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# Pulse pressure and risk of total mortality and cardiovascular events in patients on chronic hemodialysis

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**Pulse pressure and risk of total mortality and cardiovascular events in patients on chronic hemodialysis.**

*Background.* Pulse pressure (PP) has been shown as a risk factor for mortality or cardiovascular events in several studies. However, the impact of PP on prognosis in a cohort of chronic hemodialysis patients has not been sufficiently studied. We examined the effect of PP on total mortality and cardiovascular events in chronic hemodialysis patients, and whether PP adds useful value to systolic blood pressure (SBP) or diastolic blood pressure (DBP) for predicting total mortality and cardiovascular events in chronic hemodialysis patients.

*Methods.* Chronic hemodialysis patients ($N$ = 1243, 720 men, 523 women) alive on January 1, 1991 at baseline were involved in this study. Cox regression, adjusted for age, sex, and other risk factors, was used to assess the relation between blood pressure components and risk of death and cardiovascular events over a nine-year follow-up.

*Results.* The association with the risk of total mortality was positive for PP ($P$ = 0.002) and SBP ($P$ = 0.04), but not significant for DBP ($P$ = 0.4), considering each pressure individually (single blood pressure component model, SPM); of the three measurements, PP yielded the highest $\chi^2$ value. When SBP and DBP were jointly entered into the Cox regression model (dual blood pressure component model, DPM), the association with the risk of total mortality was positive for SBP (HR, 1.083; 95% CI, 1.030 to 1.137) and negative for DBP (HR, 0.886; 0.808 to 0.970). After the addition of diabetes mellitus as an adjusted variable to the model, PP was not a significant predictor for total mortality; PP was a significant predictor for total mortality in non-diabetic patients, but not in diabetic patients. PP was positively associated with the risk of stroke, and stroke and AMI; however, predictive value of PP for each endpoint was not superior to SBP and DBP in SPM. In DPM with SBP and DBP, the association with the risk of stroke and acute myocardial infarction (AMI) was positive for SBP ($P$ = 0.02) but not significant for DBP ($P$ = 0.5). In DPM with SBP and PP, the association with the risk of stroke and AMI was positive for SBP ($P$ = 0.01) but not significant for PP ($P$ = 0.5).

*Conclusions.* In non-diabetic patients on chronic hemodialysis, PP was an independent predictor of total mortality. PP was more potent predictor of total mortality than SBP or DBP. For predicting cardiovascular events, SBP was superior to PP or DBP.

**Key words:** systolic blood pressure, diastolic blood pressure, hypertension, stroke, acute myocardial infarction.

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Hypertension is a potent contributor to a poor prognosis [1], and a significant predictor of cardiovascular mortality [2] and stroke [3] in patients undergoing chronic dialysis. High systolic blood pressure (SBP) has been shown to predict a poor prognosis in hemodialysis patients [4]. In contrast, Duratini, Imperiali and Sasdelli found no significant difference in survival between normotension and hypertension in dialysis patients [5], and a "U" curve phenomenon between SBP and cardiovascular prognosis was observed by Zagar et al [6]. Moreover, Iseki et al previously reported that low diastolic blood pressure (DBP) was a significant risk factor of total mortality in chronic hemodialysis patients [7]. These results lead to the hypotheses that high SBP and low DBP may be significant predictors of mortality or subsequent cardiovascular events in chronic hemodialysis patients.

Blood pressure propagates through the arterial tree as a repetitive continuous wave and is more accurately described as consisting of a pulsatile component and a steady component [8]. The pulsatile component is pulse pressure (PP), which depends on ventricular ejection, arterial stiffness, and timing of wave reflections. The steady component is mean pressure, which is determined mainly by cardiac output and vascular resistance. PP has been shown as an independent risk factor for mortality or cardiovascular events in several studies in screened populations [9–12], hypertensive subjects [13–17], the elderly cohort [18] and patients with significant left ventricular dysfunction after myocardial infarction [19]. Amar et al examined 57 chronic hemodialysis dialysis patients and clearly demonstrated that 24-hour ambulatory PPs were potent indicators of cardiovascular death [20]. However, the impact of PP on prognosis in a relatively large cohort of chronic hemodialysis patients has not been sufficiently studied. The aim of the present study was to determine the effect of baseline levels of

PP on total mortality and cardiovascular events in a large cohort of chronic dialysis patients, and to examine whether PP adds useful value to SBP and DBP for predicting total mortality and cardiovascular events in chronic hemodialysis patients.

## METHODS

### Subjects

All hemodialysis patients in Okinawa, Japan, alive on January 1, 1991 were considered for the present study, and patients who consented were followed up until December 31, 1999. The demographics of this patient population were published previously [7]. Briefly, patients with end-stage renal disease who survived at least one month of dialysis were registered as chronic dialysis patients in the Okinawa Dialysis Study (OKIDS) registry. A total of 1243 patients (720 men, 523 women) were receiving maintenance hemodialysis as of January 1, 1991, when the study period began. All outcomes were known and confirmed. In 1041 patients (83.7%), dialysis was performed three times per week and in 708 patients (57.0%) the dialysis time was 3.5 to 4.0 hours per session. Bicarbonate solution was used as the dialysate in all patients; note that re-use of a dialyzer is not permitted in Japan. Baseline data of laboratory and clinical variables were obtained before the first dialysis session in January 1991. Similarly, baseline SBP and DBP values were recorded to establish blood pressure status pre-dialysis [21].

### Diagnosis of events

Stroke was diagnosed by both clinical symptoms and computed tomography (CT) brain scan [3] according to the criteria of the Ad Hoc Committee of the Ministry of Health and Welfare on Cerebrovascular Disease [22]. CT brain scan was performed in almost all patients with clinical disorders of stroke [23]. The time after the initial clinical symptoms of stroke was less than 48 hours, and if needed the CT scan was repeated. Therefore, we registered only definite cases of stroke that presented both CT brain scan and clinical symptoms. Acute myocardial infarction (AMI) was diagnosed when it was confirmed by electrocardiogram and/or changes in serum enzymes with the criteria used in the MONICA project [24]. Cardiovascular events were defined as events of stroke and AMI. Cardiovascular death was defined as death from stroke and AMI. Fatal stroke or fatal AMI were defined the death within 30 days after onset on the events. Previous cardiovascular complication was defined as a history of stroke and myocardial infarction. All patients were followed up until events of stroke or AMI, death from all causes, renal transplantation, transfer outside of Okinawa, or the end of 1999. All of these events were confirmed from medical records. Cause of death was determined by the criteria used in the study of Maillox et al [25]

### Statistical analysis

The unpaired $t$ test or the $\chi^2$ test was used to compare values or ratios between patients living or deceased. Trends of event rates according to the level of PP were tested by regression analysis.

