Chapter 10: Factors Which May Influence Cardiovascular Disease in Dialysis and Transplant Patients – Blood Pressure

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Summary

- Many renal units still fail to return blood pressure data to the Renal Registry. In England, Northern Ireland and Wales, the percentage of HD patients achieving the combined blood pressure standard (<140/90 pre-dialysis) average 43% (inter unit range 16–60%) and post-dialysis (<130/80) average 48% (range 22–66%). On average 27% (range 12–48%) of PD patients achieve the standard of <130/80 and 26% of renal transplant patients (range 16–40%).

- Over the last 8 years there has been no significant change in systolic or diastolic blood pressure achievement.

- Better co-morbidity data returns are required by the Registry to perform blood pressure survival analyses.

Introduction

International and UK blood pressure guidelines[1,2,3,4] recommend a target blood pressure below 130/80 mmHg for patients with chronic kidney disease (CKD), diabetes and established atherosclerosis. The intention is to reduce cardiovascular complications and progression to renal failure. So far, clinical trials involving CKD patients have all been designed to assess low blood pressure on renal progression as the primary endpoint. Cardiovascular data from these trials are inconclusive and were reviewed in some detail in last year's report. Blood pressure guidelines take no account of epidemiological data that describe a U-shaped relationship between baseline systolic blood pressure and 1 year mortality. Several reports show higher cardiovascular mortality for haemodialysis patients with baseline pre and post systolic blood pressure <110 mmHg[5,6]. The UK Renal Registry has also shown increased all-cause mortality at 1 year for incident haemodialysis patients with baseline pre and post systolic blood pressure <120 mmHg[7]. This raises concern that achieving lower blood pressure targets may be detrimental for some dialysis patients. In 2006, two studies of USA haemodialysis patients analysed the changing relationship of blood pressure with mortality over several years. In the first, hazard ratios for three year all-cause mortality for 56,338 incident patients were 2.5 for a baseline systolic blood pressure <120 mmHg and 1.4 for baseline systolic blood pressure 120–139 mmHg[8]. Hazard ratios were 5.5 and 1.9 respectively when blood pressure variability was included in the analysis. In the second study[9] the hazard ratio for two year all-cause mortality for 16,959 incident patients was 1.7 for baseline systolic blood pressure 110–119 mmHg. Interestingly, the hazard ratio fell to 0.8 and 0.7 for the third and fourth year respectively. This is the first data to suggest achieving low blood pressure guidelines may be beneficial for dialysis patients. In the same study a baseline systolic blood pressure >170 mmHg was only associated with increased all-cause mortality after three years. Intuitively one would expect early deaths to affect patients with established heart failure as hypertension precedes cardiac failure by many years but neither study included co-morbidity data to delineate causal associations. Finally, data from the Irbesartan Diabetic Nephropathy Trial[10] showed improved renal function and patient survival down to a systolic blood pressure of 120 mmHg. Below this, all-cause mortality increased (relative risk 1.25) for both patients with and without pre-existing cardiovascular disease. It will be difficult to prove whether low blood pressure may be beneficial as poor health is a common confounding factor in renal patients.

Last year less than one third of patients on RRT in England and Wales achieved the blood pressure standard. However, the renal unit at

York consistently achieves the best blood pressure results across all treatment modalities suggesting a rational approach to monitoring and therapy. Their patients are sent to a dietician for salt restriction initially. Then patients achieve dry weight by ultrafiltration or diuretics. Finally, antihypertensive medication is increased. Several publications in the last year support this strategy. An audit of 469 prevalent haemodialysis patients dialysing in seven different centres in the UK compared blood pressure control with varying dialysate sodium concentration[11]. All patients were advised to restrict salt intake to 5 g/day. Patients dialysing with sodium concentration 137–139 mmol/L had significantly lower pre and post systolic blood pressure compared to those dialysed against 140 mmol/L. They also had lower interdialytic weight gains and were prescribed fewer antihypertensive drugs. Intradialytic hypotension correlated with age rather than dialysate sodium concentration. Similarly, a prospective study of 46 prevalent peritoneal dialysis patients in Turkey showed reduced salt intake and use of hypertonic solutions could maintain blood pressure below 130/85 mmHg over a two year period without antihypertensive medication[12]. Left ventricular hypertrophy was detected in only 8% of patients after two years. No patient lost residual renal function, ultrafiltration rate or dialysis adequacy during the study. The published evidence suggests salt and water balance is important to achieve blood pressure standards in dialysis patients.

