Visit-to-Visit Blood Pressure Variability Is a Strong Predictor of Cardiovascular Events in Hemodialysis

Insights From FOSIDIAL

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Abstract—Optimal blood pressure (BP) targets are still controversial in end-stage renal disease. Recent data have highlighted shortcomings of the usual BP hypothesis in other patient populations and emphasized the importance of visit-to-visit variability of BP in predicting cardiovascular events. The Fosinopril in Dialysis Study failed to demonstrate the efficacy of 2-year angiotensin-converting enzyme inhibition with fosinopril versus placebo in 397 hemodialysis patients with left ventricular hypertrophy but provided an opportunity to assess the influence of BP variability on cardiovascular events. The primary end point was the occurrence of a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, revascularization, hospitalization for heart failure, and resuscitated cardiac arrest. The variations in BP throughout the 17 visits were assessed by within-patient overall variability of systolic, diastolic, and pulse pressures between adjacent readings, by within-patient overall variability of systolic/diastolic/pulse pressures, and the residual of the linear fit. Compared with our previous predictive model of cardiovascular events occurrence based on stroke, peripheral arterial disease, coronary artery disease, diabetes mellitus, left ventricular mass, and age (which exhibited similar coefficients herein), the percentage of explained variance improved by 30.1% (R^2=0.141–0.183) when adding the coefficient of variation of within-patient overall variability of systolic BP. Usual BP parameters were neither cardiovascular events predictors nor correlated to BP variability. Visit-to-visit BP variability was extremely high in hemodialysis patients compared with other populations and a major determinant of cardiovascular events. Such assessments should be prioritized for testing prevention strategies in end-stage renal disease. (***Hypertension.*** **2012;60:339-346.)** • **Online Data Supplement**

Key Words: blood pressure ■ renal insufficiency ■ chronic ■ hemodialysis ■ cardiovascular ■ prognosis ■ clinical trial

Hypertension is highly prevalent in patients with end-stage renal disease (ESRD), and it is often poorly controlled.[1] Hypertension, together with high pulse pressure (PP), may contribute to the observed excess in cardiovascular disease morbidity and mortality in this population.[2] ESRD is associated with a 3- to 10-fold increased risk of cardiovascular events as compared with general populations.[3] Cardiac disease is the leading cause of death among patients with ESRD, representing 42% of all-cause mortality.[4]

To date, antihypertensive drugs are the only treatment strategies that reduce cardiovascular risk in ESRD patients.[5,6] However, the relationship between blood pressure (BP) and cardiovascular outcomes is complex in these patients.[7] A reverse epidemiology has been described, with a paradoxical link between low BP and poor survival, whereas high BP appears to confer survival advantages.[8] Thus, the relationship between BP and cardiovascular events appears to be multifactorial, and variables other than absolute BP measurements may play an important role in the pathophysiology of cardiovascular disease in these patients.

Elevated systolic or diastolic BP (SBP or DBP) has generally been considered the main blood pressure–related risk factor associated with cardiovascular disease, justifying widespread use of antihypertensive drugs. However, the usual BP hypothesis (the theoretical true underlying level of BP that determines the adverse consequences of BP)[9] may not fully characterize the pathophysiologic relationship between BP and cardiovascular outcomes. Other factors, such as BP

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variability, are also prognostically important.[9] Visit-to-visit variability in SBP has been shown to strongly predict stroke in patients with treated hypertension and in patients with a previous transient ischemic attack, independent of mean SBP.[10] It has also been associated with an increased risk of all-cause mortality among adults enrolled in the National Health and Nutrition Examination Survey III Study.[11]

A high degree of visit-to-visit BP variability has been demonstrated in patients with ESRD.[12] Rohrscheib et al[12] reported a visit-to-visit BP variability of 18.03 mm Hg, a value that exceeded the variability reported in patients with previous transient ischemic attack or treated hypertension[10] and in the general population.[11] The influence of BP variability on cardiovascular outcomes in the ESRD population has not been widely studied. The Fosinopril in Dialysis (FOSIDIAL) Study evaluated the safety and efficacy of long-term angiotensin-converting enzyme inhibition with fosinopril compared with placebo on cardiovascular clinical outcomes in hemodialysis patients with left ventricular hypertrophy.[13] This database provides a unique opportunity to assess the influence of BP variability on cardiovascular outcomes in ESRD patients on maintenance hemodialysis.

