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Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study[1]

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Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study.

Background. The long-term prognostic associations of pre- and post-dialysis blood pressures, interdialytic weight gain, and antihypertensive use in hemodialysis patients are unclear.

Methods. The United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Waves 3 and 4 Study, a randomly generated sample of 11,142 subjects receiving hemodialysis on December 31, 1993, was examined, with vital status followed until May 2000.

Results. Pre- and post-dialysis blood pressure values, interdialytic weight gain and number of antihypertensives averaged 151.8/79.7, 137.0/74, 3.6% and 0.76, respectively. Prognostic discrimination was maximized by considering pre- and post-systolic and diastolic blood pressure values simultaneously, in a pattern suggesting that wide pulse pressures were associated with mortality ($P < 0.0001$). Comorbidity adjustment markedly affected associations, with low pre-dialysis diastolic ($P < 0.05$), low post-dialysis dialysis diastolic pressure ($P < 0.05$), high post-dialysis dialysis systolic pressure ($P < 0.05$), and high interdialytic weight gains ($P = 0.005$) associated with mortality. Each class of antihypertensive drug, except angiotensin-converting enzyme (ACE)-inhibitors, was associated with lower mortality in unadjusted models, an effect most pronounced for beta-blockers (hazards ratio 0.72, 95% CI 0.66 to 0.79, $P < 0.0001$). Comorbidity adjustment eliminated survival associations for each antihypertensive class except beta-blockers.

Conclusions. Pre- and post-dialysis blood pressure values have independent associations with mortality, in a way that implicates wide pulse pressures. Much of the adverse prognosis of wide pulse pressures probably reflects older age and cardiovascular comorbidity. Large interdialytic weight gains are associated with shorter survival when comorbidity is taken into account. Beta-blocker use shows a robust association with survival, and may be protective.

[1]The data reported here were supplied by the United States Renal Data System. Interpretation of these data is the responsibility of the authors, and in no way should be seen as an official policy or interpretation of the U.S. government.

Key words: hypertension, pulse pressure, chronic kidney disease, relative risk of death, renal statistics, USRS statistics.

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Hypertension and cardiovascular disease are notable features of chronic kidney disease. Only a few recent observational studies, surprisingly, have associated hypertension and shorter survival in dialysis patients [1, 2]. Most studies have shown an association between low blood pressure and increased mortality, or have shown a "U"-shaped relationship, with both low and high blood pressure being associated with an increased relative risk of death [3–6]. A credible explanation for the findings is that the patient sample includes a sizeable proportion of patients with incipient or established cardiac decompensation, with the counterintuitive relationship between lower blood pressure and survival caused by reverse causation. Alternative explanations than reverse causation are possible, however. It is conceivable that low blood pressure could jeopardize coronary perfusion in the setting of the altered cardiac energetics, diastolic dysfunction, and decreased capillary density so characteristic of uremic cardiomyopathy, leading to myocardial ischemia. Ischemia would be magnified in the presence of fixed coronary stenosis, a common entity, which is often clinically silent in dialysis patients.

To date, almost all mortality analyses in end-stage renal disease patients have used either systolic blood pressure, or diastolic blood pressure as the candidate variable. Most analyses have focused on pre-dialysis blood pressure, and very few have examined the prognostic associations of post-dialysis blood pressures. Very few epidemiological studies have attempted to quantify the relative contributions of blood pressures, interdialytic weight gains, and the number and classes of antihypertensives used, all of which are clearly interrelated.

There has been a growing realization that stiffening of large arteries is a major feature of uremic states, which has independent associations with mortality [7]. Widening arterial pulse pressure is the major clinical correlate of arterial stiffening. Pulse pressure, calculated as systolic minus diastolic blood pressure, presents some challenges in observational studies. Analyses that include either systolic or diastolic blood pressure alone, the most common approach, may fail to uncover a real association between

pulse pressure and mortality. On the other hand, using pulse pressure in isolation may create an artifactual association when high systolic blood pressure or low diastolic blood pressure is the real culprit, and pulse pressure has no causal relationship. Such problems can be uncovered when two of the three parameters (systolic, diastolic and pulse pressure) are included simultaneously in mortality analyses, an approach used recently in studies in the both the general and end-stage renal disease populations [8, 9].

