, $p<0.001$) and left ventricular hypertrophy on electrocardiogram (1.866, $p<0.001$) were significantly associated with the risk of death in the univariate Cox proportional hazards analysis. As for blood pressure values, only PP had a significant association with the incidence of death in the univariate Cox proportional hazards analysis (Table 7). In addition to PP, SBP also showed a significant relationship with the incidence of death due to cardiovascular diseases, however, no blood pressure values were significantly associated with the incidence of death by noncardiovascular causes. The 10 mmHg increase in PP corresponded to 16.1% higher risk of death in the study subjects on chronic hemodialysis.

Next, variables showing a significant association with cardiovascular events in univariate regression analyses were

Table 5. Relationship between Blood Pressure Values and the Incidence of Each Cardiovascular Disease as Evaluated by Univariate Cox Proportional Hazards Analysis

Blood pressure	Hazard ratio (95% confidence interval)	*p* value
Stroke		
Systolic blood pressure	1.016 (1.001–1.031)	0.035
Diastolic blood pressure	1.009 (0.980–1.038)	0.552
Mean blood pressure	1.018 (0.994–1.042)	0.138
Pulse pressure	1.013 (1.004–1.041)	0.016
Coronary heart disease		
Systolic blood pressure	1.012 (0.995–1.028)	0.161
Diastolic blood pressure	0.974 (0.943–1.006)	0.111
Mean blood pressure	0.999 (0.974–1.025)	0.952
Pulse pressure	1.030 (1.009–1.050)	0.004
Heart failure		
Systolic blood pressure	1.009 (0.993–1.025)	0.274
Diastolic blood pressure	0.984 (0.953–1.016)	0.326
Mean blood pressure	1.001 (0.976–1.027)	0.921
Pulse pressure	1.022 (1.002–1.043)	0.035
Arrhythmia, sudden death		
Systolic blood pressure	0.999 (0.985–1.013)	0.860
Diastolic blood pressure	0.998 (0.968–1.028)	0.884
Mean blood pressure	0.998 (0.975–1.022)	0.862
Pulse pressure	0.998 (0.980–1.017)	0.863
Other vascular disease		
Systolic blood pressure	1.018 (0.998–1.039)	0.081
Diastolic blood pressure	0.998 (0.959–1.039)	0.929
Mean blood pressure	1.015 (0.983–1.048)	0.358
Pulse pressure	1.030 (1.005–1.055)	0.019

introduced into a stepwise multivariate Cox proportional hazards regression model to evaluate the independent predictive power of each variable. Consequently, five variables listed in Table 8 remained as independent predictors of cardiovascular events. As might be anticipated, older age, diabetes, preexistence of cardiovascular diseases and electrocardiographic left ventricular hypertrophy were selected as independent risk factors. In addition, PP remained an independent variable relating to the occurrence of cardiovascular events, even after correcting for the influence of other variables.

Discussion

Effects of blood pressure on the artery consist of two components: a steady component reflected by MBP and a pulsatile component reflected by PP. While the steady component is determined by the balance between cardiac output and peripheral vascular resistance, the pulsatile component depends on left ventricular stroke volume, arterial elasticity and wave reflection. After aging 50 years, DBP tends to decrease while SBP continues to increase, resulting in the increase of PP with

Table 6. Incidence of Death Due to Cardiovascular and Non-Cardiovascular Diseases during the 5 Years of the Study

