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# Impact of Aortic Stiffness Attenuation on Survival of Patients in End-Stage Renal Failure

Alain P. Guerin, MD; Jacques Blacher, MD, PhD; Bruno Pannier, MD; Sylvain J. Marchais, MD; Michel E. Safar, MD; Gérard M. London, MD

**Background**—Aortic pulse wave velocity (PWV) is a predictor of mortality in patients with end-stage renal failure (ESRF). The PWV is partly dependent on blood pressure (BP), and a decrease in BP can attenuate the stiffness. Whether the changes in PWV in response to decreases in BP can predict mortality in ESRF patients has never been investigated.

**Methods and Results**—One hundred fifty ESRF patients (aged  $52 \pm 16$  years) were monitored for  $51 \pm 38$  months. From entry until the end of follow-up, the changes of PWV in response to decreased BP were measured ultrasonographically. BP was controlled by adjustment of “dry weight” and, when necessary, with ACE inhibitors, calcium antagonists, and/or  $\beta$ -blockers, in combination if necessary. Fifty-nine deaths occurred, including 40 cardiovascular and 19 noncardiovascular events. Cox analyses demonstrated that independent of BP changes, the predictors of all-cause and cardiovascular mortality were as follows: absence of PWV decrease in response to BP decrease, increased left ventricular mass, age, and preexisting cardiovascular disease. Survival was positively associated with ACE inhibitor use. After adjustment for all confounding factors, the risk ratio for the absence of PWV decrease was 2.59 (95% CI 1.51 to 4.43) for all-cause mortality and 2.35 (95% CI 1.23 to 4.41) for cardiovascular mortality. The risk ratio for ACE inhibitor use was 0.19 (95% CI 0.14 to 0.43) for all-cause mortality and 0.18 (95% CI 0.06 to 0.55) for cardiovascular mortality.

**Conclusions**—These results indicate that in ESRF patients, the insensitivity of PWV to decreased BP is an independent predictor of mortality and that use of ACE inhibitors has a favorable effect on survival that is independent of BP changes. (*Circulation*. 2001;103:987-992.)

**Key Words:** kidney ■ waves ■ mortality ■ hypertension

Epidemiological and clinical studies have shown that increased aortic stiffness, determined by the measurement of aortic pulse wave velocity (PWV), is an independent marker of cardiovascular risk in the general population<sup>1</sup> and a major contributor to the mortality of end-stage renal failure (ESRF) and that each aortic PWV increase of 1 m/s increased the all-cause mortality by 39%.<sup>2</sup> PWV depends on the arterial wall structure and function but is mainly influenced by age-associated alterations and blood pressure (BP).<sup>3,4</sup> Clinical studies involving essential hypertension and ESRF patients have shown that ACE inhibitors and calcium antagonists decreased aortic PWV to a large extent in response to BP lowering.<sup>5,6</sup> Nevertheless, whether the attenuation of aortic stiffening in response to BP decrease is predictive of clinical outcome has not been established. To determine the impact of the aortic stiffening response to sustained decreased BP on all-cause and cardiovascular mortality, we conducted a prospective study on a cohort of 150 ESRF patients followed for up to 136 months. The results indicate that independent of BP changes, survival was substantially better for those subjects whose aortic PWV declined in response to decreased BP.

## Methods

### Patients

Patients were eligible for inclusion when (1) they had been on hemodialysis at least for 3 months ( $67 \pm 62$  months, mean  $\pm$  SD), (2) they had no clinical cardiovascular disease during the 6 months preceding entry, and (3) they agreed to participate in the follow-up study, which was approved by our Institutional Review Board. The study began in September 1988, recruitment was closed in April 1998, and follow-up ended December 31, 1999. In all, 150 patients fulfilled the entry criteria. Patients who underwent renal transplantation and patients who moved were censored on the day of transplantation or departure. All but 12 patients were white, 60% were males, and 8% had diabetes mellitus. The mean  $\pm$  SD follow-up was  $51 \pm 38$  months (median 46 months, range 4 to 136 months). Data on mortality were obtained for the entire cohort. The mean  $\pm$  SD age of the cohort at inclusion was  $52 \pm 16$  years. During follow-up, all patients were dialyzed by use of the same techniques as previously detailed.<sup>1</sup> Patient “dry weight” is defined as the body weight below which a normal albuminemic patient experiences hypotension or muscle cramps and postural hypotension is clinically manifest.

