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Achieving blood pressure targets during dialysis improves control but increases intradialytic hypotension

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Cardiovascular disease remains the most common cause of mortality in patients with end-stage kidney disease treated by regular hemodialysis. To improve blood pressure control and reduce cardiovascular risk, the United Kingdom Renal Association standards committee introduced pre- and post-dialysis target blood pressures of less than 140/90 and 130/80 mm Hg, respectively. We audited blood pressure control and symptomatic intradialytic hypotension requiring fluid resuscitation in the Greater London area renal centers that serve 2630 patients. The study captured 7890 hemodialysis sessions during a 1-week period where only 36% of the patients achieved the pre-dialysis target and 42% the post-dialysis target, with a wide variation between centers. Different antihypertensive medication prescriptions did not affect achievement of these targets. Fifteen percent of the patients suffered symptomatic hypotension requiring fluid resuscitation associated with significantly greater interdialytic weight gains. Our study found that intradialytic hypotension was significantly greater in centers that achieved better post-dialysis blood pressure targeting.

Kidney International (2008) **73,** 759–764; doi:10.1038/sj.ki.5002745; published online 26 December 2007

KEYWORDS: hemodialysis; hypertension; hypotension; audit; targets; standards

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Received 9 July 2007; revised 12 September 2007; accepted 9 October 2007; published online 26 December 2007

Hypertension and cardiovascular risk in the general population

In the general population, there is a strong association between hypertension and death and, in particular, increasing pulse pressure as a result of decreased conduit artery compliance.[1] The relative risk of hypertension for stroke and heart attack is greatest for younger subjects, although the absolute risk increases with age. In addition to stroke and heart attack, hypertension is also causally linked with heart failure and chronic kidney disease. A nonlinear association or 'J'-shaped curve has been reported between blood pressure and recurrent events in patients with previous myocardial infarction. Despite concerns that this increased risk may have been attributable to an adverse effect of treatment, it is now considered more likely to reflect the severity of disease on blood pressure—the larger the size of myocardial infarction, the greater the fall in blood pressure—rather than the effect of blood pressure or its treatment on the disease.[2] Hypertension has been defined by the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[3] (Table 1).

Hypertension and cardiovascular risk in the chronic kidney disease population

Cardiovascular death remains the most common cause of death in the chronic hemodialysis population, however; the same strong association is not seen with hypertension.[4] For example, systolic hypertension in Japanese hemodialysis patients was not associated with any excess heart attacks and/or stroke, although there was an increased risk of intracranial hemorrhage with systolic blood pressures >180 mm Hg.[5] In addition, post-mortem studies have shown that lacunar infarcts secondary to hypertension were the most common finding, even in patients without overt cerebrovascular disease.[6]

Blood pressure targets in the chronic kidney disease population

In view of the risk of cardiovascular death in hemodialysis patients, blood pressure control has become a major target

Table 1 | JNC-VII classification of blood pressure in adults[3]

Category	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Hypertension stage 1	140–159	or 90–99
Hypertension stage 2	⩾160	⩾100

JNC-VII, Joint National Committee-VII.

for intervention. As with the general population, there is a 'J'-shaped relationship with increased mortality in both those with the highest and lowest blood pressure.[7] This may be the consequence of prolonged sustained hypertension, resulting in cardiac damage, and eventually cardiac failure, associated with a low blood pressure[8] and increased mortality.

Although there has been no adequately powered intervention to study the potential benefit of blood pressure control in hemodialysis patients, standards committees have introduced blood pressure targets for dialysis patients. In the United Kingdom, the Renal Association standards committee produced a document in 2002 that stated that hemodialysis patients with chronic kidney disease stage V should have pre- and post-dialysis blood pressures of <140/90 and <130/80 mm Hg, respectively.[9] These targets were stricter than in the previous version, based on the absolute benefits of blood pressure control being greater in those patients with a high pulse pressure and non-compliant vasculature.[10]

Purpose of audit

To determine whether these targets were achievable in clinical practice and also whether the lower pre-dialysis blood pressure targets resulted in increased intradialytic hypotension, we prospectively audited blood pressure in a cohort of thrice weekly chronic hemodialysis patients attending dialysis centers in the Greater London area.