The method of previous reports [12, 15] was modified and used for data analysis in the relationships between pressures (SBP, DBP and PP) and risk of total mortality or cardiovascular events. The associations of hazard ratios (HRs) of total mortality, stroke, AMI, and stroke + AMI to single (SBP, DBP, or PP) and dual (PP-SBP, PP-DBP, and SBP-DBP) blood pressure components, as continuous variables, were evaluated by Cox proportional hazards model [26]. Superiority of BP component in predicting end points was decided by $\chi^2$ value. Patients receiving renal transplantation or transferring outside Okinawa were included as censored cases. PP was calculated from SBP and DBP (PP = SBP − DBP). Models were adjusted for sex, age, duration of hemodialysis, smoking, serum creatinine, serum albumin, and previous cardiovascular complications. StatView 5.0 software (SAS Institute, Cary, NC, USA) was used for data analysis.

Survival curves were estimated with the Kaplan-Meier method and a log-rank test was used to compare groups according to PP. Multiple linear regression model was used to determine the independent predictors of PP. A $P$ value $<0.05$ was considered to be significant.

Hazard ratios of total mortality, and stroke and AMI were plotted with DBP for each SBP group (110, 130, 150, 170 and 190 mm Hg). An SBP of 130 and DBP of 80 mm Hg were selected as the references values having an HR of 1.0.

## RESULTS

### Characteristics of the cohort

The duration of follow-up (mean ± SD) was 75.8 ± 38.3 months. During the follow-up period, 475 patients died. Overall death rate was 60.3 deaths per 1000 patient-years. Table 1 shows the baseline variables of patients who died and who were alive. In the patients who died, age was greater, DBP was lower, and PP was higher than that in the living patients. Duration of hemodialysis was significantly shorter, and serum albumin and serum creatinine were also significantly lower in those who died. All patients had a similar percentage use of antihypertensive drug therapies. The percentage of patients diagnosed with diabetes mellitus and previous cardiovascular complications (stroke or AMI) was greater in the patients who died than that in the living patients.

**Table 1.** Characteristics of the patients

| Characteristics | All $N = 1234$ | Non-fatal $N = 768$ | Fatal $N = 475$ | $P^a$ |
|---|---|---|---|---|
| Male | 720 (58) | 451 (59) | 269 (57) | 0.44 |
| Age *years* | 52.3 ± 14.7 | 46.4 ± 12.5 | 61.9 ± 12.9 | < 0.0001 |
| Systolic blood pressure *mm Hg* | 151.5 ± 23.4 | 150.8 ± 22.9 | 152.7 ± 24.1 | 0.16 |
| Diastolic blood pressure *mm Hg* | 80.9 ± 13.4 | 82.8 ± 13.6 | 78.0 ± 12.6 | < 0.0001 |
| Pulse pressure *mm Hg* | 70.6 ± 18.1 | 68.0 ± 16.8 | 74.7 ± 19.4 | < 0.0001 |
| Body mass index $kg/m^2$ | 21.6 ± 3.2 | 21.6 ± 3.1 | 21.5 ± 3.3 | 0.58 |
| Duration of hemodialysis *months* | 62.2 ± 50.8 | 66.1 ± 50.8 | 55.9 ± 50.1 | 0.0006 |
| Serum albumin *g/dL* | 3.8 ± 0.4 | 3.9 ± 0.4 | 3.7 ± 0.4 | < 0.0001 |
| Serum creatinine *mg/dL* | 13.1 ± 3.4 | 14.0 ± 3.1 | 11.7 ± 3.3 | < 0.0001 |
| Smoker | 289 (24) | 196 (26) | 93 (20) | 0.01 |
| Antihypertensive treatment | 646 (52) | 398 (52) | 248 (52) | 0.94 |
| Diabetes mellitus | 212 (17) | 65 (8) | 147 (31) | < 0.0001 |
| Previous cardiovascular complications | 77 (6) | 32 (4) | 45 (9) | < 0.0003 |
| Duration of follow-up *months* | 75.8 ± 38.2 | 95.5 ± 28.2 | 44.2 ± 30.2 | < 0.0001 |

Values are expressed mean ± SD, or number (%).
[a] *P* value is non-fatal vs. fatal patients

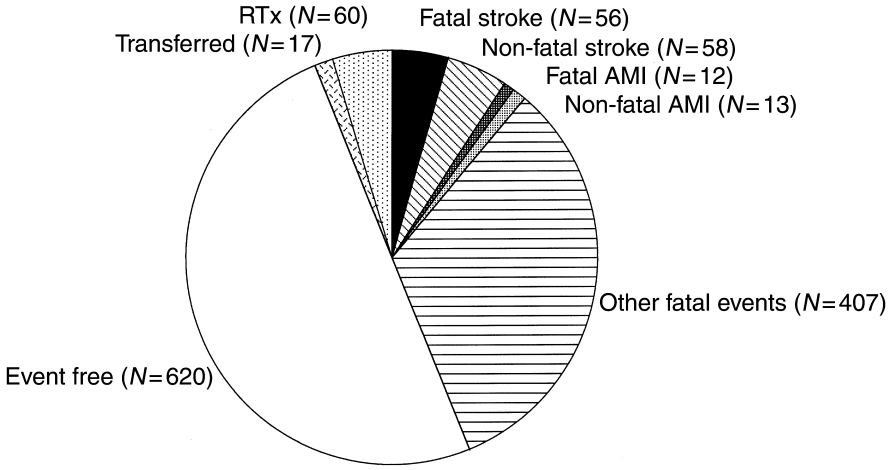


**Fig. 1. Primary events in 1243 hemodialysis patients.** *N* denotes the number of patients. Abbreviations are: RTx, renal transplantation; AMI, acute myocardial infarction.

## Outcome during nine-year-follow-up period

The outcome of 1243 patients is presented in Figure 1. The incidence of all stroke + AMI was 17.6 per 1000 patient-years. Incidence of stroke was 14.4 per 1000 patient-years and the incidence of AMI was 3.2 per 1000 patient-years. The number and event rate (%) of total mortality or cardiovascular events at each level of baseline PP are presented in Table 2. The correlation of event rate in relation to the level of PP was significant for the categories total mortality ($P = 0.01$), but not significant in other categories.