METHODS

The objectives of this study were to determine (*1*) the optimum way to handle blood pressure parameters for a hemodialysis population, in a way that maximizes prognostic discrimination, as described by the χ^2 statistic in Cox regression models of mortality; (*2*) the mortality associations of interdialytic weight gains; (*3*) the mortality associations of classes of antihypertensive used; and (*4*) the impact of comorbidity adjustment on objectives 1 to 3.

We used the United States Renal Data System (USRDS) DMMS Waves 3 and 4 Study, a historical prospective study of a randomly generated sample of 11,142 United States subjects receiving hemodialysis at the end of December 1993. Participating dialysis units were selected at random, with case records reviewed retrospectively. For this study, the following fixed patient characteristics were included, as of December 31, 1993: age, gender, ethnicity, race, primary renal disease, duration of hemodialysis, smoking, diabetic status, presence of coronary artery disease or coronary heart disease, congestive heart failure, cerebrovascular accident and peripheral vascular disease.

Pre- and post-dialysis blood pressures, and interdialytic weight gains were averaged from the three most recent values immediately preceding December 31, 1993. Vasoactive medications were grouped into the following classes: calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, alpha blockers, centrally active agents, and vasodilators.

USRDS patient numbers were used to combine the DMMS Waves 3 and 4 file with the Patient's file, with vital status ascertained up to May 2000. Cox proportional hazards modeling was the primary analytical tool employed. The analyses presented in this report did not censor patients at transplantation. However, the associations were virtually identical with such an approach.

RESULTS

The patient characteristics on December 31, 1993 are shown in Table 1. The mean pre- and post-dialysis blood pressures, averaged from the three most recent values immediately preceding December 31, 1993, were 151.8/79.7 and 137.0/74.1 mm Hg equating to pulse pressures of 72.1 and 62.9 mm Hg, respectively. On average, interdialytic weight gain was 3.6% of pre-dialysis body weight, and the patients were prescribed 0.76 antihypertensive agents. A percentage of 49.6% of patients were prescribed no antihypertensive agents, 30.9% one agent, 14.7% two agents, 3.9% three agents, 0.8% four agents, and 0.1% five agents. Calcium channel antagonists (35.0% of patients) were the most frequently prescribed class, followed by ACE inhibitors (13.9%), centrally acting agents (9.8%), beta blockers (8.5%), vasodilators (5.1%), and alpha blockers (3.4%).

Sixty-three percent of the subjects died over an average follow-up of 3.8 years, with a median survival of 3.9 years. Figure 1 shows hazards ratios and the overall model χ^2 statistics in Cox regression models of mortality which have not been adjusted for age or comorbidity.

Table 1. Patient characteristics on December 31, 1993 (N = 11,142)

	Mean (SD)	Missing data
Age *years*	59.7 (15.8)	13.1%
Gender		0.1%
Male	50.7%	
Female	49.2%	
Race		
Hispanic	13.1%	6.3%
Caucasian	51.0%	6.4%
African American	41.0%	
Asian	2.3%	
Native American	1.5%	
Other	4.2%	
Primary renal disease		7.3%
Diabetes	34.3%	
Hypertension	29.6%	
Primary glomerulonephritis	11.5%	
Other	4.2%	
Unknown	20.5%	
Smoking status		17.2%
Still smoking	16.1%	
Former, stopped <1 year ago	2.7%	
Former, stopped >1 year ago	14.2%	
Smoker, current status unknown	14.4%	
Non-smoker	52.6%	
Diabetes mellitus	42.9%	8.8%
Cardiovascular disease		
Coronary artery disease	36.0%	12.4%
Congestive heart failure	39.2%	12.2%
Peripheral vascular disease	22.1%	11.7%
Cerebrovascular disease	12.5%	11.7%
Duration of hemodialysis *years*	3.1 (3.5)	14.2%
Pre-dialysis blood pressure *mm Hg*	151.8 (22.1)/ 79.7 (12.2)	11.2%/ 11.5%
Post-dialysis blood pressure *mm Hg*	137.0 (21.0)/ 74.1 (11.3)	11.6%/ 11.9%
Interdialytic weight gain *%*	3.6 (1.9)	15.6%
Calcium channel antagonists	35.0%	Assumed[a] 0%
Angiotensin-converting enzyme inhibitors	13.9%	Assumed[a] 0%
Beta blockers	8.5%	Assumed[a] 0%
Alpha blockers	3.4%	Assumed[a] 0%
Centrally active agents	9.8%	Assumed[a] 0%
Vasodilators	5.1%	Assumed[a] 0%