Methods

The design[14] and main results[13] of FOSIDIAL have been reported previously. Briefly, 397 patients with ESRD and left ventricular hypertrophy were randomized to receive fosinopril or placebo for 24 months. The primary end point of the study was the composite of cardiovascular death, nonfatal myocardial infarction, unstable angina, stroke, revascularization, hospitalization for heart failure, or resuscitated cardiac arrest. This composite cardiovascular end point was used as the primary end point for the purpose of this analysis. All of the critical events were adjudicated by a critical event committee according to predefined criteria, as reported previously.[13]

BP Measurements and Definitions of BP Variability

At each 1 of 17 study visits, BP measurements were performed by trained hemodialysis nurses according to World Health Organization guidelines, using a mercury sphygmomanometer, with an appropriate cuff. Measurements were systematically performed predialysis, after a 10-minute rest, in a sitting position. Three consecutive measurements were performed 2 minutes apart, and the mean value was recorded.

The variation in BP with time was measured according to various parameters. All of the variables were calculated as described by Rothwell et al[10,15]: (1) the average absolute difference between adjacent readings (successive variation) of systolic BP (ASBP) calculated over the 17 BP measures at each visit and its coefficient of variation (CV)ASBP=100*ASBP/mean(SBP) and similar parameters ADBP and CVADBP were calculated for diastolic pressures; (2) the SD of the 17 SBP values at each visit and its CVSBP=SDSBP/mean(SBP) and corresponding values SDDBP and CVDBP for diastolic pressures; (3) because the CV and mean BP can still be correlated using CV variables, the residual of the linear fit between SD and the mean was also calculated for both systolic (RSSBP) and diastolic pressures (RSDBP); and (4) the within-patient overall variability of PP (SDPP) was calculated as the SD of the differences SBP−DBP for each of the 17 visits and its CV (CVPP).

Because only very few missing data were observed during the main analysis of this trial (99.2% of pressure measurements for all the visits, not including dropouts), the calculation of the above described BP parameters was based on the nonmissing values, and no missing data imputation was organized. Because outcome events were also evaluated during the same period, as BP measurements, a cause-outcome relationship may be questioned, and it is possible that BP values measured just before an event could be influenced by the event itself. A bias because of the fall or rise in the on-treatment BP as a forerunner of an event would be observed. To evaluate the potential for this bias, we constructed alternative parameters of pressure variability (CVSBP and CVDBP) in 2 different ways: CVSBP1 and CVDBP1 were calculated by suppressing measures for which the absolute value of the time lag with a critical event was <2 months. The alternative CVSBP2 and CVDBP2 were calculated on the 5 first visits corresponding with the 3 first weeks of the follow-up and excluded visits too close to a critical end point, as indicated above. These alternative measurements of BP variability were used to conduct sensitivity analyses.

Finally, the hemodialysis interval is variable. Thus, it may influence BP measurements that were obtained before every hemodialysis session. We conducted a complementary analysis in ASBP and CVASBP by adjusting each value for hemodialysis time.

Statistical Analysis

The measures of BP variability described above constitute various ways to estimate BP variability over time. BP variability parameters were calculated for each patient, and interrelationships were estimated between all of the parameters. Their consistency and interrelationships were studied through a principal components analysis.

Using the previously published Cox proportional hazards model as the reference,[13] the additional BP variability parameters were added to the model. The influence of these variables on the model was evaluated by comparing the likelihood ratios between the basic model and the model including the BP parameters. Simultaneously, Akaike Index Criteria were used to judge the supplemental information provided by these variables.

Finally, a stepwise Cox regression analysis was conducted that entered all of the variables into the analysis (including all of the baseline covariates listed in Table 1 except C-reactive protein, where only 303 patients were documented) and the variability parameters. All were continuous variables but 13 (previous cardiovascular events, coronary artery disease, peripheral arterial disease and stroke history, current smokers, diabetes mellitus, dyslipidemia, treated by erythropoietin, oral antidiabetic, insulin, hypertension, dyslipidemia, and previous transplantation, which were recorded on patient medical files) to assess the stability of our model to additional predictors. The stepwise strategy was based on $P=0.05$ and was repeated with other conditions to assess its stability: (1) $P=0.10$; (2) $P=0.05$ for main effects and $P=0.20$ for interactions; and (3) backward strategy based on $P=0.05$ and $P=0.10$.