## Hazard ratios in single blood pressure components model (SPM) or dual blood pressure component model (DPM)

Hazard ratios of total mortality, stroke, AMI, and stroke + AMI were present in both SPM and DPM (Tables 3, 4, 5, 6). Model A was adjusted for age, sex, duration of hemodialysis, smoking, serum creatinine, and

**Table 2.** Primary events and baseline pulse pressure

| | Baseline pulse pressure *mm Hg* | | | | |
|---|---|---|---|---|---|
| Event | ≤59 $N = 264$ | 60–79 $N = 544$ | 80–99 $N = 315$ | 100+ $N = 120$ | Total $N = 1243$ |
| Total mortality | 74 (28) | 184 (33) | 145 (46) | 72 (60) | 475 (38) |
| Stroke + AMI | | | | | |
| All | 17 (6.4) | 68 (12) | 36 (11) | 18 (25) | 139 (11) |
| Fatal | 9 (3.4) | 32 (5.8) | 17 (5.3) | 10 (8.3) | 68 (5.4) |
| Non-fatal | 8 (3.0) | 36 (6.6) | 19 (6.0) | 8 (6.6) | 71 (5.7) |
| Stroke | | | | | |
| All | 14 (5.3) | 59 (10) | 28 (8.8) | 13 (10) | 114 (9.1) |
| Fatal | 8 (3.0) | 28 (5.1) | 14 (4.4) | 6 (5.0) | 56 (4.5) |
| Non-fatal | 6 (2.2) | 31 (5.6) | 14 (4.4) | 7 (5.8) | 58 (4.6) |
| AMI | | | | | |
| All | 3 (1.1) | 9 (1.6) | 8 (2.5) | 5 (0.8) | 25 (2.0) |
| Fatal | 1 (0.3) | 4 (0.7) | 3 (1.2) | 4 (0.7) | 12 (0.9) |
| Non-fatal | 2 (0.7) | 5 (0.9) | 5 (1.5) | 1 (0.8) | 13 (1.0) |

Values are the number (the event rate). AMI is acute myocardial infarction.

**Table 3.** Results of Cox proportional hazards regression analysis relating incidence of total mortality to single and dual blood pressure components of SBP, DBP, and PP

| | Model A[a] | | Model B[b] | |
|---|---|---|---|---|
| | Hazard ratio/10 mm Hg (CI)[c] | *P* value | Hazard ratio/10 mm Hg (CI)[c] | *P* value |
| Single blood pressure components *mm Hg* | | | | |
| PP | 1.080 (1.030–1.137) | 0.002 | 1.040 (0.990–1.104) | 0.1 |
| SBP | 1.040 (1.000–1.082) | 0.04 | 1.020 (0.980–1.061) | 0.4 |
| DBP | 0.970 (0.904–1.051) | 0.4 | 0.970 (0.895–1.040) | 0.3 |
| Dual blood pressure components *mm Hg* | | | | |
| Model 1 | | | | |
| PP | 1.127 (1.030–1.743) | 0.01 | 1.083 (0.990–1.195) | 0.08 |
| SBP | 0.960 (0.895–1.030) | 0.2 | 0.960 (0.895–1.010) | 0.3 |
| Model 2 | | | | |
| PP | 1.083 (1.030–1.135) | 0.001 | 1.040 (0.990–1.104) | 0.09 |
| DBP | 0.960 (0.895–1.030) | 0.2 | 0.960 (0.895–1.040) | 0.3 |
| Model 3 | | | | |
| SBP | 1.083 (1.030–1.137) | 0.001 | 1.040 (0.990–1.104) | 0.09 |
| DBP | 0.886 (0.808–0.970) | 0.01 | 0.923 (0.833–1.010) | 0.08 |

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; CI, 95% confidence interval.
[a] Model A was adjusted for age, sex, duration of hemodialysis, smoking, serum creatinine, serum albumin, and previous cardiovascular complications
[b] Model B was adjusted for variables used in Model A and diabetes mellitus
[c] Associated with a 10 mm Hg increment in the corresponding blood pressure component

**Table 4.** Results of Cox proportional hazards regression analysis relating incidence of stroke to single and dual blood pressure components of SBP, DBP, and PP

| | Model A[a] | | Model B[b] | |
|---|---|---|---|---|
| | Hazard ratio/10 mm Hg (CI)[c] | *P* value | Hazard ratio/10 mm Hg (CI)[c] | *P* value |
| Single blood pressure components *mm Hg* | | | | |
| PP | 1.127 (1.010–1.243) | 0.02 | 1.105 (0.990–1.230) | 0.08 |
| SBP | 1.116 (1.030–1.207) | 0.007 | 1.105 (1.020–1.207) | 0.01 |
| DBP | 1.173 (1.020–1.357) | 0.02 | 1.173 (1.020–1.357) | 0.02 |
| Dual blood pressure components *mm Hg* | | | | |
| Model 1 | | | | |
| PP | 0.941 (0.776–1.137) | 0.4 | 0.923 (0.768–1.126) | 0.4 |
| SBP | 1.161 (1.000–1.343) | 0.04 | 1.015 (1.000–1.343) | 0.04 |
| Model 2 | | | | |
| PP | 1.094 (0.980–1.218) | 0.10 | 1.072 (0.960–1.207) | 0.1 |
| DBP | 1.161 (1.000–1.343) | 0.04 | 1.161 (1.000–1.343) | 0.04 |
| Model 3 | | | | |
| SBP | 1.094 (0.980–1.218) | 0.1 | 1.072 (0.960–1.207) | 0.1 |
| DBP | 1.061 (0.877–1.280) | 0.5 | 1.083 (0.886–1.305) | 0.4 |

Abbreviations are: SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; CI, 95% confidence interval.
[a] Model A was adjusted for age, sex, duration of hemodialysis, smoking, serum creatinine, serum albumin, and previous cardiovascular complications
[b] Model B was adjusted for variables used in Model A and diabetes mellitus
[c] Associated with a 10 mm Hg increment in the corresponding blood pressure component

previous cardiovascular complications. Model B was adjusted for variables used in model A and diabetes mellitus.