Blood Pressure Control

The RA standards for control of hypertension were established in August 2002:

Pre-haemodialysis blood pressure <140/90 mmHg.

Post-haemodialysis, peritoneal dialysis and renal transplant blood pressure <130/80 mmHg.

Methods

The Registry extracts quarterly blood pressure data electronically from UK renal units. Data from Northern Ireland is included for the first time this year. A single blood pressure reading is extracted for each patient, the last BP recorded in quarter four. If this is not available, the last BP from quarter three is taken. Patients with no blood pressure data for the last two quarters of 2005 are excluded. All patients with data are included in the statistical analysis. Renal units with sparse data for a given treatment modality (data for less than 50% of patients or less than 20 patients) are omitted from renal unit level results/figures. This approach is taken because small numbers do not skew the data but do give unreliable estimates at the renal unit level.

Each year a number of analyses are performed for the prevalent cohort on RRT (see Appendix at the end of the Chapter for definition of prevalent cohort). This report presents data for 2005.

- Completeness of data is analysed at renal unit and national level for patients on haemodialysis, peritoneal dialysis and renal transplant recipients.

- Distributions of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and pulse pressure (PP) are defined for different treatment modalities. Maximum and minimum values are recorded and average values (mean and median), standard deviations and quartile ranges calculated. The data are presented as caterpillar plots showing median values and quartile ranges for renal units and nations. Data were also analysed by primary diagnosis. The number preceding each centre name indicates the percentage of patients with missing data at that centre.

- These data are analysed to calculate summary statistics (maximum, minimum, mean and median values in addition to standard deviation and quartile ranges). These data are represented as caterpillar plots showing median values and quartile ranges. Where applicable, the percentage achieving Renal Association or other surrogate standard is also calculated and represented as caterpillar plots with 95% confidence intervals. For the percentage achieving standards, chi-squared testing is used to identify significant variability between centres and countries. Data are also analysed by primary diagnosis.

Results

Data Returns

Poor returns (less than 50%) were obtained from 20 centres for HD data, 31 centres for PD data and 35 centres for Tx data (Table 10.1). For most renal units, the problem is in transferring the clinical data to their renal IT systems. For a few units, the data may not be extracted from the correct database table within their renal IT system, in which case they should contact the Registry directly.

Overall the completeness of returns is improving but still remains poor for transplant patients. Northern Ireland is omitted from the figures for PD as data is available for only twelve patients.

Distribution of blood pressure by modality

Figures 10.1 and 10.2 show histograms of systolic and diastolic blood pressure, for pre-HD data. Blood pressure distributions for post-HD, PD and Tx are also approximately normal. Peaks above the curve indicate digit bias. Figure 10.3 shows systolic, diastolic and pulse pressure distributions for each modality (post-HD data is shown).

The median blood pressure pre-HD, post-HD, PD and Tx is 143/75, 128/69, 136/80 and 136/79 mmHg. Median pulse pressure for each group is 66, 59, 57 and 57 mmHg respectively. The HD population has the widest spread for blood pressure. Standard deviations (SBP/DBP) pre-HD, post-HD, PD and Tx are 26/15, 25/14, 23/13 and

Table 10.1: Percentage of patients with complete returns of blood pressure values by modality