[a] All medications were recorded in 15 data-fields. Dichotomous 'yes' or 'no' variables asking whether specific drug classes were used were not used.

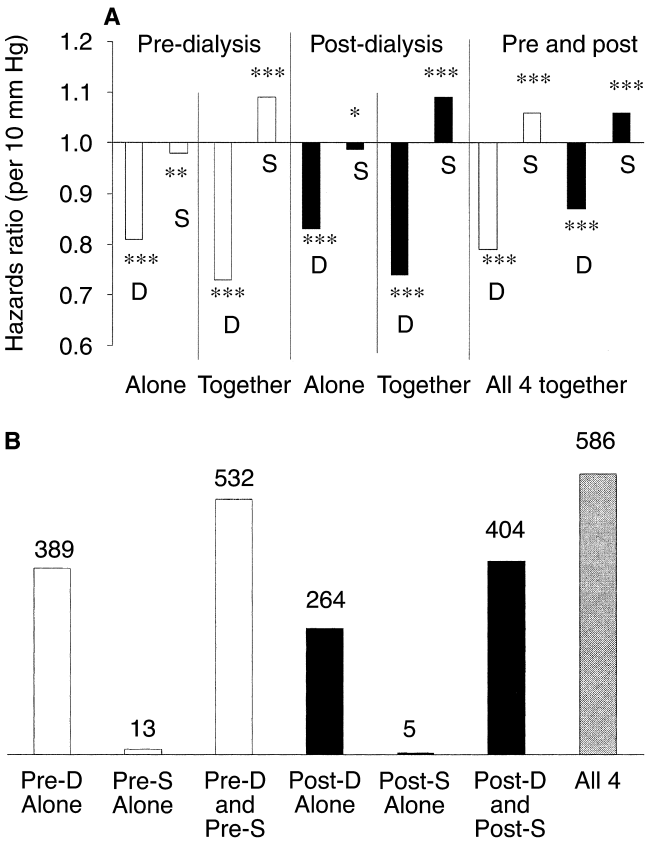

Fig. 1. (*A*) Cox regression models relating blood pressure levels to subsequent mortality rates, expressed as hazards ratios per 10 mm Hg. Symbols are: (□) pre-dialysis parameters; (■) post-dialysis parameters. Abbreviations are: S, systolic blood pressure; D, diastolic blood pressure; Alone, only that single parameter was entered in the Cox model; together, all of the parameters shown were entered simultaneously in the model. Hazards ratios greater than 1 imply higher mortality rates, while hazards ratios less than 1 imply lower mortality rates. $***P < 0.0001$; $**P < 0.001$; $*P < 0.05$. (*B*) Cox regression models relating blood pressure levels to subsequent mortality rates. The columns show the variance explained, expressed as the associated χ^2 statistic for different models. Symbols are: (□) models with only pre-dialysis parameters; (■) models with only post-dialysis parameters; (▩) models with both pre-dialysis and post-dialysis parameters.

Judged in terms of the χ^2 value, the prognostic discrimination was maximized by analyzing diastolic and systolic blood pressure values simultaneously, both before and after dialysis. In the latter models, the hazards ratios for systolic blood pressures increased, while those for diastolic blood pressures decreased, suggesting that wide pulse pressure may be a better marker of mortality risk than systolic or diastolic blood pressure in isolation.