## Total mortality

Of the three components (SBP, DBP, PP) in SPM, model A, PP was the most significant predictor of total mortality risk (Table 3); the $\chi^2$ values were 3.9 for SBP, 0.4 for DBP, and 9.2 for PP. In DPM, when SBP and DBP were jointly entered into the model (model 3), the association with risk of total mortality was positive for SBP and negative for DBP: HR values (95% confidence interval) were 1.083 (1.030 to 1.137) for SBP and 0.886 (0.808 to 0.970) for DBP. No incremental value of SBP or DBP was observed in the combination of PP and SBP (model 1) or PP and DBP (model 2), respectively, in predicting total mortality. When diabetes mellitus was added to the adjusted variables (model B), neither SBP, DBP, nor PP was significant predictor of total mortality in SPM or DPM (Table 3).

## Stroke

In model A, the association with stroke risk was positive for SBP, DBP, and PP, considering SPM (Table 4).

**Table 5.** Results of Cox proportional hazards regression analysis relating incidence of AMI to single and dual blood pressure components of SBP, DBP, and PP

| | Model A[a] | | Model B[b] | |
|---|---|---|---|---|
| | Hazard ratio/10 mm Hg (CI)[c] | *P* value | Hazard ratio/10 mm Hg (CI)[c] | *P* value |
| Single blood pressure components *mm Hg* | | | | |
| PP | 1.246 (1.000–1.552) | 0.05 | 1.150 (0.922–1.438) | 0.2 |
| SBP | 1.233 (1.040–1.466) | 0.01 | 1.185 (1.000–1.410) | 0.04 |
| DBP | 1.323 (0.970–1.790) | 0.07 | 1.323 (0.970–1.790) | 0.07 |
| Dual blood pressure components *mm Hg* | | | | |
| Model 1 | | | | |
| PP | 0.960 (0.637–1.438) | 0.84 | 0.878 (0.586–1.305) | 0.5 |
| SBP | 1.271 (0.932–1.724) | 0.12 | 1.296 (0.951–1.757) | 0.09 |
| Model 2 | | | | |
| PP | 1.221 (0.970–1.538) | 0.09 | 1.138 (0.904–1.424) | 0.2 |
| DBP | 1.271 (0.932–1.724) | 0.1 | 1.296 (0.951–1.757) | 0.09 |
| Model 3 | | | | |
| SBP | 1.221 (0.970–1.538) | 0.09 | 1.138 (0.904–1.424) | 0.2 |
| DBP | 1.040 (0.693–1.567) | 0.8 | 1.138 (0.768–1.693) | 0.5 |

Abbreviations are: AMI, acute mycardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; CI, 95% confidence interval.
[a] Model A was adjusted for age, sex, duration of hemodialysis, smoking, serum creatinine, serum albumin, and previous cardiovascular complications
[b] Model B was adjusted for variables used in Model A and diabetes mellitus
[c] Associated with a 10 mm Hg increment in the corresponding blood pressure component

**Table 6.** Results of Cox proportional hazards regression analysis relating incidence of stroke and AMI to single and dual blood pressure components of SBP, DBP, and PP

| | Model A[a] | | Model B[b] | |
|---|---|---|---|---|
| | Hazard ratio/10 mm Hg (CI)[c] | *P* value | Hazard ratio/10 mm Hg (CI)[c] | *P* value |
| Single blood pressure components *mm Hg* | | | | |
| PP | 1.127 (1.030–1.243) | 0.01 | 1.105 (1.000–1.218) | 0.04 |
| SBP | 1.138 (1.061–1.230) | 0.0006 | 1.127 (1.040–1.270) | 0.002 |
| DBP | 1.197 (1.051–1.370) | 0.006 | 1.197 (1.051–1.370) | 0.007 |
| Dual blood pressure components *mm Hg* | | | | |
| Model 1 | | | | |
| PP | 0.951 (0.792–1.126) | 0.5 | 0.923 (0.843–1.093) | 0.3 |
| SBP | 1.173 (1.030–1.343) | 0.01 | 1.185 (1.040–1.343) | 0.01 |
| Model 2 | | | | |
| PP | 1.116 (1.010–1.230) | 0.02 | 1.094 (0.990–1.207) | 0.09 |
| DBP | 1.173 (1.030–1.343) | 0.01 | 1.185 (1.159–1.343) | 0.01 |
| Model 3 | | | | |
| SBP | 1.116 (1.010–1.230) | 0.02 | 1.094 (0.990–1.207) | 0.09 |
| DBP | 1.051 (0.886–1.255) | 0.5 | 1.083 (0.913–1.292) | 0.3 |

Abbreviations are: AMI, acute myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; CI, 95% confidence interval.
[a] Model A was adjusted for age, sex, duration of hemodialysis, smoking, serum creatinine, serum albumin, and previous cardiovascular complications
[b] Model B was adjusted for variables used in Model A and diabetes mellitus
[c] Associated with a 10 mm Hg increment in the corresponding blood pressure component

Of the three components, SBP was the most significant, and PP and DBP were similar in predicting stroke. DPM showed that SBP or DBP was superior to PP for predicting stroke (Table 4, model 1, model 2). After an adjustment for diabetes mellitus, the predictive values of SBP and DBP were preserved, but that of PP was lost.

## AMI

Only SBP had a positive association with the stroke risk in SPM (Table 5, model A). The significance was preserved after adjustment for diabetes mellitus. PP showed only borderline significance in SPM (model A). No pressure component was a significant predictor of AMI in DPM (Table 5, models 1, 2 and 3).

## Stroke and AMI

Systolic blood pressure, DBP, and PP had a positive association with stroke risk (Table 6, model A, SPM). SBP ($\chi^2 = 11.8$) was superior to PP ($\chi^2 = 6.4$) or DBP ($\chi^2 = 7.5$) in predicting stroke and AMI. The significance was not lost in any of the three pressure components