	% completed data					% completed data			
	Pre HD	Post HD	PD	Tx		Pre HD	Post HD	PD	Tx
Antrim	7	3	0	0	Middlesbrough	97	96	100	52
Bangor	88	88	100	0	Newcastle	0	0	0	1
Barts	0	0	0	0	Newry	0	0	0	4
Basildon	99	99	87	4	Norwich	99	98	4	0
Belfast	86	85	18	22	Nottingham	99	99	100	88
Bradford	2	2	100	94	Oxford	87	84	82	10
Brighton	6	6	0	0	Plymouth	0	0	0	0
Bristol	100	99	98	69	Portsmouth	0	99	0	0
Cambridge	66	65	1	0	Preston	0	0	0	0
Cardiff	5	0	4	94	QEH	37	0	0	0
Carlisle	93	93	0	0	Reading	96	49	99	96
Carshalton	78	77	1	0	Royal Free	0	0	0	0
Chelmsford	98	98	91	22	Sheffield	100	97	99	97
Clwyd	4	2	75	86	Shrewsbury	100	99	18	5
Coventry	99	97	90	72	Southend	96	95	0	0
Derby	98	98	95	0	Stevenage	99	98	16	1
Dorset	99	99	68	11	Sunderland	96	96	0	0
Dudley	77	77	62	81	Swansea	79	79	18	9
Exeter	99	99	91	23	Truro	77	76	68	91
Gloucester	96	0	0	0	Tyrone	95	94	0	0
Guys	73	73	6	1	Ulster	100	97	100	50
H&CX	0	0	0	0	Wirral	3	0	4	n/a
Heartlands	94	94	0	1	Wolverhampton	3	99	98	85
Hull	92	92	57	1	Wrexham	0	0	0	n/a
Ipswich	99	98	92	94	York	100	99	100	95
Kings	0	0	0	0	England	58	58	43	30
Leeds	98	98	96	68	Northern Ireland	64	62	12	15
Leicester	95	92	96	81	Wales	32	30	18	81
Liverpool	19	2	29	71	England, Northern Ireland and Wales	57	56	40	32
ManWst	0	0	0	0					