The associations between blood pressure, related variables, and mortality are shown in Table 2. All four blood pressure variables, that is, pre- and post- systolic and diastolic values, were entered simultaneously. When analyzed by quintiles, all relationships tended to be monotonic, with the possible exception of pre-dialysis systolic blood pressure, for which the hazards ratios were equivalently higher for second, third and fourth quintiles, with a further rise in hazards ratio for the fifth quintile. Percentage of interdialytic weight gain exhibited a weak inverse association with mortality in unadjusted analyses. Each antihypertensive class, except ACE inhibitors, was associated with statistically significantly longer survival. This effect was greatest for beta blocker use (hazards ratio 0.72, 95% CI 0.66 to 0.79, $P < 0.0001$) and vasodilator use (hazards ratio 0.73, 95% CI 0.65 to 0.82, $P < 0.0001$).

When an adjustment was made for comorbidity, low pre-dialysis diastolic, low post-dialysis diastolic, and high post-dialysis systolic blood pressure values were associated with higher mortality, albeit much less strongly than in unadjusted models. Percentage interdialytic weight gain, on the other hand, showed a direct association with mortality, most apparent for weight gains in the highest quintile, greater than 4.8% of pre-dialysis body weight. All classes of antihypertensive lost their mortality associations in comorbidity-adjusted models, with the exception of beta-blockers, which retained their association with lower mortality rates (hazards ratio 0.84, 95% CI 0.75 to 0.93, $P = 0.001$).

DISCUSSION

Considering pre- and post-systolic and -diastolic blood pressure values simultaneously maximized the prognostic discrimination in this study, in a pattern suggesting that wide pulse pressure may be a marker of short survival. Adjustment for older age and comorbidity greatly modified these associations. Similarly, complex associations were found between interdialytic weight gain and mortality, with shorter associated survival apparent after comorbidity adjustment. Finally, we observed that beta-blocker use was associated with longer survival, whether or not comorbidity adjustment was undertaken.

Hypertension in the general population increases the long-term risk of end-stage renal disease [10, 11]. Among patients with renal impairment, strategies that lower blood pressure, including ACE inhibitors and angiotensin II receptor inhibitors, are known to retard the rate of loss of renal function, and to delay the onset of end-stage renal disease [12–17]. It is likely that blood pressure reduction per se contributes to these salutary effects [18]. Hypertension is an almost universal feature of end-stage renal disease, and this group of patients is at the highest cardiac risk. Unfortunately, there are no large hypertension-management trials in dialysis patients. It could be argued that such trials might not be needed if the epidemiological patterns linking blood pressure and outcome in the dialysis population were similar to those seen in the general population. Most recent studies, however, have been at variance to those seen in non-renal populations, with inverse or "U"-shaped relationships with mor-