The model calibration (goodness of fit between observed and expected [predicted] values of response irrespective of prediction level) was evaluated by the Hosmer and Lemeshow goodness-of-fit test.[16] A correction factor[17] was also evaluated.

A bootstrapping technique was used to reduce the overfit of the model and to obtain relatively unbiased estimates.[18] The same analysis was replicated (n=250), and the result was summarized by a shrinkage factor, used to correct the final model.

Results

Patient Demographics

In the main FOSIDIAL Study, 201 patients were randomized to placebo, and 196 patients were randomized to fosinopril. Of these, 10 had missing BP data such that the BP parameters of interest could not be calculated on ≥3 consecutive visits and were excluded from this analysis. Thus, the analysis population consists of 388 patients (197 and 191 under placebo and fosinopril, respectively).

Baseline characteristics were almost similar between treatment groups (Table 1). The overall primary composite cardiovascular end point event rate was 32.7% over the 2-year follow-up.[13] BP measurements over the course of the study are shown in the Table 2.

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Table 1. Baseline Characteristics

Features	Placebo	Fosinopril
Age, y	67.22±7.95	66.39±7.89
Women proportion	(99) 49.3	(90) 45.9
BMI (before dialysis), kg/m^2	27.31±5.77	25.99±5.19
Baseline SBP, mm Hg	145.07±19.89	146.49±19.27
Baseline DBP, mm Hg	76.88±10.92	76.52±11.42
Baseline pulse pressure, mm Hg	70.00±17.42	69.54±17.05
Log(left ventricular mass in g)	2.21±0.11	2.25±0.14
Previous cardiovascular events	(62) 30.8	(68) 34.7
Coronary artery disease history	(21) 10.4	(32) 16.3
Peripheral arterial disease history	(28) 13.9	(35) 17.9
Stroke history	(11) 5.5	(18) 9.2
Current smokers	(22) 10.9	(24) 12.2
Diabetes	(59) 29.4	(69) 35.2
Dyslipidemia	(73) 36.3	(83) 42.3
Residual diuresis, mL/d	160 (400)*	50 (4000)*
Duration of renal replacement therapy, y	4.36±4.71	5.30±6.04
Duration of dialysis, y	3.10 (1.5)*	3.40 (1.8)*
Kt/V	1.33±0.31	1.38±0.44
HDL, mmol/L	1.11±0.34	1.13±0.35
LDL, mmol/L	3.12±1.01	3.09±1.03
Log(CRP), mg/L	0.93±0.36	0.96±0.41
Parathormone, pg/mL	168 (156)*	176 (172)*
Hemoglobin, g/dL	11.71±5.18	11.35±3.75
Associated treatments		
Erythropoietin	(156) 77.6	(157) 80.1
Oral antidiabetic	(3) 1.5	(12) 6.1
Insulin	(41) 20.4	(40) 20.4
Dyslipidemia	(49) 24.4	(51) 26.0
Hypertension	(103) 51.2	(107) 54.6
Previous transplantation	(11) 5.5	(18) 9.2

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; Kt/V, volume of fluid cleared of urea during a single treatment; LDL, low-density lipoprotein; SBP, systolic blood pressure; CRP, C-reactive protein. Continuous variables are reported as mean±SD, or dichotomous variables are reported as frequency (%).

*Continuous variable were reported as median (interquartile range).

BP Variability

The results of the BP variability parameters are shown in Table 3.

Contribution of BP Parameters on the Cardiovascular Prediction Model

Using the previously published Cox proportional hazards model (which included previous experienced cardiovascular occurrence binary variables [stroke, peripheral arterial disease, and coronary artery disease], diabetes mellitus, left ventricular mass, and age) as the reference,[13] each additional BP parameter was added to the model. The influence of these variables on the model was evaluated by comparing the likelihood ratios between the basic model and the model including the BP parameters; the additional P values of the BP variability parameters are shown in the online-only Data Supplement Table.