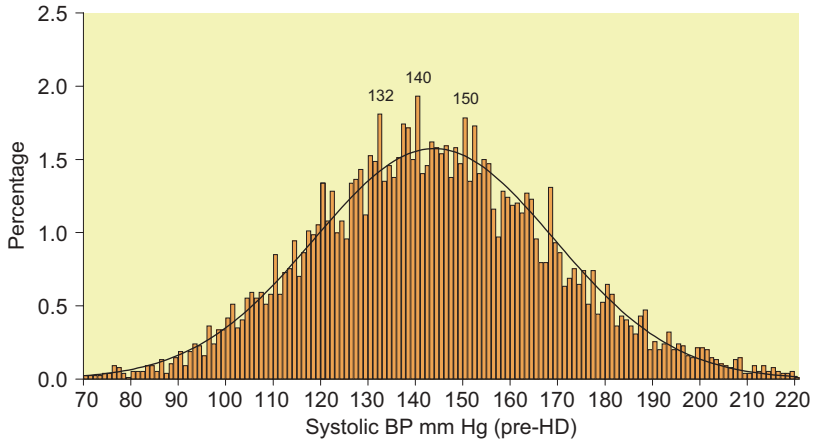

Figure 10.1: Systolic BP distribution pre-HD

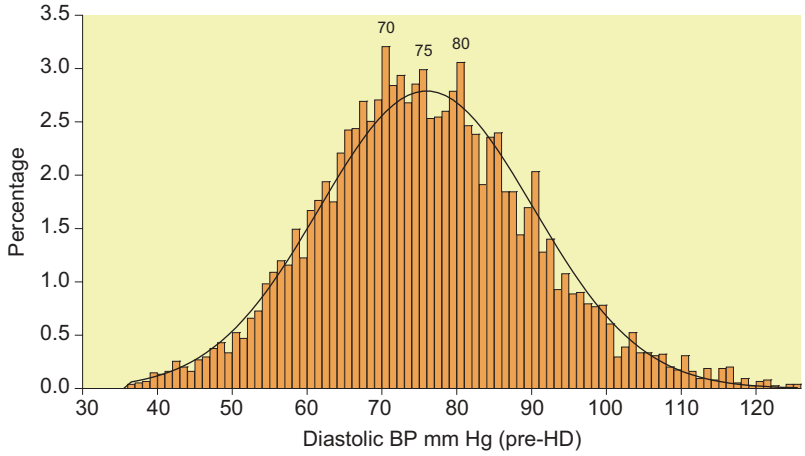

Figure 10.2: Diastolic BP distribution pre-HD

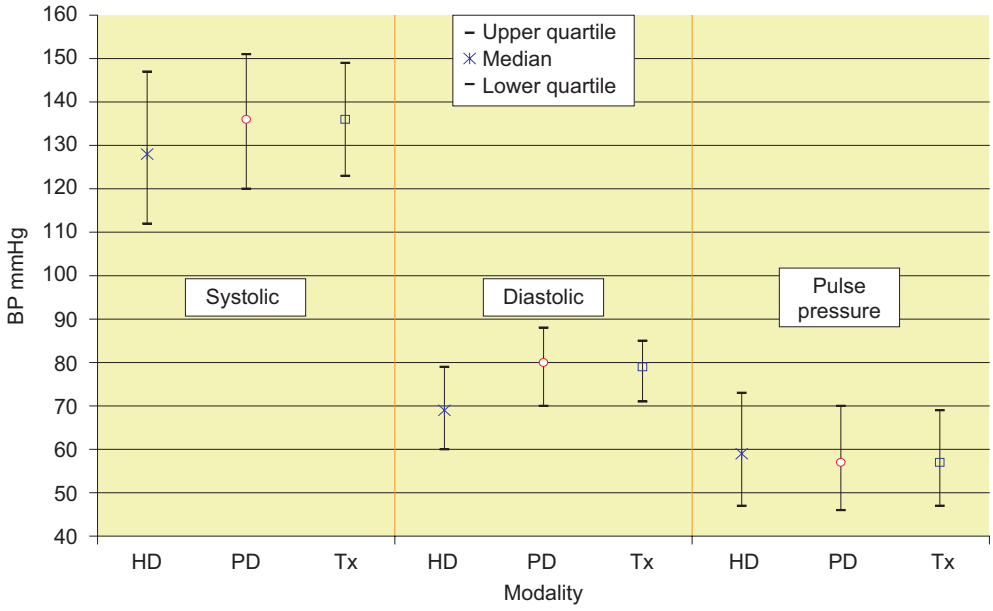

Figure 10.3: Summary of BP achievements

19/11 respectively. This compares to 18/10 for a hypertensive population. Last year in a single centre study of 317 prevalent HD patients, the Registry showed blood pressure was significantly higher at the start of the dialysis week. The wider blood pressure distribution for HD may partially therefore reflect the random timing of readings and influence of fluid overload.

Achievement of combined systolic and diastolic Standard

Figures 10.4–10.7 show a wide variation between renal units achieving the combined blood pressure standard for each modality. In England, Northern Ireland and Wales, the percentage of HD patients achieving the standard pre-dialysis averages 43% (range over renal units 16–60%) and post-dialysis averages 48% (range 22–66%). Only 27% of PD patients achieve the standard (range 12–48%) and 26% of Tx patients (range 16–40%). Chi squared testing indicates the variation between centres for HD and Tx is significant ($p < 0.001$) but not for PD. The variation between nations is also significant for HD and Tx ($p \leqslant 0.008$) but not for PD. The results are similar to last year and show control of hypertension remains inadequate across all treatment modalities but is significantly better in the HD population.