### Data Collection

Information compiled from the questionnaire filled out at inclusion included personal and family histories, smoking habits, and prior

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history of cardiovascular disease, including coronary artery disease, angina pectoris, cardiac insufficiency, peripheral vascular disease, and cerebrovascular disease. The baseline measurements were made during the 2 weeks after inclusion, on the morning before the midweek hemodialysis. Blood chemistry analyses at baseline and at monthly intervals included blood urea, hemoglobin, serum albumin, blood lipids, parathyroid hormone, serum calcium, and serum phosphate. BP was measured after 15 minutes of recumbency in the arm contralateral to the arteriovenous shunt with a mercury sphygmomanometer and a cuff of appropriate size. Phases I and V of the Korotkoff sounds were taken as the systolic BP (SBP) and diastolic BP (DBP), respectively. The mean BP (MBP) was calculated as follows:  $MBP = DBP + [(SBP - DBP)/3]$ . Five measurements were made at 2-minute intervals; the last 3 were averaged and considered to be representative. The heart rate was determined from the 3-lead orthogonal ECG. Echocardiography was performed by using a Hewlett-Packard Sonos 100 equipped with a 2.25-MHz probe. Measurements were made according to the recommendations of the American Society of Echocardiography.<sup>7</sup> Left ventricular (LV) mass was calculated according to the Penn convention and expressed as LV mass index.<sup>8</sup>

Baseline aortic PWV was determined by using transcutaneous Doppler flow recordings and the foot-to-foot method.<sup>1,3</sup> Two simultaneous Doppler flow tracings were taken from the common carotid artery opposite the side of the arteriovenous fistula and the femoral artery in the groin. Flow waves were measured with a nondirectional Doppler unit (SEGA M842, 10 MHz) and recorded on a Gould 8188 recorder (Gould Electronics) at a speed of 100 or 200 mm/s. The time interval (t) was measured between the feet of the flow waves and was averaged over 10 beats. The distance (D) traveled by the flow wave was measured over the body surface as the distance between the 2 recording sites, and the distance from the suprasternal notch to the carotid was subtracted. PWV was calculated as  $PWV = D/t$ . The mean  $\pm$  SD intraobserver repeatability of aortic PWV measurements was  $5.8 \pm 1\%$ .<sup>6</sup> The PWV was measured at inclusion, after reaching the target BP (see below), and quarterly thereafter until the end of follow-up. The change of aortic PWV ( $\Delta$ PWV, in meters per second), used as a prognostic variable, was quantified as follows:  $\Delta$ PWV = (PWV at inclusion) - (PWV at target BP).

### Therapeutic Strategy

Under physiological conditions, arterial stiffness indexes are BP dependent, and a pressure decrease could be followed by a parallel decrease of stiffness. Therefore, to analyze the aortic PWV response to BP changes, the first step was aimed at obtaining a long-term and stable normal BP or a 15 mm Hg decrease of SBP. According to the definition of hypertension proposed in the 1980s, normotension was defined as predialysis BP <160/90 mm Hg. The first step for all patients was an attempt to achieve a dry weight. For ethical reasons, a placebo-controlled study was not feasible, and when this attempt failed, antihypertensive drug therapy was initiated. Experimental and clinical studies have shown that ACE inhibitors, calcium antagonists, and (to a lesser degree) selective or nonselective  $\beta$ -blockers decrease arterial stiffness.<sup>5,6,9,10</sup> Patients were randomly assigned to receive the ACE inhibitor perindopril or the dihydropyridine calcium antagonist nitrendipine. The pharmacokinetic study in hemodialyzed patients showed that 2 to 4 mg perindopril given every 48 hours produced a significant long-standing antihypertensive effect.<sup>11</sup> Nitrendipine lowered BP in hemodialyzed patients for 24 hours, and its pharmacokinetics were unaltered in ESRF patients.<sup>12,13</sup> Perindopril was administered at a dose of 4 to 8 mg every 48 hours, and nitrendipine was administered at a dose of 10 to 20 mg/d. If the drug was not well tolerated (intradialytic hypotension, ankle edema, flush, and/or cough), the drugs were interchanged. If the target BP was still not achieved, the  $\beta$ -blocker atenolol was prescribed at a dose of 25 to 50 mg/d. Finally, if this combined bitherapy did not achieve the target BP, a combination of ACE inhibitor, calcium antagonist, and  $\beta$ -blocker was prescribed. The target BP was achieved after 3 to 16 weeks (median 8 weeks).