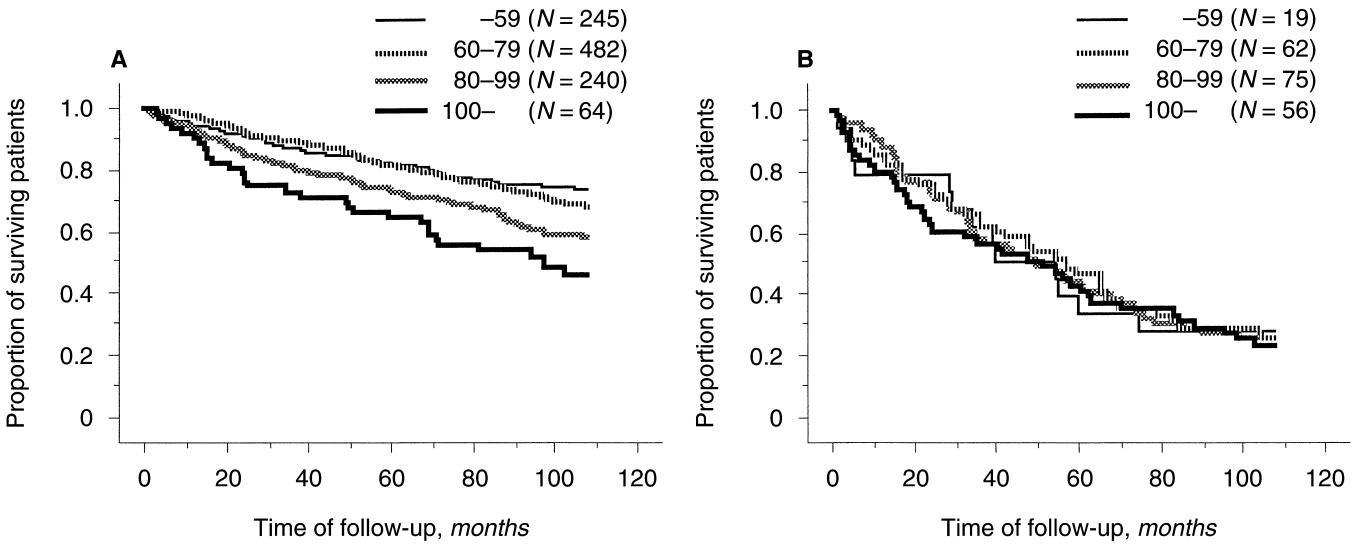


**Fig. 2. Survival curves by the baseline pulse pressure (PP) in non-diabetic (*A*; $N = 1031$; $P < 0.0001$) and diabetic (*B*; $N = 212$; $P = 0.9$) patients on chronic hemodialysis.** The follow-up period was from January 1, 1991 to December 31, 1999.

after an adjustment for diabetes mellitus. In DPM, SBP (mode 1) or DBP (model 2) was superior to PP in predicting stroke and AMI (Table 6). In DPM with SBP and DBP (model 3), SBP was significantly positive for predicting stroke and AMI ($P = 0.02$), but DBP was not significant ($P = 0.5$). The significance in SBP was lost after adjustment for diabetes mellitus.

### HRs of PP in diabetic patients

When considered the subjects with the presence ($N = 212$) or absence of diabetes mellitus ($N = 1031$), PP predicted total mortality (HR, 1.072; CI 1.010 to 1.149; $P < 0.05$), and stroke and AMI (HR, 1.138; CI 1.010 to 1.280; $P < 0.05$) in non-diabetic patients but not in diabetic patients, after adjusting for age, sex, duration of hemodialysis, smoker, serum creatinine, serum albumin, and previous cardiovascular complications.

### PP and survival curves

Patients with and without diabetes were analyzed for the relationship between PP and total mortality, or cardiovascular events by the Kaplan-Meier method. Figure 2 shows the survival curves of total mortality in relation to baseline levels of PP. Higher baseline PP ranges were associated with high mortality in non-diabetic patients. However, no appreciable differences were observed among the subgroups in diabetic patients. Figure 3 shows the event-free rates for cardiovascular events (stroke and AMI) by baseline levels of PP. Higher baseline PP ranges were associated with higher rates of cardiovascular events in non-diabetic patients, whereas no difference was observed among the subgroups in diabetic patients.

### Joint influence of SBP and DBP on risk of total mortality, and stroke and AMI

For any level of DBP, subjects with higher SBP, that is, a higher PP value, had greater mortality risk ($P = 0.001$, Fig. 4); alternatively, for any level of SBP, those with lower DBP had greater risk ($P = 0.01$). For any given level of DBP, subjects with higher SBP (that is, higher PP) also had greater risk of stroke and AMI ($P = 0.02$, Fig. 5), and in contrast, for any given level of SBP, those with lower DBP seemed to have a greater risk, but it was not significant ($P = 0.5$).

### Factors correlate with PP

To analyze which characteristics of this patient cohort was associated with a wide PP, we performed multiple linear regression analysis with PP as the dependent variable (Table 7). Independent variables in the analysis are all presented in the Table. In all patients, age, body mass index, duration of hemodialysis, serum albumin, antihypertensive treatment, and diabetes mellitus were significant predictors of PP. When considered with or without diabetes mellitus, age, duration of hemodialysis, serum albumin, antihypertensive treatment were significant predictors of PP in non-diabetic patients; body mass index and antihypertensive treatment were significant predictors of PP in diabetic patients.

### Relationship between SBP, DBP and PP

Figure 6 shows the relation between SBP, DBP, and quintiles of PP ($N = 1234$). Higher SBP and lower DBP generated a wider range of PP. Higher SBP contributed more to a wide PP than did lower DBP values.