Systolic pressure alone

Figures 10.8–10.15 show wide variation between renal units achieving the systolic blood pressure (SBP) standard. In England, Northern Ireland and Wales, the percentage of HD patients achieving the standard pre-dialysis averages 45% (range 19–62%) and post-dialysis averages 51% (range 30–69%). On average 37% of PD patients achieve the standard (range 12–59%) and 35% of Tx patients (range 24–55%). Chi squared testing indicates that the variation

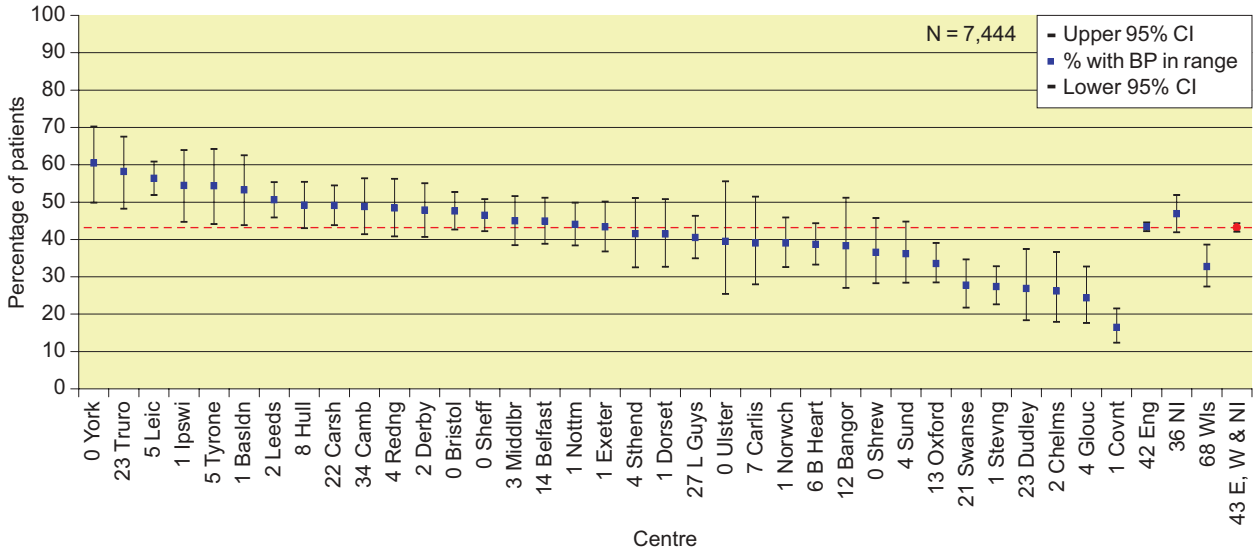

Figure 10.4: Percentage of patients with BP <140/90 mmHg: pre-HD

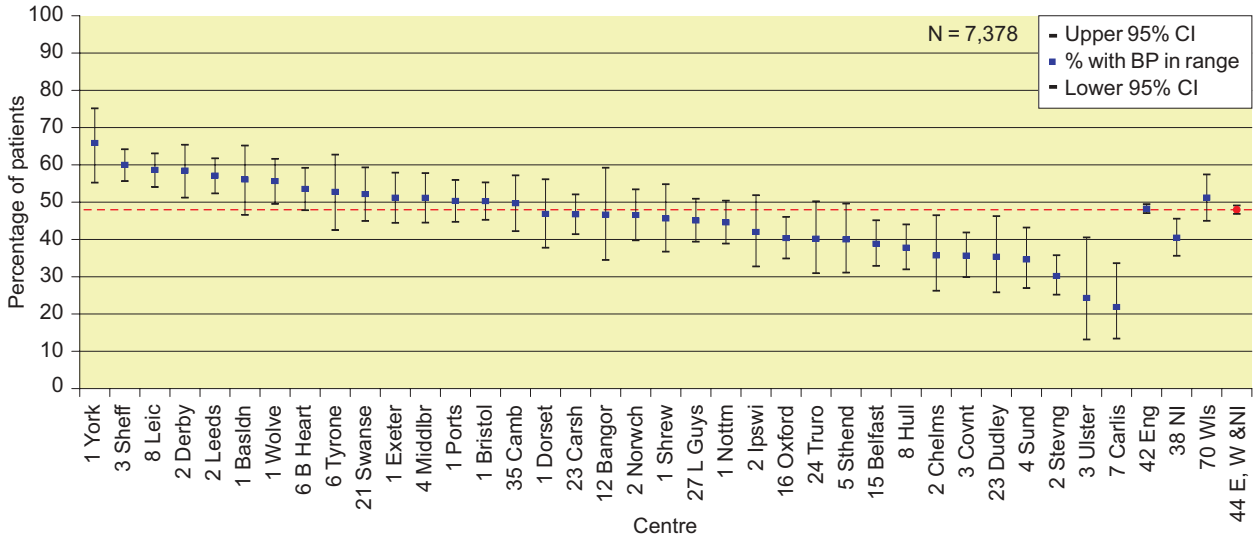