### Analyses

The outcome events studied were all-cause and cardiovascular mortality. The primary analysis concerned the survival curves and Cox proportional hazards model. Survival was estimated by the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. Factors prognostic of survival were identified with use of the Cox proportional hazards regression model. The assumption of proportional hazards over time was verified before the analyses and was met by all covariates. The assumption concerning linearity of continuous covariates was also verified before analysis. Stepwise, multivariate Cox modeling was the primary statistical analysis used to determine the independent relationship of PWV changes and other baseline characteristics to survival. Each significant predictor ( $P < 0.05$ ) identified by this analysis was subsequently tested in a backward selection process with all candidate variables forced into the model. The following variables were considered along with sex, age, smoking, and diabetes in the modeling procedures:  $\Delta$ PWV; duration of dialysis before inclusion; baseline, target, and follow-up BP; type of antihypertensive treatment; preexisting cardiovascular disease; LV mass index; and blood lipids, Kt/V (product of dialyzer urea clearance [K] and treatment time [t] normalized to urea distribution volume [V]), and changes in blood chemistries. Variables were considered to be prognostic when they were found to be statistically significant in the Cox proportional hazards regression model ( $P < 0.05$ , adjusted for all variables retained in the final model). Adjusted hazard rate ratios (RRs) were calculated as the antilogarithm of the  $\beta$  coefficient of the Cox proportional hazards regression of the outcome events with all the prognostic variables entered in the models. The 95% CI for the adjusted RR estimates were obtained with the following formula: antilogarithm ( $\beta \pm 1.96SE$ ), where SE is the standard error of  $\beta$ . To assess  $\Delta$ PWV as a prognostic variable test with the use of receiver operating characteristic (ROC) curves, we calculated sensitivities, specificities, positive predictive values, and negative predictive values to predict mortality at different cutoff values. Optimal PWV cutoff values were defined as the maximization of the sum of sensitivity and specificity.<sup>14</sup> Data are expressed as mean  $\pm$  SD, unless otherwise specified. ANOVA was used for comparison of normally distributed variables. Differences in frequency were tested by  $\chi^2$  analysis. Sex (0, male; 1, female), history of cardiovascular disease (0, no; 1, yes), ACE inhibitor (0, no; 1, yes),  $\beta$ -blocker (0, no; 1, yes), nitrendipine (0, no; 1, yes), and  $\Delta$ PWV (0, negative  $\Delta$ PWV; 1, positive  $\Delta$ PWV) were used as dummy variables. All tests were 2-sided, and analyses were performed with NCSS 6.0.21 software. Reproducibility of the methods was defined by the British Standards Institution.<sup>15</sup> A value of  $P < 0.05$  was considered significant.

## Results

### Patient Characteristics

The characteristics of the cohort at inclusion are shown in Table 1. The BP and aortic PWV changes from inclusion to target BP and at the end of follow-up are reported in Table 2. Target BP was obtained by adjustment of dry weight in only 44 (29%) patients; antihypertensive drugs alone or in combination were prescribed to 106 patients. Among patients receiving antihypertensive drugs, 49 (46%) took perindopril, 56 (53%) took atenolol, and 83 (78%) took nitrendipine. The patients received an average of  $1.7 \pm 0.7$  antihypertensive drugs. At target BP, SBP and DBP had decreased significantly in the entire cohort (Table 2). During follow-up, BP remained stable (Table 2), and at the end of follow-up, 48 (46%) patients were taking an ACE inhibitor, 50 (47%) were taking a  $\beta$ -blocker, and 79 (74%) were taking a calcium antagonist. At target BP, the aortic

**TABLE 1. Characteristics of Studied Population**

Parameters	All Patients (n=150)
Sex, male/female	91/59
Duration of dialysis at inclusion, mo	66±61
Previous cardiovascular events, %	43
Tobacco (lifelong dose), pack-years	8.0±14
Serum total cholesterol, mmol/L	5.3±1.1
Serum HDL cholesterol, mmol/L	1.1±0.3
Serum LDL cholesterol, mmol/L	3.9±1.0
Total/HDL cholesterol ratio	5.0±1.9
Serum triglycerides, mmol/L	1.6±0.9
Parathyroid hormone, mmol/L	244±254
Serum albumin, g/L	40±2.2
Hemoglobin, g/L	87±15
LV mass, g/m <sup>2</sup>	169±43
LV shortening, %	35±6

Values are mean±SD.