RESULTS

The first part of the audit was designed to assess how many patients achieved the UK Renal Association targets of pre- and post-dialysis blood pressures of <140/90 and <130/80 mm Hg, respectively. A total of 2630 patient *pro formas* were completed and returned for the audit, capturing 7890 hemodialysis sessions. The number of patients dialysing in the 11 centers ranged from 91 to 408, with median of 244 patients. The average pre-dialysis blood pressure recorded before the three dialysis sessions was 146.9 ± 23.6/88.2 ± 13.1 mm Hg. The pre-dialysis blood pressure standard was achieved in 36% of all patients. This varied between the 11 hospital centers, ranging from 28 to 57% (Figure 1). The average post-dialysis blood pressure was 134.5 ± 28.2/72.3 ± 12.8 mm Hg, and 42% of all patients achieved the post-dialysis standard of <130/80 mm Hg, with a range of 32–51% (Figure 1). Only 26% of all patients met both standards, ranging from 19 to 45% between the 11 hospital centers. There was an inverse relationship between the size of the center and the percentage of patients achieving the pre-dialysis target blood pressure, with smaller centers having greater success, $r = -0.71$, $P = 0.018$, but there was no correlation between center size and achievement of post-dialysis blood pressure and/or both targets.

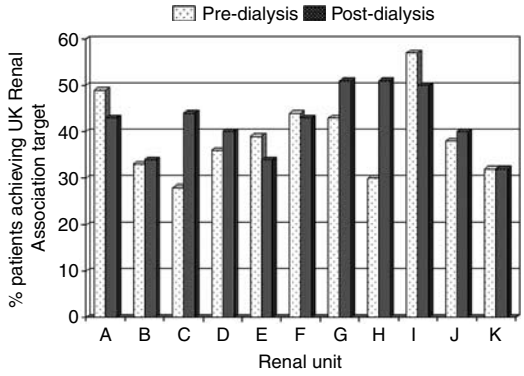

Figure 1 | Percentage of patients in each of the 11 hospital dialysis centers achieving pre- and post-dialysis UK Renal Association blood pressure targets of <140/90 and <130/80 mm Hg, respectively.

Seventy percent of all patients were prescribed antihypertensives, whether as blood pressure control or as cardioprotective agents. This ranged from 49 to 94% of patients between centers. On average, 57% of patients were instructed not to take their antihypertensive medications before hemodialysis, although this practice varied markedly between hospitals, ranging from 0 to 100%.

There was no correlation between the percentage of patients taking antihypertensive medications in centers and the percentage of patients achieving the pre-dialysis blood pressure target, $r = -0.16$, $P = 0.6$ and/or both targets, $r = -0.44$, $P = 0.17$. There was a direct correlation between the percentage of patients in a center not prescribed antihypertensives and that center achieving the post-dialysis target blood pressure (Figure 2).

Of those prescribed antihypertensive agents, angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) were the most commonly prescribed, with 42% of all patients prescribed these medications, and ranging from 28 to 76% patients between centers. β-Blockers were the next most commonly prescribed antihypertensive agents, 27% (ranging between 15 and 47% between the centers). There was no difference in achieving either pre-dialysis blood pressure targets, in those patients prescribed ACEIs/ARBs compared to other antihypertensives, 18 vs 10%, respectively ($\chi^2 = 2.29$, $P > 0.1$), or post-dialysis target, 20 vs 13%, respectively ($\chi^2 = 0.43$, $P = 0.5$), and both targets, 11 vs 6%. In addition, there was no significant difference in achieving either the pre-dialysis blood pressure target, whether patients were prescribed antihypertensive medication, or not (Figure 3).

There was no difference in the number of patients selected to be on the cadaveric renal transplant waiting list achieving either the pre-dialysis blood pressure target, 40% compared

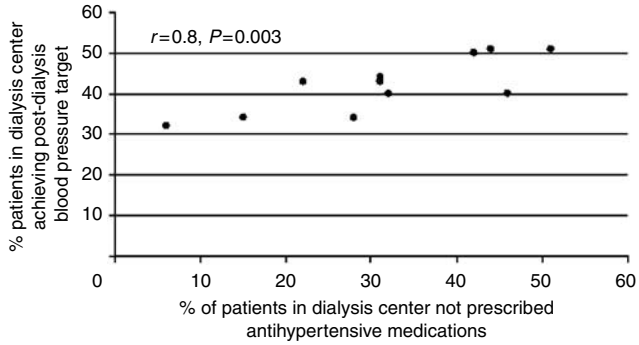

Figure 2 | Relationship between the percentage of patients not prescribed antihypertensive medications in each of the 11 dialysis centers and percentage of patients in that center achieving the pre- and post-dialysis UK Renal Association blood pressure targets.