Table 2. Measurements of SBP and DBP (in Millimeters of Mercury) at Every Visit (Mean+SD)

Time Points	SBP	DBP	n
Inclusion	145.77±19.57	76.70±11.15	397
Wk 0	147.11±21.43	77.29±11.88	396
Wk 1	143.10±21.18	75.66±11.28	395
Wk 2	143.32±21.76	75.59±11.64	391
Wk 3	143.13±23.55	75.49±12.77	387
Wk 4	139.10±25.43	73.75±13.39	141
Wk 5	132.70±24.98	69.78±12.67	99
Wk 6	129.87±23.97	68.75±12.05	80
Wk 8	142.77±24.50	75.09±12.69	388
Mo 3	141.47±21.43	75.15±12.07	380
Mo 6	141.97±21.27	74.90±11.78	366
Mo 9	144.57±21.58	75.10±11.65	354
Mo 12	144.34±21.72	76.07±11.50	339
Mo 15	143.98±21.83	76.73±12.26	330
Mo 18	142.65±22.02	75.42±11.66	311
Mo 21	143.31±23.84	74.37±12.08	294
Mo 24	141.69±21.88	74.96±11.30	284
Mean value	142.73±16.37	75.11±8.61	397

Values are reported as mean±SD, n=frequency. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

Parameters describing the absolute values of BP (SBP, DBP, and PP) means during the whole trial and binary variables based on these continuous variables (SBP <140 mm Hg and DBP <90 mm Hg) were not found associated with a significant additional contribution. SDPP and CVPP, measuring PP variability, were of borderline significance for additional contribution (P=0.05). ABP and CVASBP, measuring the variability of adjacent values, were found with a modest significance ($0.01<P<0.05$). Finally, SDSBP, SDDBP, CVSBP, SVDBP, and RSSBP measuring the overall variability of the within-patient pressure in time with slightly different formulations were found highly significant (all $P<0.001$).

Stability of the Prediction Model

As a supportive analysis of the previous results, instead considering the initial predictive model as known, all of the variables of the previous model and all of the BP parameters were entered in a stepwise Cox regression model where the composite cardiovascular outcome was the dependent end point. Our final model contains all of the previous variables (with very similar coefficients), associated with the basic predictive model in addition to CVSBP (Table 4). This model remained unchanged irrespective of the various planned stepwise strategies.

Adding CVSBP into the equation increased the determination coefficient by 30% (from R^2=0.151 to R^2=0.183). The predictive positive and negative values were evaluated for fixed values of the cutoff probability on a receiver operating characteristic curve, with an observed C statistic of 73.8 (95%

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Table 3. Blood Pressure Variability Parameters

Parameters	Mean±SD
Rssbp	0.00±4.60
ASBP	18.64±6.28
ADBP	10.75±3.57
Sdsbp	14.82±4.75
Sddbp	8.18±2.66
Sdpp	15.87±5.09
CvASBP	13.45±4.13
CvADBP	14.49±5.01
Cvsbp	10.43±3.30
Cvdbp	11.03±3.77
Cvpp	24.02±7.82
Mean SBP	142.73±16.37
Mean DBP	75.11±8.61
Mean PP	67.68±13.46

Rssbp indicates residual of the linear fit between standard deviation and the mean for systolic blood pressure; ASBP, average absolute difference between adjacent readings of systolic blood pressure; ADBP, average absolute difference between adjacent readings of diastolic blood pressure; Sdsbp, standard deviation of the systolic blood pressure values at each visit; Sddbp; standard deviation of the diastolic blood pressure values at each visit; Sdpp, within-patient overall variability of pulse pressure; CvASBP, coefficient of variation of the average absolute difference between adjacent readings of systolic blood pressure; CvADBP, coefficient of variation of the average absolute difference between adjacent readings of diastolic blood pressure; Cvsbp, coefficient of variation of the systolic blood pressure values at each visit; Cvdbp, coefficient of variation of the diastolic blood pressure values at each visit; Cvpp, coefficient of variation of the within-patient overall variability of pulse pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

CI, 68.4–78.2). The original model without pressure variability was characterized by a C statistic of 68.9 (95% CI, 63.8–73.5).

A previous article based on this trial allowed us to describe a structural modeling approach in which we confirmed our initial predictive model but in which we tested some other potential predictors.[19] C-reactive protein in particular was found to be an important predictor; however, only 303 patients in this study were measured on this value. In a new stepwise analysis by adding C-reactive protein in the model (and only based on 303 patients), C-reactive protein log-transformed value was a highly determinant predictor (hazard ratio, 3.61 [95% CI, 2.35–5.53]; $P<0.001$), and the coefficients of the other predictors (including CVSBP) were very close to the primary analysis.