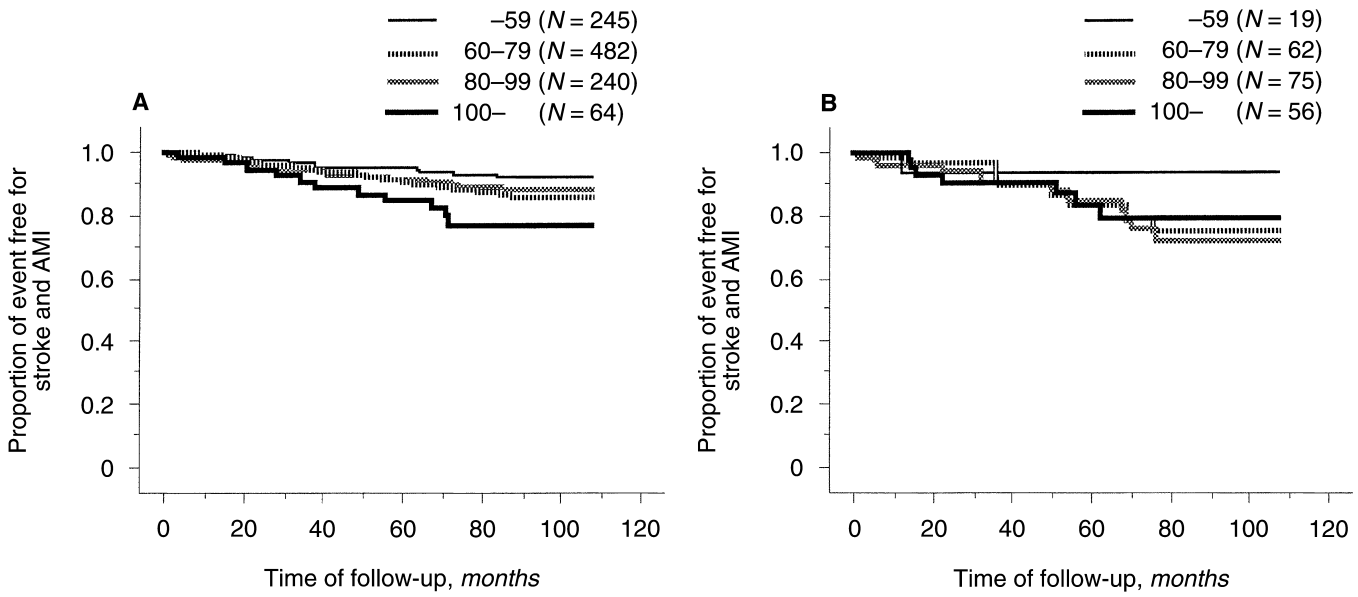


**Fig. 3. Event free rates for stroke and acute myocardial infarction (AMI) by the baseline pulse pressure in non-diabetic (*A*; $N = 1031$; $P = 0.01$) and diabetic (*B*; $N = 212$; $P = 0.7$) patients on chronic hemodialysis.** The follow-up period was from January 1, 1991 to December 31, 1999.

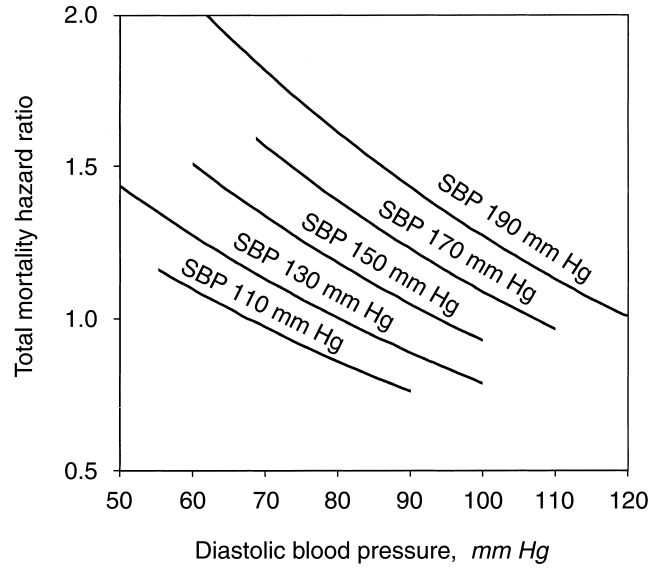


**Fig. 4. Joint effects of systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the risk of total mortality.** Total mortality ratios were calculated from the level of DBP with the SBP groups in the dual BP component model (Table 3, Model A, Model 3). Hazard ratios were set to a reference value of 1.0 for SBP of 130 mm Hg and DBP of 80 mm Hg. Hazard ratios were plotted for SBP values of 110, 130, 150, and 170 mm Hg, respectively. The range of DBP in the patients for each level of SBP was used to define the plotted range of DBP. All estimates were adjusted for age, sex, duration of hemodialysis, smoking, serum creatinine, serum albumin and previous cardiovascular complications.

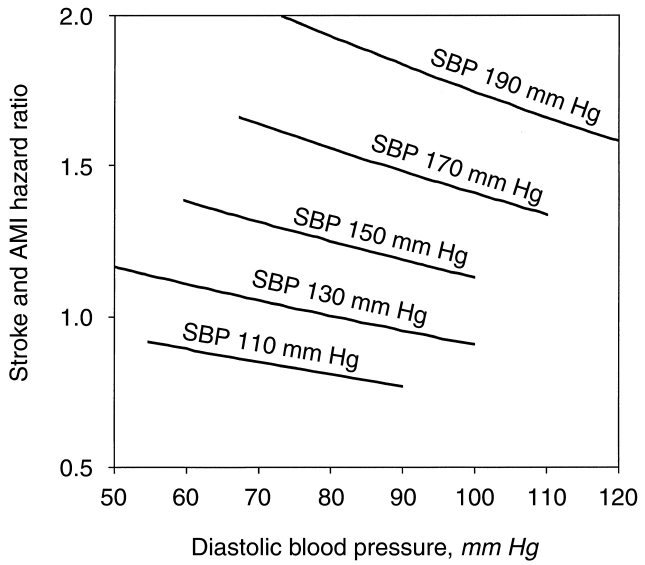


**Fig. 5. Joint effects of systolic blood pressure (SBP) and diastolic blood pressure (DBP) on the risk of stroke and acute myocardial infarction (AMI).** Stroke and AMI hazard ratios were calculated from the level of DBP within the SBP groups in the dual BP component model (Table 6, Model A, Model 3). Hazard ratios were set to a reference value of 1.0 for an SBP of 130 mm Hg and DBP of 80 mm Hg. Hazard ratios were plotted for SBP values of 110, 130, 150, 170, and 190 mm Hg, respectively. The range of DBP in the patients for each level of SBP was used to define the plotted range of DBP. All estimates were adjusted for age, sex, duration of hemodialysis, smoking, serum creatinine, serum albumin and previous cardiovascular complications.

**Table 7.** Results of multiple linear regression analysis with pulse pressure as the dependent variable

| | All | | Non-DM | | DM | |
|---|---|---|---|---|---|---|
| Independent variables | β | *P* | β | *P* | β | *P* |
| Sex (male = 1, female = 0) | 0.67 | 0.53 | 1.14 | 0.31 | −2.8 | 0.36 |
| Age *years* | 0.17 | <0.0001 | 0.19 | <0.0001 | 0.03 | 0.75 |
| Body mass index $kg/m^2$ | −0.30 | 0.04 | −0.15 | 0.36 | −0.91 | 0.02 |
| Duration of hemodialysis *months* | −0.04 | <0.0001 | −0.04 | <0.0001 | −0.002 | 0.96 |
| Serum albumin *g/dL* | −3.0 | 0.003 | −3.0 | 0.0009 | −3.2 | 0.27 |
| Serum creatinine *mg/dL* | 0.22 | 0.20 | 0.22 | 0.16 | 0.13 | 0.79 |
| Smoker (yes = 1, no = 0) | 1.9 | 0.09 | 1.9 | 0.24 | 5.3 | 0.17 |
| Antihypertensive treatment (treated = 1, not treated = 0) | 10.6 | <0.0001 | 10.1 | <0.0001 | 12.3 | <0.0001 |
| DM (present = 1, none = 0) | 9.8 | <0.0001 | — | — | — | — |
| Previous cardiovascular complications (present = 1, none = 0) | −0.5 | 0.76 | 0.4 | 0.83 | −1.06 | 0.80 |

$R^2 = 0.21$, F = 34.2, $P < 0.0001$ for all; $R^2 = 0.15$, F = 20.4, $P < 0.0001$ for non-DM; $R^2 = 0.13$, F = 3.4, $P = 0.0005$ for DM. DM is diabetes mellitus. In the multiple regression analysis, pulse pressure was assigned dependent factor, and sex, age, body mass index, duration of hemodialysis, serum albumin, serum creatinine, smoker, antihypertensive treatment, DM, and previous cardiovascular complications were assigned independent factors.