Cause of death	Number	Percentage (%)
Cardiovascular disease		
Stroke	26	4.7
Myocardial infarction	20	3.6
Heart failure	16	2.9
Arrhythmia, sudden death	17	3.1
Other vascular disease	6	1.1
Subtotal	85	15.4
Non-cardiovascular disease		
Infection	41	7.4
Cancer	17	3.1
Gastrointestinal bleeding	6	1.1
Hepatic failure	9	1.6
Respiratory failure	4	0.7
Disseminated intravascular coagulation	3	0.5
Accident, suicide	8	1.4
Subtotal	88	15.9
Total	173	31.3

advancing age (*8*). This increase in PP with age in later life is mainly brought about by stiffening of large arteries as a result of arteriosclerosis. It has been shown that increased PP is associated with the risk of developing cardiovascular diseases not only in hypertensive patients but also in normotensive subjects (*9*). It has also been shown that the progression of atherosclerosis and arterial calcification is accelerated in hemodialysis patients, resulting in increased arterial stiffness and increased PP (*10–13*). In addition, the existence of arteriovenous fistula for blood access increases left ventricular ejection and reduces total vascular resistance, resulting in the increase of PP in hemodialysis patients. Therefore, it is intriguing to obtain particular information about the implications of PP for cardiovascular risk in hemodialysis patients.

In the present study, PP better predicted the incidence of cardiovascular events than other blood pressure values in chronic hemodialysis patients. PP was significantly related to the risk of stroke, coronary heart disease, heart failure and peripheral vascular disease, while only the incidence of stroke was significantly related to SBP. Other blood pressure values did not significantly associate with the risk of developing cardiovascular events. PP was the only blood pressure value that was significantly associated with the incidence of death in hemodialysis patients. The results of present study also indicated a U-shaped relationship between DBP and cardiovascular events. Although the number of events did not afford enough statistical power, the higher incidence of coronary artery disease and arrhythmia seems to contribute to the increased cardiovascular events in the lower quintiles.

Table 7. Relationship between Blood Pressure Values and the Incidence of Death as Evaluated by Univariate Cox Proportional Hazards Analysis

Blood pressure	Hazard ratio (95% confidence interval)	*p* value
Total death		
Systolic blood pressure	1.007 (0.999–1.015)	0.074
Diastolic blood pressure	0.993 (0.978–1.009)	0.398
Mean blood pressure	1.003 (0.991–1.016)	0.588
Pulse pressure	1.015 (1.005–1.025)	0.003
Cardiovascular death		
Systolic blood pressure	1.014 (1.002–1.025)	0.018
Diastolic blood pressure	1.000 (0.978–1.022)	0.994
Mean blood pressure	1.012 (0.994–1.030)	0.192
Pulse pressure	1.023 (1.008–1.037)	0.001
Non-cardiovascular death		
Systolic blood pressure	1.001 (0.991–1.012)	0.855
Diastolic blood pressure	0.987 (0.966–1.009)	0.238
Mean blood pressure	0.995 (0.978–1.013)	0.604
Pulse pressure	1.007 (0.993–1.021)	0.329

Table 8. Stepwise Multivariate Cox Proportional Hazards Analysis of Factors Relating to the Incidence of Fatal and Nonfatal Cardiovascular Events in Chronic Hemodialysis Patients

Parameter	Hazard ratio (95% confidence interval)	*p* value
Age	1.019 (1.006–1.033)	0.004
Diabetes	1.629 (1.194–2.222)	0.002
Preexistence of cardiovascular diseases	2.209 (1.668–2.925)	<0.001
Pulse pressure	1.011 (1.001–1.022)	0.034
Left ventricular hypertrophy	1.752 (1.312–2.338)	<0.001

Because coronary blood flow largely depends on the diastolic phase, it is speculated that low DBP causes myocardial ischemia and thereby induces arrhythmia as well (*14*).