Table 4. Cox Proportional Hazards From a Stepwise Strategy

Variables	HR	95% CI	*P* Value
Age, y	1.036	1.012–1.062	<0.001
Stroke	1.514	0.878–2.611	<0.001
PAD	2.043	1.354–3.082	<0.001
CAD	1.733	1.126–2.667	<0.001
Diabetes	1.396	0.962–2.026	<0.001
Log(LVM)	13.129	3.742–46.062	<0.001
CVSBP	1.083	1.028–1.141	<0.001

HR indicates hazard ratio; PAD, history of peripheral arterial disease; CAD, history of coronary arterial disease; LVM, left ventricular mass (g); CVSBP, coefficient of variation of within-patient overall variability of systolic blood pressure (%).

To further evaluate the contribution of CVSBP in the context of other risk factors, we estimated the survival curve associated with some categories of patients, patients with no previous cardiovascular comorbidities, patients with coronary artery disease only, patients with peripheral arterial disease only, patients with CVSBP at 12% and no cardiovascular comorbidity, and patients with CVSBP at 25% and no cardiovascular comorbidity. Examination of the Cox regression survival curves revealed that event-free survival was lowest in the subgroup of patients with the highest CVSBP (Figure). These data should be interpreted cautiously given the limited predictive value of this model, but the finding warrants further study.

Analysis of BP Variability Parameters

The principal components analysis identified 3 well-separated subsets of variables that were strongly intercorrelated, the absolute mean values, all of the variability pressures (with r always >5), and PP, which was found to be a stand-alone group that could not be aggregated with the other groups. The correlation among the 3 groups is very small and close to $r=0$. The interrelationships between all of the variability parameters were strong, with only a small difference in RSSBP originating from the residual analysis reducing the correlation with mean values (data not shown).

Sensitivity Analyses Using Alternative Measurements of Pressure Variability

To assess the possible bias of cause-outcome relationship, we derived alternative measurements CVSBP1 and CVDBP1 calculated by excluding measures for which the absolute value of the time lag with a critical event was <2 months and alternative CVSBP2 and CVDBP2 simply calculated on the 5 first visits. First we entered these variables in the previous principal component analysis. Virtually no change was found in the results. The minimum Pearson correlations between CVSBP and its alternatives were 0.86, and the mean correlation was 0.93.

The influence of these alternative variables was retested as above in the Table 4 model in additive contributions and its *P* value. The contributions of CVSBP1 or CVDBP1 were almost comparable to contributions of CVSBP and CVDBP ($P<0.005$), whereas the same *P* values associated with CVSBP2 and CVDBP2 were lower but remained significant ($P<0.019$).

Because the time between each visit is not the same, we also recalculated ASBP and CVSBP by weighting each value according to the time lag between the previous visit. Very few differences were found between these values, and no change was found in the main model.

Adjustment for Time Between Hemodialyses

Intervals for hemodialysis were shown to vary between 2 and 3 days. A significant but modest increase of pressure was found with increasing time. However, this change was much smaller than the within-patient variability measured by

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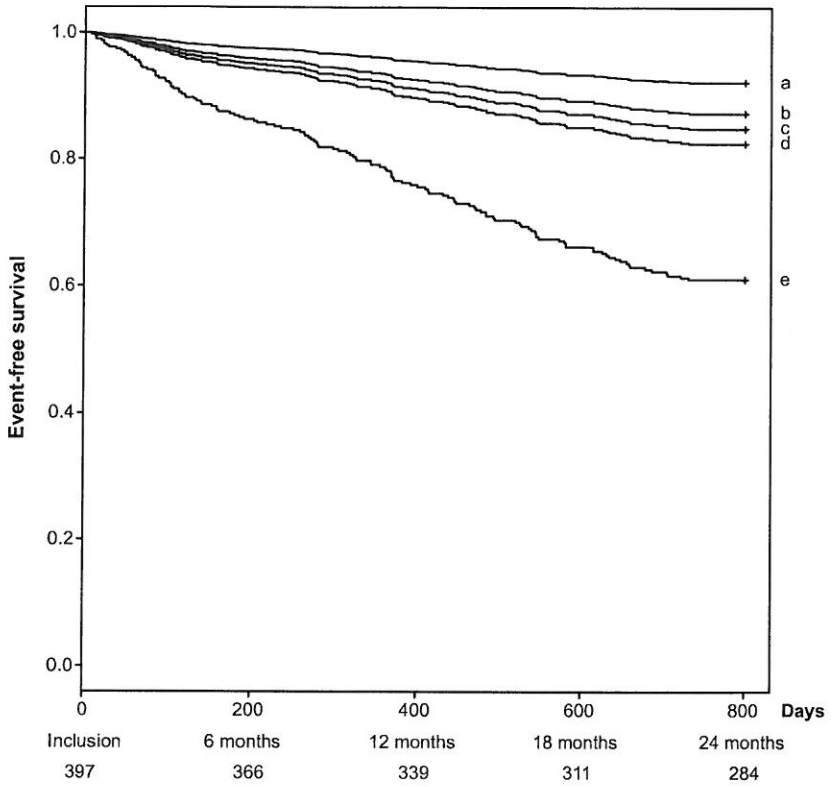