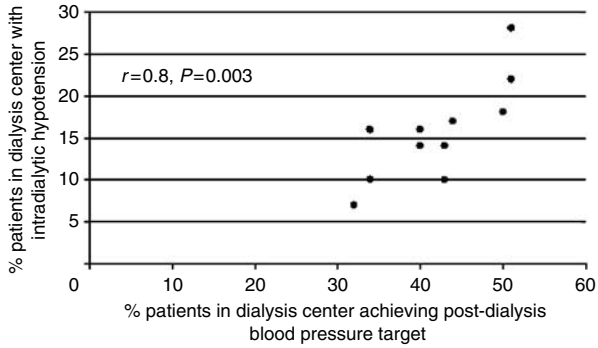

Figure 4 | Relationship between the percentage of patients achieving the UK Renal Association post-dialysis blood pressure target in each of the 11 dialysis centers and the percentage of dialysis patients with clinically symptomatic intradialytic hypotension requiring intravenous fluid resuscitation in that center.

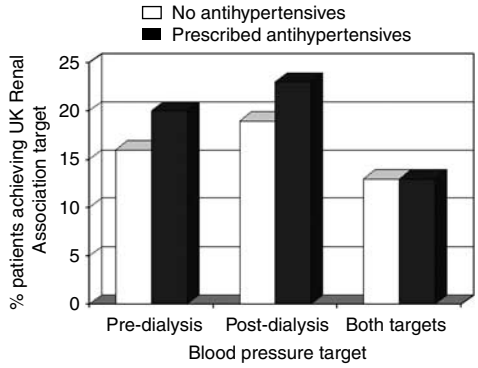

Figure 3 | Percentage of all hemodialysis patients audited achieving the pre-, post-dialysis, and both UK Renal Association blood pressure targets, whether they were prescribed antihypertensive medications or not.

to 35% not on the waiting list, or the post-dialysis target, 45 vs 40%, respectively.

There was no difference between ethnic groups in terms of achieving the UK Renal Association blood pressure targets, with 39% of Caucasian, 33% black, 33% Asian, and 33% of other races achieving the pre-dialysis standard, and 43% Caucasian, 41% black, 41% Asian, and 41% of other races achieving the post-dialysis target. Although more patients from ethnic minorities were prescribed antihypertensive medication, including 74% of blacks, 73% of Asians, 73% for other races, and 66% Caucasians, there was no statistical difference in blood pressure control between ethnic groups.

There was a very weak correlation between interdialytic weight gain for all patients and pre-dialysis blood pressure, $r=0.1$, $P<0.01$, but not post-dialysis blood pressure. Similarly, there was a weak correlation between dialysate sodium concentration and pre-dialysis systolic blood pressure, $r=0.032$, $P<0.05$. There was a direct correlation between dialysate sodium concentration and interdialytic weight gain, $r=0.137$, $P<0.01$. However, there was an unexpected correlation between dialysate sodium concentration and the post-dialysis blood pressure, $r=-0.56$, $P<0.01$, and this may have been due to clinicians trying to sustain blood pressure in severely hypotensive patients by deliberately increasing the dialysate sodium.

Hypotension during dialysis requiring intravenous fluid resuscitation was recorded in 7% of all hemodialysis sessions, which varied from 4 to 13% between centers. Overall, some 15% of patients experienced at least one hypotensive episode over the three dialysis sessions and 2% of patients suffered hypotensive episodes during each of the three dialysis sessions. The incidence of persistent clinically symptomatic intradialytic hypotension, requiring intravenous fluid resuscitation, varied from 0 to 4% between centers. There was a correlation between the percentage of patients achieving the post-dialysis blood pressure standard in a center and the percentage of symptomatic intradialytic hypotensive episodes requiring intravenous fluid resuscitation, $r=0.81$, $P=0.003$ (Figure 4), but there was no correlation between intradialytic hypotension and achievement of the pre-dialysis blood pressure target, $r=-0.12$, $P=0.71$.