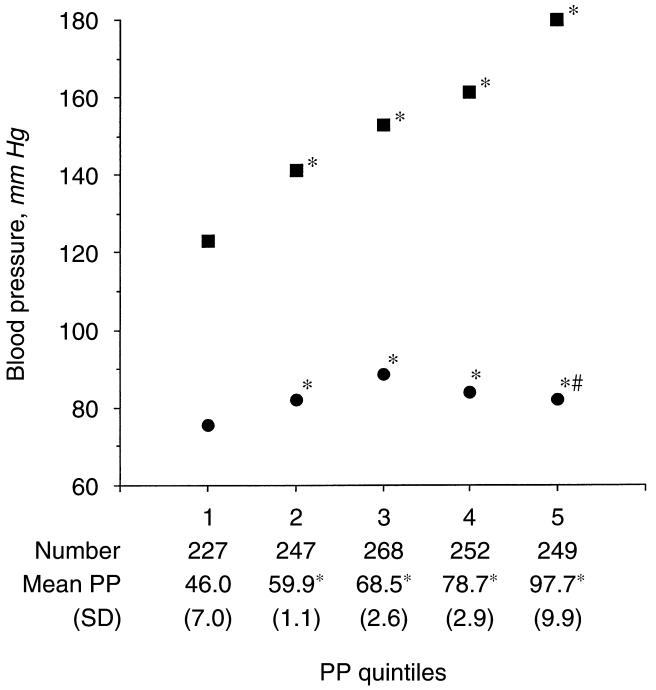


**Fig. 6. Relationship between SBP (■) and DBP (●), and the quintile of pulse pressure (PP).** *$P < 0.05$ vs. the first quintile of PP; #$P < 0.05$ vs. the third quintile of PP. SD is standard deviation.

## DISCUSSION

The major findings of this nine-year follow-up study were that in a large cohort of chronic hemodialysis patients, baseline PP independently predicted the incidence of total mortality in non-diabetic patients. The wider the range of PP, the greater the increased risk of mortality. Higher SBP [4] or lower DBP [7] values increased the risk of mortality in hemodialysis patients. The results of the present study not only support the results of previous reports, but also confirm that higher SBP and lower DBP values, that is, a wider PP range, correlate with a significant risk of death in patients on hemodialysis. Furthermore, in the present study the power of PP for predicting total mortality was more potent than that of SBP or DBP alone. In SPM, the association with the risk of stroke and AMI was positive for SBP, DBP and PP, respectively. However, in DPM with SBP and PP, the association with the risk of stroke and AMI was positive for SBP, but not significant for PP. Furthermore, in DPM with SBP and DBP model, only SBP was significantly positive for predicting stroke and AMI. These results indicate that PP may be dependent on SBP for predicting stroke and AMI. Previous reports showed that PP was superior to SBP, DBP, or mean pressure in predicting cardiovascular events [11, 12, 15, 19]. However, the superiority of PP to SBP or DBP for predicting the risk of cardiovascular events was not evident in the present study. For predicting cardiovascular events, SBP was superior to PP or DBP.

Diabetes mellitus accelerates the reduction of compliance of the vessel [27], and stiffening of arteries results in increased PP through an increase in both aortic impedance and pulse wave velocity as described by Domanski et al [17]. Therefore, a widening PP can be driven by diabetes mellitus, and a correlation between presence of diabetes mellitus and wider PP was expected. Indeed, the mean (±SD) PP in diabetic patients (82 ± 20 mm Hg) was significantly higher than in non-diabetic patients (68 ± 16 mm Hg, $P < 0.0001$) in the present study. And a multiple linear regression analysis showed that a correlation between presence of diabetes mellitus and wider PP was significant (Table 5). The strong association between diabetes mellitus and PP explains why the PP was not the predictor for the total mortality and cardiovascular events in diabetic patients.

The high prevalence of atherosclerosis-related complications and marked abnormalities of arterial compliance

have been well documented in hemodialysis patients [28, 29]. It also is known that prolonged uremia has a deleterious effect on stiffening of the artery wall [30]. Such known complications help rationalize the positive relationship between a wide PP range and mortality or cardiovascular events in hemodialysis patients, as shown in this study. However, the mechanisms of accelerated atherogenesis in hemodialysis patients remain a matter for debate [31].

Hypertension is a significant predictor of cardiovascular mortality [2, 3] in hemodialysis patients. However, hypertension has not been adequately controlled in patients [21, 32]. Amar et al reported that 24-hour ambulatory PP ranges were predictors of mortality in hemodialysis patients [20]. The present study showed that PP was a risk of total mortality. Therefore, we suggest that the goal of antihypertensive therapy in hemodialysis patients not only should be to reduce blood pressure, but also decrease PP. Although it was reported that angiotensin II type 1-receptor blockers reduced PP [33], a drug of choice in terms of controlling and reducing wide PP ranges should be explored further. The present study also showed that treatment of antihypertensive medication was positively correlated with a wide PP (Table 7), and higher SBP contribute more to a wider PP than did lower DBP (Fig. 6). Therefore, control of systolic hypertension may be a strategy to reduce the wide PP range.

Antihypertensive medication was only a common predictor of PP between non-diabetes and diabetes patients (Table 7). In the present cohort, we previously reported that a SBP in patients with diabetes mellitus was significantly higher (mean ± SEM, 161.4 ± 1.6 mm Hg, $P < 0.001$) than that of non-diabetics (149.4 ± 0.7 mm Hg); the DBP in diabetes mellitus patients (78.8 ± 0.9 mm Hg) was significantly lower than that of non-diabetics (81.3 ± 0.4 mm Hg) [21]. The percentage of patients with antihypertensive medication was higher in diabetes (65%, $P < 0.0001$) than in non-diabetes patients (49%). This suggested that control of systolic hypertension in diabetic patients was poor in spite of a higher percentage of antihypertensive medication. This may contribute to the wider PP found in diabetes than in non-diabetes patients.