PWV decreased in 100 patients ( $-1.32\pm 0.98$  m/s) but increased or was unchanged in 50 patients ( $0.95\pm 0.91$  m/s). After adjustment for age and prior cardiovascular disease, the  $\Delta$ PWV was correlated with changes in SBP ( $r=0.538$ ,  $P<0.0001$ ) but not to the type of antihypertensive medication (ACE inhibitor  $-1.02\pm 1.40$  m/s, calcium blocker  $-0.62\pm 1.66$  m/s;  $P=NS$ ).

### Outcome and Prognostic Impact of $\Delta$ PWV

During the follow-up period, 59 deaths were recorded. Forty patients died from cardiovascular complications, and 19 died from noncardiovascular events. Absence of PWV decrease (positive  $\Delta$ PWV) was a predictor associated with all-cause and cardiovascular mortality (Table 3). When in the Cox model the  $\Delta$ PWV was expressed in meters per second, the adjusted RR for a PWV decrease of 1 m/s was 0.71 (95% CI 0.60 to 0.86) for all-cause mortality and 0.79 (95% CI 0.69 to 0.93) for cardiovascular mortality. Increased LV mass index had a negative impact on all-cause and cardiovascular mortality. Age had a negative impact on overall survival but not on cardiovascular mortality, which was positively associated with a history of prior cardiovascular diseases. Use of an ACE inhibitor, either alone or in combination, had a favorable impact on all-cause and cardiovascular mortality. The prescription of atenolol or nitrendipine was not predictive of outcome. The adjusted RRs for baseline SBP and DBP were not

**TABLE 2. Changes in BP From Inclusion Until End of Follow-Up in Entire Cohort**

Parameter	Inclusion	Target BP	End of Follow-Up
SBP, mm Hg	169±31	151±25*	148±24*
DBP, mm Hg	90±16	81±13*	79±14*
Heart rate, bpm	75±13	73±12	71±11*

Values are mean±SD.

\* $P<0.001$  vs corresponding inclusion values.

significant; their respective values were 1.1 (95% CI 0.97 to 1.22) and 0.9 (95% CI 0.64 to 1.18) for overall mortality, and they were similar for cardiovascular mortality (not shown). The adjusted RRs for  $\Delta$ SBP and  $\Delta$ DBP were 0.98 (95% CI 0.79 to 1.17) and 1.15 (95% CI 0.75 to 1.56), respectively, and were not significant for overall mortality or cardiovascular mortality. The role of factors such as sex, smoking, time on dialysis, and blood chemistry abnormalities were not significant. Figure 1 shows the ROC curve; the cutoff value for  $\Delta$ PWV was 0.04 m/s (ie,  $\cong 0$ ). The negative predictive value of  $\Delta$ PWV was 70% (70% of patients with positive  $\Delta$ PWV died during follow-up), and the positive predictive value was 74% (74% of patients with negative  $\Delta$ PWV survived during follow-up). The sensitivity of  $\Delta$ PWV was 56%, and its specificity was 84%. Figure 2 shows the probabilities of survival of patients with negative  $\Delta$ PWV or positive  $\Delta$ PWV. Figure 3 shows the MBP and aortic PWV changes measured during follow-up of survivors and nonsurvivors. In survivors, the aortic PWV changes initially paralleled BP changes and remained stable despite aging. Although BP changes were similar in nonsurvivors, their aortic PWV steadily increased until the end of follow-up.

### Discussion

PWV measurement offers a simple and reproducible evaluation of regional arterial stiffness.<sup>1,3</sup> Recent studies have shown that aortic PWV is a marker of cardiovascular risk in essential hypertension<sup>2</sup> and an independent predictor of mortality of ESRF patients.<sup>1</sup> Arterial stiffness depends on the geometry and structure of the arterial wall and is influenced by BP. Aortic stiffening can be functional, resulting from high BP without structural changes of the artery, and can be reversed with BP lowering.<sup>3-5</sup> Arterial stiffness may also increase because of disease-induced structural changes of the artery. In the presence of structural changes, the stiffening is less dependent on BP.<sup>16</sup> The results of the present study showed that survival of ESRF patients was significantly better for patients whose aortic PWV declined in response to BP lowering. The adjusted RRs for all-cause and cardiovascular mortality in those whose PWV did not decline in response to BP changes were 2.59 (95% CI 1.51 to 4.43) and 2.35 (95% CI 1.23 to 4.51), respectively ( $P<0.01$ ). The prognostic value of PWV sensitivity to BP lowering on survival was independent of age, BP changes including pulse pressure, and blood chemistry abnormalities. The findings reported in the present study indicate that arterial stiffness is not only a risk factor contributing to the development of cardiovascular disease but also a marker of established, more advanced, less reversible arterial changes. This concept is supported by the loss of aortic PWV sensitivity to BP lowering in nonsurvivors compared with survivors in whom arterial stiffness remained pressure sensitive (Figure 3). As shown by Cox analysis, the outcome was not affected by BP changes per se. Lower BPs were observed in patients regardless of whether their aortic PWV decreased or increased during the course of the study, and BP