Considering that PP is increased by stiffening of the arteries, it seems reasonable that increased PP is associated with the increased risk of cardiovascular diseases caused by the progression of arteriosclerosis. Arteriosclerosis of the cerebral arteries contributes to the onset of stroke and arteriosclerosis of the coronary arteries naturally causes ischemic heart disease. Several earlier studies have analyzed the relationship between PP and mortality and the risk of cardiovascular events in patients with ESRD. Klassen *et al*. (*15*) have reported the association between PP and mortality in hemodialysis patients, and Tozawa *et al*. (*16*) have reported the association of PP and the incidence of stroke and myocardial infarction in patients on chronic hemodialysis. In addition, the present study indicated that PP is a significant predictor of heart failure and peripheral vascular diseases. It would be expected that coronary artery disease and left ventricular hypertrophy, which progress along with arteriosclerosis, impair left ventricular function and facilitate the development of heart failure (*17*, *18*). Peripheral vascular diseases such as arteriosclerotic obliteration are obviously related to the development of arteriosclerosis, which causes arterial stiffening and an increase in PP. Compared with these triggers, the cause of arrhythmia may not have a direct relationship with stiffening of the arteries, and PP did not show a significant association with the occurrence of arrhythmia and sudden death in the present study.

It is known that arteriosclerosis and stiffening of arteries progress with increasing age and with the existence of diabetes. Because aging and diabetes are certain risk factors for death and cardiovascular diseases, the relationship between PP and the incidence of death and cardiovascular events observed in this study may be mediated by influences of aging and diabetes. However, the relationship between PP and the cardiovascular event incidence was still significant, even when analyzed in the multivariate model incorporating other factors such as age and diabetes as covariates. Therefore, increasing PP is thought to be associated with an increasing risk of developing cardiovascular diseases in chronic hemodialysis patients.

It has been reported that the indices of arteriosclerosis such as pulse wave velocity, ultrasonographic measurement of carotid intima media thickness and radiological evaluation of aortic calcification were predictive of mortality or cardiovascular morbidity (*19–21*). Compared with these parameters of arteriosclerosis, measurements of blood pressure and calculation of PP is feasible in clinical practice. Regarding the blood pressure evaluation, 24-h blood pressure monitoring has been shown to correlate with cardiovascular organ injuries better than clinical measurements (*22*). In the present study, we used the averaged values of pre-dialysis blood pressure measurements over a 2 week period. It has been reported that such averaged values of repeated blood pressure measurements showed a close correlation with 24-h blood pressure and left ventricular mass in hemodialysis patients (*6*, *7*).

Because hypertension is prevalent in patients with ESRD, intensive antihypertensive treatment is required for the control of blood pressure in hemodialysis patients. Among the classes of antihypertensive drugs, calcium channel blockers are most frequently used in hemodialysis patients. Calcium channel blockers lower SBP by directly dilating the arteries, but may not be very effective at reducing PP because DBP is lowered as well. On the other hand, inhibitors of the renin-angiotensin system, such as angiotensin II receptor blockers, have been shown to reduce PP (*23*). It is also speculated that β-blockers may be effective at reducing PP by reducing left ventricular ejection, another determinant of PP. In this context, angiotensin converting enzyme (ACE) inhibitors and β-blockers have been reported to improve survival of hemodialysis patients, and this may be related to the reduction in PP (*24*, *25*). Further prospective investigations are needed to delineate effective antihypertensive therapy in reducing PP and improving the cardiovascular risk and prognosis of patients with ESRD.

Considering that hemodialysis patients are at markedly high risk for developing cardiovascular diseases, adequate blood pressure control is strongly desired for the reduction of cardiovascular events and mortality. The results of the present study suggest that care should be taken to reduce not only SBP, but also PP in the antihypertensive treatment of chronic hemodialysis patients in order to improve their prognosis.