Table 2. Blood pressure and mortality associations

	Unadjusted hazards ratio[a]	Adjusted hazards ratio[b]
Pre-dialysis DBP[c]	0.79 (0.76, 0.82) per 10 mm Hg	0.95 (0.91, 0.99) per 10 mm Hg
Quintiles	$P < 0.0001$	$P = 0.03$
≤70	1.06 (reference category)	1 (reference category)
70.1 to 76.7	0.79 (0.73, 0.85)	0.90 (0.82, 0.98)
76.8 to 82.0	0.73 (0.67, 0.79)	0.97 (0.88, 1.07)
82.1 to 89.3	0.64 (0.59, 0.71)	0.94 (0.84, 1.05)
>89.3	0.49 (0.44, 0.55)	0.90 (0.77, 1.02)
Pre-dialysis SBP[c]	1.06 (1,04, 1.08) per 10 mm Hg	0.99 (0.97, 1.02) per 10 mm Hg
Quintiles	$P < 0.0001$	$P = 0.6$
≤133.3	1 (reference category)	1 (reference category)
133.4 to 146.7	1.14 (1.05, 1.24)	0.97 (0.93, 1.01)
146.8 to 157.3	1.16 (1.06, 1.28)	0.89 (0.79, 0.99)
157.4 to 170.0	1.15 (1.04, 1.27)	0.87 (0.77, 0.97)
>170.0	1.38 (1.22, 1.55)	0.96 (0.83, 1.10)
Post-dialysis DBP[c]	0.87 (0.76, 0.82) per 10 mm Hg	0.94 (0.90, 0.98) per 10 mm Hg
Quintiles	$P < 0.0001$	$P = 0.006$
≤64.7	1 (reference category)	1 (reference category)
64.8 to 70.7	0.92 (0.85, 1.00)	0.95 (0.87, 1.05)
70.8 to 76.7	0.86 (0.79, 0.93)	0.95 (0.86, 1.05)
76.8 to 83.0	0.83 (0.75, 0.92)	0.93 (0.82, 1.04)
>83.0	0.65 (0.57, 0.73)	0.85 (0.73, 0.99)
Post dialysis SBP[c]	3 (1.03, 1.08) per 10 mm Hg	1.03 (1.00, 1.05) per 10 mm Hg
Quintiles	$P < 0.0001$	$P = 0.03$
≤119.3	1 (reference category)	1 (reference category)
119.4 to 130.7	1.11 (1.02, 1.21)	0.93 (0.84, 1.03)
130.8 to 141.3	1.15 (1.05, 1.27)	0.95 (0.85, 1.06)
141.4 to 154.0	1.22 (1.11, 1.35)	0.97 (0.86, 1.06)
>154.0	1.31 (1.16, 1.47)	1.07 (0.93, 1.22)
Interdialytic weight gain	0.99 (0.97, 1.00) per %	1.02 (1.01, 1.03) per %
Quintiles	$P = 0.05$	$P = 0.005$
≤2.3 (reference)	1 (reference category)	1 (reference category)
2.3 to 3.1	0.97 (0.90, 1.06)	0.96 (0.88, 1.05)
3.2 to 3.9	1.02 (0.94, 1.10)	1.03 (0.94, 1.13)
4.0 to 4.8	0.99 (0.91, 1.07)	1.03 (0.94, 1.14)
>4.8	0.92 (0.85, 1.00)	1.12 (1.02, 1.23)
Calcium channel antagonists[d]	0.95 (0.90, 1.00)	1.0 (0.94, 1.07)
	$P = 0.04$	$P = 0.9$
Angiotensin-converting enzyme inhibitors[d]	0.94 (0.88, 1.01)	1.05 (0.96, 1.17)
	$P = 0.07$	$P = 0.3$
Beta blockers[d]	0.72 (0.66, 0.79)	0.84 (0.75, 0.93)
	$P < 0.0001$	$P = 0.001$
Alpha blockers[d]	0.87 (0.77, 1.00)	0.93 (0.80, 1.09)
	$P = 0.05$	$P = 0.4$
Centrally active agents[d]	0.89 (0.82, 0.96)	4 (0.97, 1.17)
	$P = 0.004$	$P = 0.2$
Vasodilators[d]	0.73 (0.65, 0.82)	0.99 (0.86, 1.14)
	$P < 0.0001$	$P = 0.9$

[a] Hazards ratios greater than 1 imply higher mortality rates, while hazards ratios less than 1 imply lower mortality rates

[b] Adjusted for age, gender, ethnic status, race, cause of renal disease, duration of end-stage renal disease, smoking, diabetes, coronary artery disease, congestive heart failure, peripheral vascular disease, and interdialytic weight gain

[c] Predialysis-SBP (systolic blood pressure), Predialysis-DBP (diastolic blood pressure); postdialysis-SBP and postdialysis-DBP have been included simultaneously in the unadjusted and adjusted models

[d] Reference categories are subjects not on calcium channel antagonists, angiotensin-converting enzyme inhibitors, beta blockers, alpha blockers, centrally active agents, and vasodilators, respectively

tality [3–6]. Few studies in end-stage renal disease patients have examined non-fatal cardiovascular end-points. Some studies have tried to address this issue indirectly, using cause-specific mortality in registry databanks. This approach may not be very reliable, as inter-rater discordance regarding cause of death has been reported to occur in approximately two out of every three cases in one study, while a more recent study suggested that discordance may occur even more commonly for cardiovascular causes of death [19, 20].