Figure. Cox prediction of cardiovascular events for (a) patients with no previous cardiovascular comorbidities; (b) patients with coronary artery disease only; (c) patients with peripheral arterial disease only; (d) patients with CVSBP=12% and no cardiovascular comorbidity; and (e) patients with CVSBP=25% and no cardiovascular comorbidity. CVSBP indicates coefficient of variation of within-patient overall variability of systolic blood pressure.

SDSBP, for instance. However, we modified the calculations CVSBP into CVSBPa by adjusting each value for hemodialysis time. The Pearson correlations between the 2 variables was 0.97, and the 2 values were not significantly different (paired t test, $P=0.81$). The effect of CVSBPa was retested by assessing the additive contributions in the model and its P value, and very similar results were found compared with CVSBP ($P=0.005$).

As a last sensitivity analysis, we checked the possible effect of regression to the mean or any other trend in time that might have an effect on the measurement of pressure variability. Mean pressures values remained constant during the treatment, except in treatment effect, where a constant difference was observed compared with placebo over time. We calculated the values of CVSBP and CVDBP by adjusting the values for treatment in time. These 2 values were slightly higher. In using these new parameters in the model (Table 4), our results were unchanged. The results of our model did not change by using this modified measurement.

Table 5. Stepwise Linear Regression of the Coefficient of Variation of Within-Patient Overall Variability of Systolic Blood Pressure (CVSBP) Associated Factors Using All of the Baseline Variables (Excluding CRP)

Variables	Coeff	95% CI	P Value
Intercept	7.491	5.886–9.095	<0.001
Body mass index, kg/m^2	0.085	0.028–0.143	0.004
History of stroke	1.651	0.434–2.868	0.008
Antihyperensive treatment	1.028	0.395–1.661	0.002

Linear model at end of selection. Adjusted $R^2=0.05$. Coeff indicates regression coefficient estimate; CRP, C-reactive protein.

Finally, we evaluated the association between baseline patient parameters and the degree of BP variability as a continuous dependent variable. A stepwise linear regression model was conducted by using CVSBP as the representative measurement of BP variability (Table 5). Body mass index, previous occurrence of stroke, and current antihypertensive medication at enrollment were significantly associated with CVSBP. No other baseline parameter was associated with BP variability, specifically BP, fosinopril treatment assignment (versus placebo), or dialysis performance (as assessed by volume of fluid cleared of urea during a single treatment). However, the discrimination of this model was small ($R^2=0.057$). In a sensitivity analysis, body weight and hemoglobin variations throughout the study were also tested and were not associated with BP variability.

Discussion

Visit-to-visit variability in SBP or DBP but not baseline SBP and DBP themselves predicts cardiovascular events in patients with ESRD and left ventricular hypertrophy who are receiving maintenance hemodialysis. Measures reflecting within-patient overall variability of SBP were significant predictors of subsequent cardiovascular events. Each factor (SDSBP, SDDBP, CVSBP, CVDBP, and RSSBP) was similarly predictive of the composite cardiovascular outcome. Of these, RSSBP requires a complex calculation and, therefore, may be less useful clinically. The bootstrap analyses revealed that CVSBP and CVDBP were the best (but equivalent) alternatives. In addition, these measures are more straightforward statistically because CV is dimensionless and generally more stable than SD. Based on these findings, CVSBP and

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CVDBP are the most suitable measures of BP variability for clinical use in this population.