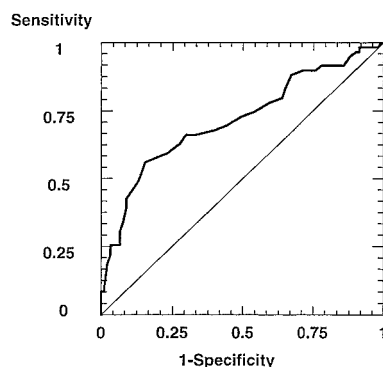
**TABLE 3. Proportional Hazard Regression Analyses of All-Cause and Cardiovascular Mortality**

Variable	RR (95% CI)	z Statistic	P	Pseudo-r <sup>2</sup>
All-cause mortality				
Age (10 y)	1.69 (1.32–2.17)	4.15	0.00003	0.15346
LV mass index (10-g increase)	1.08 (1.04–1.15)	2.27	0.02322	0.05144
ΔPWV (1=positive/0=negative)	2.59 (1.51–4.43)	3.46	0.00053	0.11215
ACE inhibitor (1=yes/0=no)	0.19 (0.14–0.43)	–3.93	0.00027	0.13956
Cardiovascular mortality				
CVD (yes/no)	4.72 (1.91–11.61)	3.36	0.00077	0.13097
LV mass index (10-g increase)	1.11 (1.03–1.19)	2.63	0.00844	0.00847
ΔPWV (1=positive/0=negative)	2.35 (1.23–4.51)	2.57	0.01004	0.08110
ACE inhibitor (1=yes/0=no)	0.18 (0.06–0.55)	–3.00	0.00274	0.10689

CVD indicates prior cardiovascular disease. Adjustments were made on all prognostic variables considered in model. Results of analyses were model  $\chi^2=83.06$ ,  $P<0.00001$ , and pseudo- $r^2=0.46648$  for all-cause mortality and model  $\chi^2=59.54$ ,  $P<0.00001$ , and pseudo- $r^2=0.44254$  for cardiovascular mortality.

changes were similar in nonsurvivors and survivors, in contrast to their aortic PWV changes (Figure 3). These data suggest that the presence of an intrinsic vasculopathy characterized by the loss of sensitivity to BP and reversibility of aortic stiffness is a major factor contributing to the mortality of ESRF patients.

The role of BP in predicting the prognosis of hemodialyzed patients is quite controversial. Charra et al<sup>17</sup> reported more prolonged survival of patients with an MBP <99 mm Hg than of patients with an MBP ≥99 mm Hg. However, those data were not adjusted for confounders such as age, sex, or prior history of cardiovascular disease. To the contrary, Zager et al<sup>18</sup> showed that the impact of BP on cardiovascular mortality was modest, and recent studies on ESRF patients showed that low DBP was associated with higher mortality.<sup>1,19</sup> The data in the literature indicate that the majority of hemodialyzed patients have DBP within the normal range and exhibit systolic hypertension with widely ranging pulse pressures.<sup>20</sup> Increased pulse pressure is a cardiovascular risk factor in the general population.<sup>21,22</sup> The wide range of pulse pressures in ESRF patients is principally the consequence of arterial stiffening<sup>23</sup> and, as such, is a marker of underlying arterial

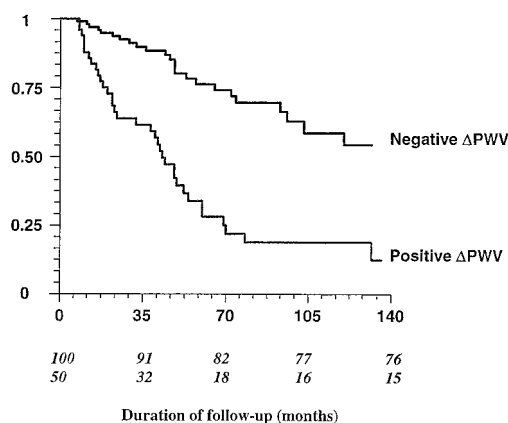


**Figure 1.** ROC curve: ability of adjusted aortic PWV change between inclusion and target BP to predict death. Area under curve is  $0.72 \pm 0.11$ .