In one long-term prospective inception cohort study, higher time-averaged blood pressures predated the development of echocardiographic left ventricular hypertrophy, new-onset ischemic heart disease and new-onset cardiac failure. In this latter study, new-onset cardiac failure was a lethal event, which came before two-thirds of all the observed causes of mortality, and was followed by a fall in blood pressure. The degree of hypotension was the only predictor of mortality after cardiac failure [21]. This is a plausible, though partial, explanation for the paradox that high blood pressure comes before a major apparent killer, cardiac failure, while low blood pressure is a better predictor of death. These data suggest that the association between high blood pressure and longer survival may be due to reverse causality. Blood pressure is a problematic parameter in dialysis studies with several inherent limitations. Ambulatory blood pressure monitoring was not used in this study, but would have an obvious attraction in comparison to single values immediately before and after dialysis. For example, a recent study performed 48-hour interdialytic ambulatory blood pressure monitoring on 21 hemodialysis patients on two different occasions two months apart. Blood pressure was analyzed according to three different methods on each occasion: isolated levels before and after dialysis, levels averaged over five dialysis sessions, and 48-hour interdialytic ambulatory blood pressure monitoring. Variability was considerable, even with ambulatory blood pressure (the most reproducible measure of blood pressure, followed by averages and single values), with coefficients of variation 7.5% for systolic and 8.1% and discordance rates for nocturnal dipper status of 43% [22].

Hypertension has been consistently associated with left ventricular enlargement in observational studies in chronic renal insufficiency, which is likely to be a potentially reversible intermediate stage between cardiac health and clinical cardiovascular disease, as is the case in the general population [23–27]. Hypertension in dialysis patients is often due to subclinical salt and water overload [28–30]. For example, a recent crossover trial was reported comparing short daily and conventional, three times weekly hemodialysis sessions. Although weekly urea removal was similar with either strategy, blood pressure was significantly better in the daily dialysis group, in whom antihypertensives were discontinued in most patients. Left ventricular hypertrophy regressed in the daily hemodialysis group, probably due to lowering of extracellular fluid volume [31]. A number of other studies have shown that inexorable progression of left ventricular hypertrophy is not inevitable in dialysis patients. In one study, dialysis patients with left ventricular hypertrophy and hypertension were randomly assigned to an ACE inhibitor or a dihydropyridine calcium antagonist for one year. Left ventricular hypertrophy regressed in both groups, but more so in the ACE inhibition group, despite the fact that blood pressures were similar, suggesting an independent impact of ACE inhibitors on left ventricular hypertrophy regression [32]. Similarly, another study used ACE inhibitors as the primary antihypertensive therapy in hemodialysis patients, and observed a gradual regression of left ventricular hypertrophy over a period of several years [33]. Thus, the consistent association between echocardiographic left ventricular hypertrophy and mortality is at variance with the inconsistent association between blood pressure and mortality in large registry studies, as higher blood pressure levels have consistently been associated with the development of left ventricular hypertrophy.

Stiffening of the vascular tree appears to be a characteristic feature of uremia, which has recently been demonstrated to be highly predictive of short survival [7]. Widened pulse pressure, a clinical hallmark of vascular rigidity, lately has become a focus of more intensive investigation. For example, a very interesting report from the Framingham Heart Study suggests that parameters like systolic and diastolic blood pressures, in isolation, have less predictive power in general population subjects over 60, in whom high pulse pressures are more highly predictive of adverse cardiovascular events [8]. Similar findings were reported from a French hypertensive population [34]. If pulse pressure is indeed a superior prognostic discriminate, analyses that use either systolic or diastolic blood pressures alone should have less predictive power, while analyses that include both systolic and blood pressure parameters simultaneously should have more predictive power. This pattern was seen in our current study, which suggested that high pulse pressure, whether before or after dialysis, is a marker of short survival in dialysis, mostly, but not completely, as a marker of underlying comorbidity. These findings are consistent with those recently reported by Tozawa and co-workers, who examined a cross-section of 1243 chronic hemodialysis patients alive on January 1, 1991 followed for nine years [9]. Pulse pressure was found to be an independent predictor of total mortality, and was a superior predictor of total mortality than systolic or diastolic pressures. For predicting cardiovascular events, however, systolic blood pressure was better than either pulse pressure or diastolic blood pressure [9]. In epidemiological analyses, pulse pressure is necessarily handled as a somewhat static parameter, in the sense that a single unique value exists for each study subject. However, from a pathophysiological perspective, pulse pressure is clearly a composite parameter determined by parameters of left ventricular ejection, opposition to ejection, and wave reflections. Thus, the pathways to a given pulse pressure must be very diverse in the population examined in this study. It is believed that in older subjects the wide pulse pressure reflects increased stiffness, a characteristic feature of end-stage renal disease patients, which accelerates dia-