Using sensitivity analyses, we first assessed the possible bias of the cause-outcome relationship by measuring pressure variability on all of the measurements irrespective of the occurrence of critical end points close to these measurements. The alternative measurements CVSBP1 and CVDBP1 were highly correlated with their original values, and the additive contribution on the model was almost identical to original values. This result suggests that cause-outcome bias is probably very limited. We conducted another sensitivity analysis by measuring pressure variability CVSBP2 and CVDBP2 simply calculated on the 5 first visits. This measurement is also useful clinically, because these calculations are much simpler. Our results provide some evidence that the additive contribution and discrimination of pressure variability, as measured by this simpler calculation, remain important, although they are associated with a less important determination on the model. We may conclude that a measurement of pressure variability based on the first weeks may provide a useful index. However, it remains less accurate than an index calculated on more visits. This finding warrants additional prospective studies.

Time between hemodialysis is expected to have an effect in elevating BP, which may cause a bias on the measurement of pressure variability. When CVSBP and its corresponding value were tested after adjusting for between-hemodialysis time, the results were virtually unchanged.

ASBP and CVASBP measured the variability of adjacent values, and these parameters were found to predict cardiovascular events with a modest significance ($0.01<P<0.05$). Measures reflecting adjacent values may have been less predictive of outcome than measures of overall variability, but they may be useful from a practical point of view on an individual patient basis for the early detection of a high-risk patient.

Baseline continuous and dichotomized SBP or DBP did not predict the composite cardiovascular outcome. This finding suggests that normal BP determined by SBP <140 mm Hg and/or DBP <90 mm Hg is of limited prognostic value in this population. This observation is consistent with the results of a retrospective analysis that showed that achieving the recommended BP guideline targets in hemodialysis patients may be associated with increased mortality.[20] The totality of evidence suggests that a comprehensive approach is needed with regard to managing BP in the ESRD population. The focus should not be limited to individual BPs in isolation. Understanding the variability in BP patterns over time appears to be of particular prognostic importance.

In high-risk hypertensive patients, kidney function is linearly negatively associated with BP variability in multivariate analyses.[10] It is hypothesized that the disruption of mechanisms maintaining BP homeostasis and large and small artery damage amplify BP fluctuations in response to environmental or central stimuli.[21] These fluctuations are associated with end organ damage, cardiovascular events, and cardiovascular risk factors. The BP variability features in hemodialysis patients may contribute to the complexity of the relationship between BP and cardiovascular outcomes in these patients. Recent data obtained with home BP monitoring revealed a W-shape relationship[22] instead of the reverse epidemiology suggested by usual BP measurement.[8]

After inclusion of CVSBP in the original FOSIDIAL reference model, the original predictors of outcome remained significant with very similar coefficients. In addition, the percentage of explained variance improved by 30.1% simply by adding pressure variability to the model. These results provide evidence of the independent effect of pressure variability on cardiovascular events and of the stability of these findings.

BP variability over 24 hours has traditionally dominated this field of research.[21] However, evidence from recent studies suggests that visit-to-visit variability over longer periods of follow-up may have greater prognostic value than average BP or short-term variability.[9,10,21] BP variability over 1 year has been shown to predict all-cause mortality in patients undergoing hemodialysis, but the number of vascular deaths (n=6) supporting this observation was small.[23] Interestingly, in this study, the average CVSBP was 10.2%, which was similar to the CVSBP in FOSIDIAL (10.43%). The SDSBP of 14.82 mm Hg observed in FOSIDIAL was slightly lower than that reported in a data registry of 9849 US ESRD patients on hemodialysis.[12] Altogether these data indicate that hemodialysis patients display a high visit-to-visit BP variability, similar or even higher to that reported in other high-risk (poststroke) populations (SDSBP, 11.4–14.9 mm Hg; CVSBP, 8.2–10%),[10] higher than that observed in treated hypertensives (SDSBP, 10.99–14.38 mm Hg; CVSBP, 7.69–9.41%),[15] and the general population (SDSBP, 7.7 mm Hg; CVSBP: 6.1%).[11] These findings have important implications for clinical practice. The optimal treatment goal for patients with ESRD may be to reduce BP variability rather than mean BP values.