Patients were more likely to suffer clinically symptomatic hypotensive episodes requiring intravenous fluid resuscitation if they were not prescribed antihypertensives, 21% compared to 13% of those prescribed antihypertensives, ($\chi^2=20.2$, $P<0.001$). This apparent difference could have been potentially exaggerated, as patients prone to intradialytic hypotension prescribed antihypertensive medications may have been advised to withhold their antihypertensives before dialysis. The advice regarding taking prescribed antihypertensive medication varied from center to center, with 57% of patients advised not to take their medication before dialysis, but this advice varied from 0 to 100% between centers. Eleven percent of patients who omitted their antihypertensives before dialysis suffered one or more hypotensive episodes compared to 7% of those who took their medication ($\chi^2=0.58$, $P=0.44$). There was no significant difference between the incidence of recorded

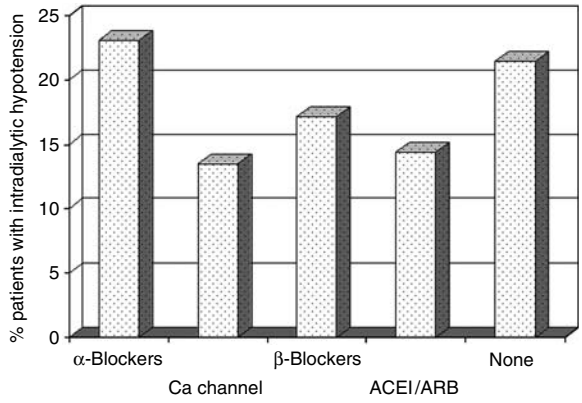

Figure 5 | The effect of different drug classes on clinically symptomatic intradialytic hypotension. Percentage of patients developing intradialytic hypotension prescribed α-blockers, calcium channel antagonists (Ca channel), β-blockers, and angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (ACEI/ARBs) as monotherapy, and also those who were prescribed no antihypertensive medications (none).

hypotensive episodes and drug prescription; 23.1% of patients prescribed α-blocker monotherapy, 15.6% calcium channel blockers, 20.7% β-blockers, and 16.9% prescribed ACEIs/ARBs (Figure 5).

Patients who developed clinically symptomatic intradialytic hypotension requiring intravenous fluid resuscitation had greater median interdialytic weight gains as both absolute weight gain, 2.42 kg (1.8–3.0) vs 2.1 kg (1.3–2.8), $P<0.01$ and percentage increase compared to target dry weight, median 3.2% (2.4–4.3) vs 2.8% (1.8–3.9), $P<0.0001$.

Those patients who suffered clinically symptomatic intradialytic hypotension had a lower pre-dialysis mean diastolic pressure, median 75 mm Hg (66–85) compared to those who did not, median 78 mm Hg (69–88), $P<0.001$. In addition, hypotensive-prone patients were also noted to have a lower pulse pressure, 64 mm Hg (50–81) vs 68 mm Hg (54–81), $P<0.01$.

DISCUSSION

Whereas in the general population there is a strong causal association between hypertension and both cardiovascular morbidity and mortality, the association is less clear in hemodialysis patients. Some studies have reported that although hypertension was not associated with early mortality of hemodialysis patients, it did have a later effect when systolic blood pressure was >160/90 mm Hg,[8] whereas other studies have reported increased mortality only when the systolic pressure is greater than 180 mm Hg.[11] A review of the US renal database reported that a low pre-dialysis systolic blood pressure was associated with increased risk of mortality, but there was no increased mortality risk with systolic hypertension, although there was an increased risk of stroke.[7] Similarly, the Japanese renal registry does show an increased risk of cerebral hemorrhage in patients with both pre- and post-dialysis hypertension.[5] However, post-dialysis systolic blood pressure has been associated with an elevated mortality risk both for low and high levels as compared with mid-range blood pressures.[7]

Compliance with blood pressure targets

In this audit of 2630 established thrice weekly hemodialysis patients, only 36% achieved the UK Renal Association pre-dialysis blood pressure target of <140/90 mm Hg, 42% the post-dialysis standard of <130/80 mm Hg, and 26% met both standards. The percentage of patients achieving the targets varied between the 11 centers, ranging from 28 to 57% for pre-dialysis and 32 to 51% for post-dialysis targets. The pre-dialysis target blood pressure was more readily achieved in those centers with the smaller hemodialysis program, although program size had no effect on achieving either the post-dialysis target and/or both blood pressure targets.