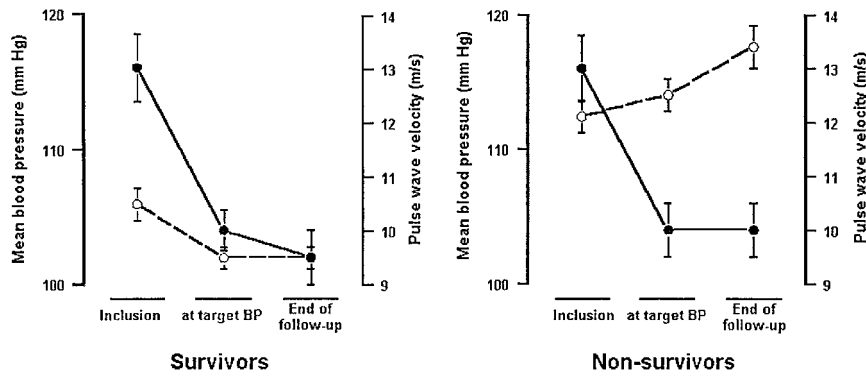
abnormalities. After adjustment for arterial stiffness, it was found not to be an independent risk factor in the present population

In agreement with data published on ESRF patients, age was the most significant prognostic factor for all-cause mortality but not for cardiovascular mortality.<sup>1</sup> The positive history of prior cardiovascular disease was the strongest independent predictor of cardiovascular mortality. In agreement with published data, the presence of LV hypertrophy was also an independent predictor of all-cause mortality, but it was more significantly a predictor of cardiovascular mortality<sup>24,25</sup> (Table 3).

In agreement with Salem and Bower,<sup>26</sup> the present results suggest that antihypertensive treatment per se has a favorable effect. As our results show, prolonged survival seems to more closely reflect the use of an ACE inhibitor than the other drugs or the number of drugs per se. The use of  $\beta$ -blockers and/or dihydropyridine calcium blockers had no direct rela-



**Figure 2.** Probability of all-cause survival according to  $\Delta$ PWV under antihypertensive therapy. Comparison between BP responders (negative  $\Delta$ PWV) and nonresponders (positive  $\Delta$ PWV) was highly significant ( $\chi^2=28.03$ ,  $P<0.00001$ ). Numbers of patients at each time point are in italics (top row, responders; bottom row, nonresponders).



**Figure 3.** Changes of MBP (solid circle) and aortic PWV (open circle) from inclusion to end of follow-up for survivors and nonsurvivors. Values are mean  $\pm$  SEM.

relationship with the outcome. The relationship between survival and perindopril seems to be one of the strongest statistically (Table 3) but must be interpreted cautiously, inasmuch as the present study was not designed to compare the effect of different antihypertensive drugs on survival as such, and the regimen at target BP was influenced by their tolerance and the optimal effect on BP. Several studies on high-risk populations have shown that ACE inhibitors have a favorable prognostic effect, reducing death rates and cardiovascular complications.<sup>27,28</sup> The present findings suggest that a similar favorable effect of ACE inhibitors could be observed in ESRF patients, but a specifically designed, prospective, therapeutic trial is needed to confirm them. The influence of the ACE inhibitor did not reflect a difference in BP control or a direct and better effect on aortic stiffness. A blinded and controlled study on ESRF patients showed that perindopril induced a pressure-independent decrease of LV hypertrophy that was due to reduction of the LV diameter and cavity volume, which are independent predictors of survival in these patients.<sup>29</sup>

In conclusion, the present data indicate that persistence of aortic stiffness reversibility (or sensitivity) in response to BP lowering had a beneficial and BP-independent impact on the survival of ESRF patients, suggesting that the presence of more advanced vascular lesions characterized by the loss of BP reversibility of aortic stiffness is a major factor contributing to the mortality of ESRF patients. This finding emphasizes the need to test other alternative therapies in ESRF patients in whom antihypertensive drugs are unable to alter aortic PWV. The second finding of the present study suggests that ACE inhibitors have a favorable effect on the patient's outcome. However, this observation needs confirmation in a specifically designed, prospective, therapeutic trial. Finally, the extrapolation of the conclusions based on the present study may be limited because of the particular clinical characteristics of ESRF patients, who are at very high risk of cardiovascular complications; thus, further studies are needed to extend these findings to other populations.

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