A lower body mass index and serum albumin are thought to be indices of malnutrition, and using these indices, several studies have suggested that malnutrition is a significant determinant of clinical outcomes in chronic hemodialysis patients [34]. In the present study, a lower body mass index or serum albumin was an independent predictor of a wide PP in diabetic or non-diabetic patients (Table 7). Some nutritional factors would affect the range of PP. However, whether to restore good nutritional status will make a PP smaller has not been determined.

In summary, in a large cohort of chronic hemodialysis patients studied for nine years, a wider PP range was found to be a significant independent predictor of total mortality in the non-diabetic patient. PP was superior to SBP and DBP in predicting total mortality. For predicting cardiovascular events, SBP was superior to PP and DBP. Further evidence for PP as a risk factor of total mortality should be clarified by randomized prospective studies.

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## REFERENCES

1. Charra B, Calemard E, Ruffet M, *et al*: Survival as an index of adequacy of dialysis. *Kidney Int* 41:1286–1291, 1992
2. Foley RN, Parfrey PS, Harnett JD, *et al*: Impact of hypertension on cardiomyopathy, morbidity and mortality in end-stage renal disease. *Kidney Int* 49:1379–1385, 1996
3. Iseki K, Fukiyama K: Predictors of stroke in patients receiving chronic hemodialysis. *Kidney Int* 50:1672–1675, 1996
4. Tomita J, Kimura G, Inoue T, *et al*: Role of systolic blood pressure in determining prognosis of hemodialyzed patients. *Am J Kidney Dis* 25:405–412, 1995
5. Duranti E, Imperiali P, Sasdelli M: Is hypertension a mortality risk factor in dialysis? *Kidney Int* 55:S173–S174, 1996
6. 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* 54:561–569, 1998
7. 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* 51:1212–1217, 1997
8. Nichols WW, O'Rourke MF: Properties of the arterial wall, in *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles* (4th ed), London, Arnold, 1998
9. Benetos A, Safar M, Rudnichi A, *et al*: Pulse pressure: A predictor of long-term cardiovascular mortality in a French male population. *Hypertension* 30:1410–1415, 1997
10. Fang J, Madhavan S, Cohen H, Alderman MH: Measures of blood pressure and myocardial infarction in treated hypertensive patients. *J Hypertens* 13:413–419, 1995
11. Scuteri A, Cacciafesta M, Di Bernardo MG, *et al*: Pulsatile versus steady-state component of blood pressure in elderly females: an independent risk factor for cardiovascular disease? *J Hypertens* 13:185–191, 1995
12. Franklin SS, Khan SA, Wong ND, *et al*: Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation* 100:354–360, 1999
13. Benetos A, Rudnichi A, Safar M: Guize: Pulse pressure and

cardiovascular mortality in normotensive and hypertensive subjects. *Hypertension* 32:560–564, 1998
14. Madhavan S, Ooi WL, Cohen H, Alderman MH: Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension* 23:395–401, 1994
15. Blacher J, Staessen JA, Girerd X, *et al*: Pulse pressure not mean pressure determines cardiovascular risk in older hypertensive patients. *Arch Intern Med* 160:1085–1089, 2000
16. Millar JA, Lever AF, Burke V: Pulse pressure as a risk factor for cardiovascular events in the MRC Mild Hypertension Trial. *J Hypertens* 17:1065–1072, 1999
17. Domanski MJ, Davis BR, Pfeffer MA, *et al*: Isolated systolic hypertension: Prognostic information provided by pulse pressure. *Hypertension* 34:375–380, 1999
18. Chae CU, Pfeffer MA, Glynn RJ, *et al*: Increased pulse pressure and risk of heart failure in the elderly. *JAMA* 281:634–639, 1999
19. Mitchell GF, Moye LA, Braunwald E, *et al*: Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. *Circulation* 96:4254–4260, 1997
20. Amar J, Vernier I, Rossignol E, *et al*: Nocturnal blood pressure and 24-hour pulse pressure are potent indicators of mortality in hemodialysis patients. *Kidney Int* 57:2485–2491, 2000
21. Tozawa M, Iseki K, Fukiyama K: Hypertension in dialysis patients: A cross-sectional analysis. *Nippon Jinzo Gakkai Shi* (*Jpn J Nephrol*) 38:129–135, 1996
22. Kinjo K, Kimura Y, Shinzato Y, *et al*: An epidemiological analysis of cardiovascular disease in Okinawa, Japan. *Hypertens Res* 15:111–119, 1992
23. Special Report from the National Institute of Neurological Disorders and Stroke: Classification of cerebrovascular disorders III. *Stroke* 21:637–676, 1990
24. Tuomilehto J, Kuulasmaa K, WHO MONICA Project: Assessing CHD mortality and morbidity. *Int J Epidemiol* 18(Suppl 1):S38–S45, 1989
25. Mailloux LU, Bellucci AG, Wilkes BM, *et al*: Mortality in dialysis patients: Analysis of the causes of death. *Am J Kidney Dis* 18:326–335, 1991
26. Cox DR: Regression models and life tables. *J R Stat Soc B* 34:187–220, 1972
27. Salomaa V, Riley W, Kark JD, *et al*: Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation* 91:1432–1443, 1995
28. Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290:697–701, 1974
29. London GM: Increased arterial stiffness in end-stage renal failure: Why is it of interest to the clinical nephrologist? *Nephrol Dial Transplant* 9:1709–1712, 1994
30. Luik AJ, Spek JJ, Charra B, *et al*: Arterial compliance in patients on long-treatment-time dialysis. *Nephrol Dial Transplant* 12:2629–2632, 1997
31. Meeus F, Kourilsky O, Guerin AP, *et al*: Pathophysiology of cardiovascular disease in hemodialysis patients. *Kidney Int* 58 (Suppl 76):S140–S147, 2000
32. Salem MM: Hypertension in the hemodialysis population: A survey of 649 patients. *Am J Kidney Dis* 26:461–468, 1995
33. Asmar R, Lacourcière Y, on behalf of the Candesartan cilexetil in Hypertension Ambulatory Measurement of Blood Pressure (CHAMP) Study Investigators: A new approach to assessing antihypertensive therapy: Effect of treatment on pulse pressure. *J Hypertens* 18:1683–1690, 2000
34. Bergström J: Nutrition and mortality in hemodialysis. *J Am Soc Nephrol* 6:1329–1341, 1995