Interestingly, visit-to-visit BP variability in our study population was not associated with usual BP levels or PP, whereas it was found to be associated with these measures in poststroke patients[10] and, to a lesser extent, in type 1 diabetic patients.[24] This suggests that this population of very high added cardiovascular risk may have developed an autonomous BP variability phenotype overtime, which may have paralleled the progressive and sustained cardiovascular target organ damage associated with ESRD. Consistent with other reports, this analysis demonstrated that body mass index,[10] a history of stroke,[10] and baseline antihypertensive treatment[10,11] were associated with increased BP variability. In FOSIDIAL, angiotensin-converting enzyme inhibitor treatment was not associated with an increase in BP variability compared with placebo. In other populations, angiotensin-converting enzyme inhibitors and β-blockers have been associated with increased variability.[25] Disappointingly, the analysis model only explained ≈5% of BP variability, highlighting the need to design studies to prospectively determine the causes of BP variability and whether treatments that reduce BP variability improve clinical outcomes. Moreover, our data highlight the need to take visit-to-visit BP variability into account beyond casual BP measurements. Data assessing the difference in group SD can also be informative,[9,25] and taking advantage of this, data from randomized studies

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suggest that neither dry weight reduction[26] nor daily dialysis (compared with traditional dialysis) influence BP variability, despite decreasing BP.[27] Whether erythropoietin-stimulating agents may contribute to higher BP variability in addition to BP[28] is currently not known. Notwithstanding these hypotheses, further pathophysiological investigations regarding visit-to-visit BP variability in ESRD patients receiving hemodialysis are warranted.

Strengths and Limitations

The major strengths of our study are, first, its external validity, because this analysis provided a contemporary accurate estimate of cardiovascular event rates in patients with ESRD in a typical European country. Clinical events were adjudicated by a critical event committee using a rigorous, prespecified adjudication process to classify clinical events. However, developing a prognostic model from a randomized population may be misleading, because inclusion and exclusion criteria are different from those of a hemodialysis registry, and selection bias may have been introduced. However, the annual mortality rate in FOSIDIAL was 12.3%, which was very similar to that found in the European portion of the Dialysis Outcomes and Practice Patterns Study registry (16%).[29] Second, the multivariate model in predicting cardiovascular events was stable, irrespective of the statistical techniques, and remained valid after bootstrapping. Third, all of the BP measurements were performed following a standardized World Health Organization procedure, before the dialysis sessions, over a long-term 2-year follow-up, which included 17 visits. However, postdialysis BP measurements and home BP measurements could also be relevant but were not performed herein.

Perspectives

Visit-to-visit BP variability was high in this population of patients with ESRD receiving hemodialysis, and it was a major predictor of cardiovascular events, whereas baseline SBP and DBP were not. These data suggest that assessments of BP variability using CVSBP may be appropriate in the clinical care of these patients. Future studies should evaluate the role of BP variability in the pathophysiology of cardiovascular disease in the setting of ESRD, beyond casual SBP and DBP themselves, and whether reducing BP variability influences the occurrence of cardiovascular events.

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Novelty and Significance

What Is New?

- Visit-to-visit BP variability was high in this population of patients with ESRD receiving hemodialysis, and it was a major predictor of cardiovascular events.

What Is Relevant?

- Visit-to-visit BP variability but not baseline continuous and dichotomized SBP or DBP predicted the composite cardiovascular outcome. This suggests that normal BP determined by SBP <140 mm Hg and/or DBP <90 mm Hg is of limited prognostic value in this population.

Summary

Visit-to-visit BP variability assessment using CVSBP may be appropriate in the clinical care of these patients beyond usual BP.

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VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY IS A STRONG PREDICTOR OF CARDIOVASCULAR EVENTS IN HEMODIALYSIS: INSIGHTS FROM FOSIDIAL

ONLINE SUPPLEMENT

Short title: Blood pressure variability in FOSIDIAL

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Table S1: Significance by descending value of the additional contribution of each blood pressure parameter when separately entered into the reference multivariate predictive model

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RSSBP	0.005

("SBPgroup" with 0 or 1 values when baseline SBP was above or below 140 mm Hg, respectively, and "DBPgroup" with 0 or 1 values when baseline DBP was above or below 90mm Hg, respectively)

Other abbreviations: see the methods section

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