stolic decay rates, leading to lower diastolic blood pressure and wider pulse pressure [35].

It has long been a doctrine of dialysis treatment that blood pressure and extracellular fluid volumes are closely related. It makes intuitive sense that patients who will develop overt cardiovascular disease in the future may not exhibit symptoms of cardiac decompensation with higher interdialytic fluid gains. Our current study suggests that interpreting the relationship between interdialytic fluid gains and mortality is heavily dependent on considering the underlying comorbidity of the population.

We observed an association between beta-blocker use and longevity in this study, an association that was only partly affected by comorbidity adjustment. Clearly, an observational study like this cannot account for the selection biases connecting different patients to different classes of antihypertensive drugs, and cannot adduce causality. However, beta blockers have several theoretically appealing features in uremic populations. They reduce stroke volume and thus would be attractive agents to interrupt the vicious cycle whereby high stroke volumes and large vessel rigidity exacerbate each other. Sympathethic overload and cardiomyopathy are cardinal features of uremia [36, 37]. In non-uremic subjects, beta-blockers have been shown to improve outcome in the setting of decompensated cardiomyopathy and ischemic heart disease, which are common occurrences in dialysis populations [38–40]. A highly noteworthy, randomized, placebo-controlled trial assessed the effect of carvedilol in dialysis patients with symptomatic heart failure [41]. Over a study duration of 12 months, carvedilol treatment led to sustained improvements in left ventricular ejection fraction and reduced left ventricular end-diastolic and end-systolic volumes, associated with improvements in New York Heart Association cardiac failure symptom severity [41]. Finally, beta blockers have anti-arrhythmic properties that make them attractive in a population where dysrhythmia, ion shifts, and sudden death are very common. The associations between antihypertensive class and mortality were not seen in the recent study of Guerin and co-workers of 150 dialysis patients followed for an average of 51 months. Cox analyses showed that failure of pulse wave velocity to decline in response to lowering of blood pressure, while left ventricular mass, older age, cardiovascular disease at study inception were associated with higher all-cause and cardiovascular mortality rates. ACE inhibitor use, in contrast to our current study, was independently associated with longer survival [42]. The disparity may reflect the fact that the mean age of their study population was significantly younger, 52 years old compared to 60 years old in our current study. In addition, the proportion of patients with diabetes mellitus and cardiovascular disease was higher in our study. In addition, associations between antihypertensive classes and outcome are highly questionable in diseased populations, especially when multiple strategies, both pharmacological and non-pharmacological, can be used to achieve a given blood pressure level. Similarly, a given antihypertensive class may be used more as the treatment for ischemic heart disease, cardiac failure, systolic dysfunction or left ventricular hypertrophy, all of which are common in dialysis patients.

Randomized controlled trials are sorely needed in dialysis populations to define optimal strategies for managing blood pressure. It is possible that relatively recent observational studies linking higher blood pressures to longer survival have engendered therapeutic uncertainty and neutrality, and lessened enthusiasm to undertake adequately powered clinical trials. Blood pressure levels in a modern dialysis population are likely to reflect the age and comorbidity of the population, deviations from euvolemia, and antihypertensive use. This study, in which the follow-up period was long, suggests that high blood pressure (pulse pressure), high interdialytic weight gains, and not being on antihypertensives (beta blockers) define a dialysis population at high risk, which may be modifiable.

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