Differences in clinical practice between centers

There was tremendous variation in clinical practice between the centers, in terms of the prescription of antihypertensive medications, varying from 49 to 94%. Those centers with the highest rate of prescription of antihypertensive medications did not dialyse their patients against significantly higher dialysate sodium concentrations. There was no correlation between the centers in terms of prescription of antihypertensive medications and achieving the pre-dialysis blood pressure targets. Whether dialysis centers advised patients to take their antihypertensives before attending for dialysis had no effect on centers achieving the pre-dialysis blood pressure target.

Achieving the pre-dialysis blood pressure target may reflect differences in clinical practice as to whether clinicians were more concerned in controlling post-dialysis blood pressure rather than pre-dialysis blood pressure, as there has been great debate as to which blood pressure recording more accurately reflects the interdialytic blood pressure.[12] Thus, when targets are set, there are two key points: firstly, the validity of the target, in terms of evidence base, and secondly, the achievability of the target.[9] Probably because of the lack of strong evidence linking pre-dialysis hypertension and mortality, this target was achieved only in 36% of patients. Although there is greater evidence for an effect of post-dialysis blood pressure on mortality, again this was achieved in only 42% of patients. There was a direct correlation between the percentage of patients not prescribed antihypertensive medication in a center and achievement of the target blood pressure by the center. This suggests that other factors play a key role in determining blood pressure in hemodialysis patients, for example, interdialytic weight gains and dialysate sodium.[13] In this audit, there was a direct correlation between both interdialytic weight gain and dialysate sodium concentration and the pre-dialysis systolic blood pressure.

Achieving the blood pressure targets was not influenced by the choice of antihypertensive medication, although marginally more patients achieved the target blood pressures when

prescribed ACEIs/ARBs, but this was not statistically significant compared to other antihypertensives.

Blood pressure control was no different between those patients selected for the renal transplant waiting list and for those deemed medically unsuitable for transplantation. Similarly, although a greater percentage of patients from the ethnic minorities were prescribed antihypertensive medications, blood pressure control was similar between Caucasians and other ethnic groups. Thus, there were no biases in how patients were treated.

Incidence of clinically significant intradialytic hypotension requiring intravenous fluid resuscitation

The second purpose of the audit was to determine whether the setting of more rigorous pre- and post-dialysis blood pressure targets led to increased intradialytic hypotension.[14] More recently, it has been shown that mortality is increased in those hemodialysis patients prone to intradialytic hypotension.[15] Cohort studies have reported an incidence varying from 6 to 27%, but the definition has often varied from study to study.[16] In this audit, we recorded hypotensive episodes requiring intravenous fluid resuscitation. Fifteen percent of patients suffered at least one interdialytic episode of hypotension and 43 patients (2%) experienced hypotension during all three dialysis sessions. By taking a strict definition of including only those hypotensive episodes requiring active intervention, the potential number of patients who suffered intradialytic hypotension would have been much greater, using the newly published European Best Practice Guidelines, which conform with the proposed K/DOQI definition of a fall in systolic blood pressure of $\geqslant$20 mm Hg, or lesser in mean arterial pressure of 10 mm Hg, associated with clinical events and need for nursing intervention.[16] Not only may intradialytic hypotension lead to a reduction and compromise in coronary artery and cerebral perfusion pressure, but also hypotension requiring intervention, by stopping ultrafiltration, is likely to result in failure to achieve the desired target or dry weight, thus leading to hypervolemia in the subsequent interdialytic period.

The incidence of clinically symptomatic intradialytic hypotension varied from center to center from 7 to 28% of patients. This was not associated with the size of the dialysis program, but was more common in those centers that had greater achievement of the post-dialysis blood pressure target. The question arises as to whether the increased incidence of hypotension was driven by trying to achieve the post-dialysis blood pressure goal. It is therefore important that clinical recommendations and/or targets are based on sound evidence and that if substantive proof is lacking, then potential adverse events are fully recognized.