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References

1. Levey AS, Beto JA, Coronado BE, *et al*: Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? *Am J Kidney Dis* 1998; **32**: 853–906.
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
3. Zager PG, Nikolic J, Brown RH, *et al*: "U" curve association of blood pressure and mortality in hemodialysis patients. Medical Directors of Dialysis Clinic, Inc. *Kidney Int* 1998; **54**: 561–569.
4. Iseki K, Miyasato F, Tokuyama K, *et al*: Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. *Kidney Int* 1997; **51**: 1212–1217.
5. Gasowski J, Fagard RH, Staessen JA, *et al*: Pulsatile blood pressure component as predictor of mortality in hypertension: a meta-analysis of clinical trial control groups. *J Hypertens* 2002; **20**: 145–151.
6. Conion PJ, Walshe JJ, Heinle SK, Minda S, Krucoff M, Schwab SJ: Predialysis systolic blood pressure correlates strongly with mean 24-hour systolic blood pressure and left ventricular mass in stable hemodialysis patients. *J Am Soc Nephrol* 1996; **7**: 2658–2663.
7. Zoccali C, Mallamaci F, Tripepi G, *et al*: Prediction of left ventricular geometry by clinic, pre-dialysis and 24-h ambulatory BP monitoring in hemodialysis patients: CREED investigators. *J Hypertens* 1999; **17**: 1751–1758.
8. Franklin SS, Gustin W 4th, Wong ND, *et al*: Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation* 1997; **96**: 308–315.
9. Benetos A, Safar M, Rudnichi A, *et al*: Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 1997; **30**: 1410–1415.
10. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974; **290**: 697–701.
11. Rahn KH, Barenbrock M, Hausberg M, Kosch M, Suwelack B, Witta J: Vessel wall alterations in patients with renal failure. *Hypertens Res* 2000; **23**: 3–6.
12. Ritz E: Atherosclerosis in dialyzed patients. *Blood Purif* 2004; **22**: 28–37.
13. Ketteler M, Westenfeld R, Schlieper G, Brandenburg V: Pathogenesis of vascular calcification in dialysis patients. *Clin Exp Nephrol* 2005; **9**: 265–270.
14. Cruickshank J: The J-curve in hypertension. *Curr Cardiol Rep* 2003; **5**: 441–452.
15. Klassen PS, Lowrie EG, Reddan DN, *et al*: Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. *JAMA* 2002; **287**: 1548–1555.
16. Tozawa M, Iseki K, Iseki C, Takishita S: Pulse pressure and risk of total mortality and cardiovascular events in patients on chronic hemodialysis. *Kidney Int* 2002; **61**: 717–726.
17. Nitta K, Akiba T, Uchida K, *et al*: Left ventricular hypertrophy is associated with arterial stiffness and vascular calcification in hemodialysis patients. *Hypertens Res* 2004; **27**: 47–52.
18. Yildiz A, Memisoglu E, Oflaz H, *et al*: Atherosclerosis and vascular calcification are independent predictors of left ventricular hypertrophy in chronic haemodialysis patients. *Nephrol Dial Transplant* 2005; **20**: 760–767.
19. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM: Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int* 2003; **63**: 1852–1860.
20. Benedetto FA, Mallamaci F, Tripepi G, Zoccali C: Prognostic value of ultrasonographic measurement of carotid intima media thickness in dialysis patients. *J Am Soc Nephrol* 2001; **12**: 2458–2564.
21. Kushiya F, Wada H, Sakakura M, *et al*: Prognostic impact of aortic calcification index and ankle-arm blood pressure index in patients under hemodialysis. *Clin Appl Thromb Hemost* 2005; **11**: 161–169.
22. Ertürk S, Ertuğ AE, Ateş K, *et al*: Relationship of ambulatory blood pressure monitoring data to echocardiographic findings in haemodialysis patients. *Nephrol Dial Transplant* 1996; **11**: 2050–2054.
23. Asmar R, Lacourcière Y: A new approach to assessing antihypertensive therapy: effect of treatment on pulse pressure. Candesartan cilexetil in Hypertension Ambulatory Measurement of Blood Pressure (CHAMP) Study Investigators. *J Hypertens* 2000; **18**: 1683–1690.
24. Efrati S, Zaidenstein R, Dishy V, *et al*: ACE inhibitors and survival of hemodialysis patients. *Am J Kidney Dis* 2002; **40**: 1023–1029.
25. Foley RN, Herzog CA, Collins AJ, *et al*: Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int* 2002; **62**: 1784–1790.