As expected from previous studies, the incidence of hypotension was associated with greater absolute and percentage interdialytic weight gains.[16,17] In those patients prescribed antihypertensive agents, whether patients took their medications before dialysis or not had no impact on the frequency of intradialytic hypotension, and similarly for those prescribed a single antihypertensive agent, there were no differences between ACEIs/ARBs, β-blockers, calcium channel blockers, and α-blockers. Patients who suffered intradialytic hypotension had lower pre-dialysis blood pressure, with a lower pulse pressure, and were more likely not to be prescribed antihypertensive agents. This is in keeping with previous reports of increased morbidity and mortality in hemodialysis patients with a low blood pressure.[7,11]

Summary

In this audit of hemodialysis patients, the number of patients achieving the more rigorous UK Renal Association guideline pre- and post-dialysis blood pressure targets was 36 and 42%, respectively, with only 26% achieving both targets, suggesting that blood pressure control needs to be improved. There was a wide variation between dialysis centers, suggesting that clinical practice plays an important role in determining blood pressure control in dialysis patients. Interestingly, the variation between the dialysis centers in terms of prescription of antihypertensive medication did not have any measurable effect on achieving blood pressure targets. One potential side effect of rigorous blood pressure targets is an increase in symptomatic intradialytic hypotension requiring intravenous fluid resuscitation. In this audit, 7% of all treatments were complicated by symptomatic hypotension. This was more common in patients with large interdialytic weight gains and more likely in those with lower pre-dialysis blood pressures and pulse pressures. Intradialytic hypotension was not made worse by the prescription of antihypertensive agents and similarly was not affected whether patients took or abstained from their medication before dialysis.

This audit raises the question as to whether the introduction of strict pre- and post-dialysis blood pressure targets for hemodialysis patients is beneficial, as evidence is currently lacking as to the survival benefit of such strict targets and any potential benefit may be obviated if attempts to achieve the target result in increased symptomatic intradialytic hypotension.

MATERIALS AND METHODS

The project was initiated by the London Renal Modernization Audit Group and implemented by the Audit, Information and Analysis Unit. Participation approval was obtained from each center's Trust and data protection policies were followed. Data were prospectively collected during a 7-day period in September 2004 from adult hemodialysis patients who had been dialysing thrice weekly for $>$90 days, in 13 main hospitals and 30 satellite dialysis units, located in the Greater London area. Patients dialysing for 90 days or less were excluded on the basis that they may still not have achieved their appropriate target weight, and similarly patients dialysing twice weekly or less were also excluded, as these patients may potentially have had significant residual renal function.

Patient demographics

Data were collected on 2628 chronic dialysis patients, 1180 main hospitals, and 1448 satellite dialysis patients. The majority of

patients were male (60.5%) and Caucasian (49%), with 24% classified as from the Asian subcontinent and 23% black. The median age for the group was 61.2 years (interquartile range 46.9–72.3 years) but varied from 56.2 years (44.7–67.9) to 67.4 years (56.3–78.3). Overall, 32% of all patients were diabetic and this ranged from 21 to 37% between the 11 main renal units. However, 44% of Asian patients were diabetic, compared to 35% of blacks and 25% of Caucasian and other patients.

The majority of patients dialysed with an arteriovenous fistula (60%) and 31% used tunneled central venous access catheters. All patients used bicarbonate dialysate and polysulfone membrane dialyzers; apart from two centers that used modified cellulose acetate, the modal dialysis time was 4 h. Dialysate sodium concentrations varied within centers, and most centers dialysed patients prone to hypotension with cooled dialysate.

Blood pressure was routinely measured electronically in all units, although in 2% of cases a mercury sphygmomanometer was used. Blood pressure and weight were recorded pre- and post-dialysis in each of the three dialysis sessions. Intradialytic hypotension was defined as a sudden decrease in blood pressure that required intravenous fluid replacement to restore the blood pressure.

Statistical analysis was by Student's *t*-test, Mann–Whitney *U*-test, χ^2-test, and either Pearson's or Spearman's correlation analysis. Data are expressed as mean ± s.d. or median and interquartile range. Statistical significance was taken at or below the 5% level.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank all the local co-ordinators in the 11 main and 30 satellite dialysis centers, who collected and submitted the patient data. Pan Thames Renal Audit Group; Andrew Frankel—Charring Cross Hospital, Anthony Warrens—Hammersmith Hospital, Adam McLean—St Mary's Hospital, Michael Almond—Southend Hospital, Paul Donohoe—King's College Hospital, Cormac Breen—Guy's and St Thomas's Hospital, Jonathon Kwan—St Helier Hospital, Steven Nelson—St George's Hospital, Guy Neild—The Middlesex Hospital and Aroon Lal—Basildon Hospital.

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