Figure 10.5: Percentage of patients with BP <130/80 mmHg: post-HD

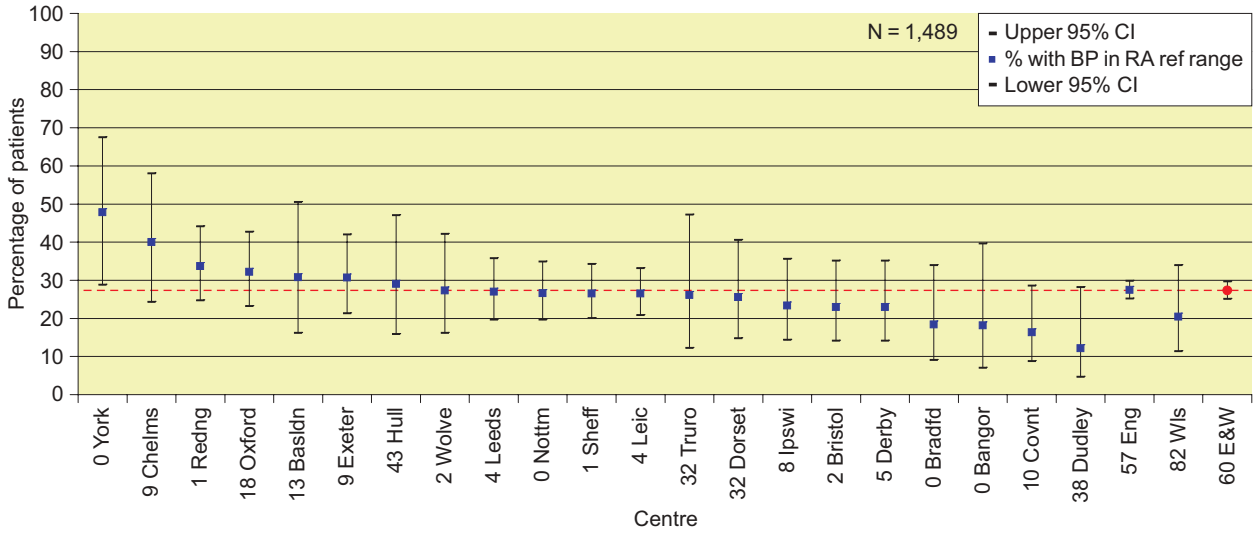

Figure 10.6: Percentage of patients with BP <130/80 mmHg: PD

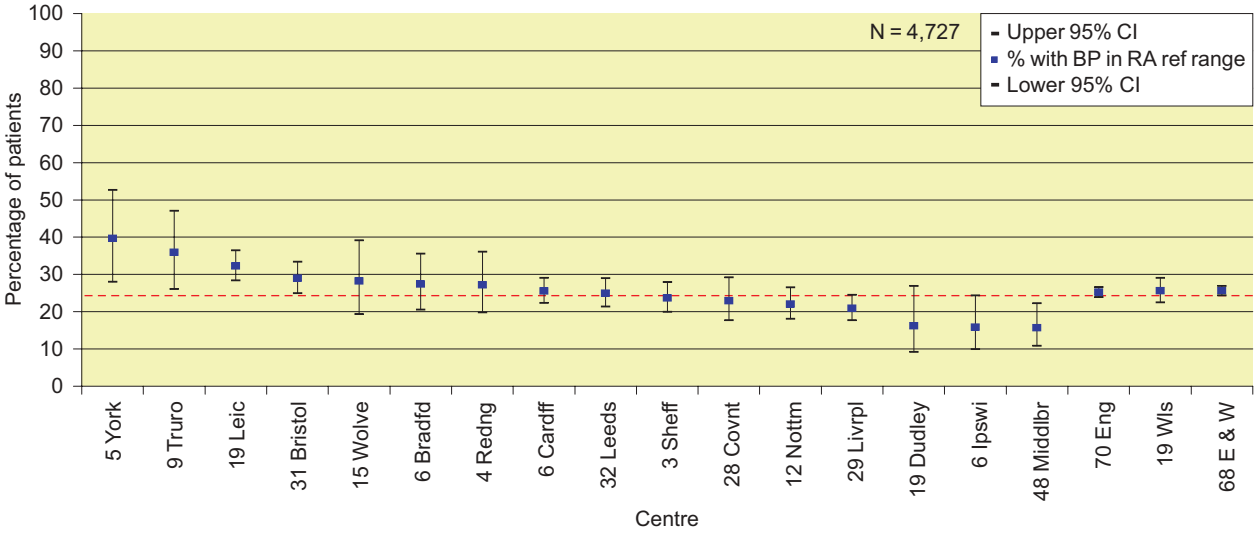

Figure 10.7: Percentage of patients with BP <130/80 mmHg: Tx

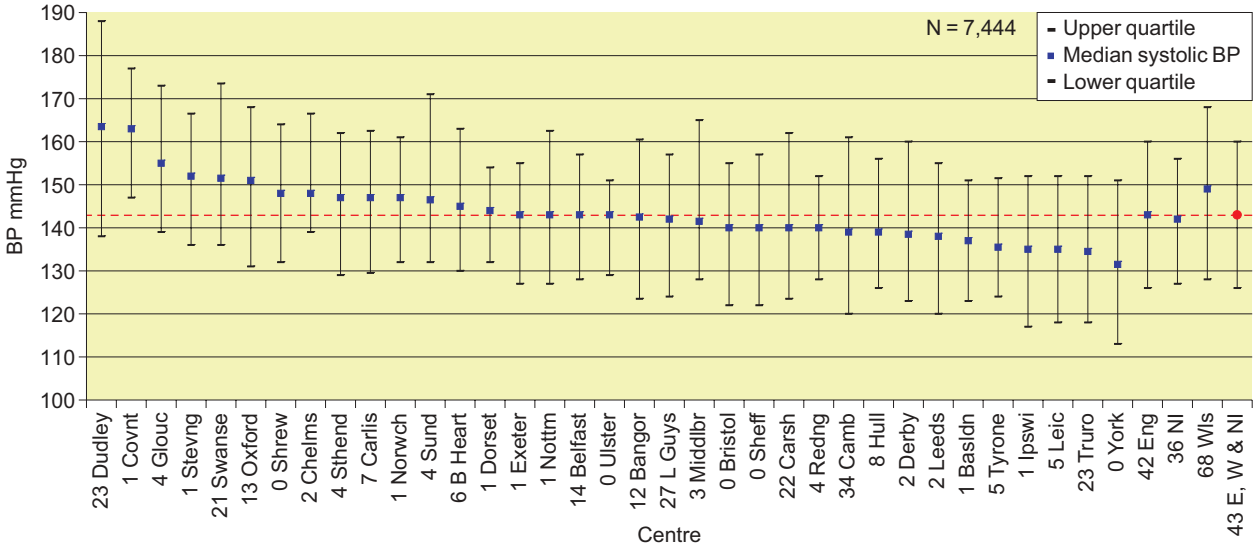

Figure 10.8: Median systolic BP: pre-HD

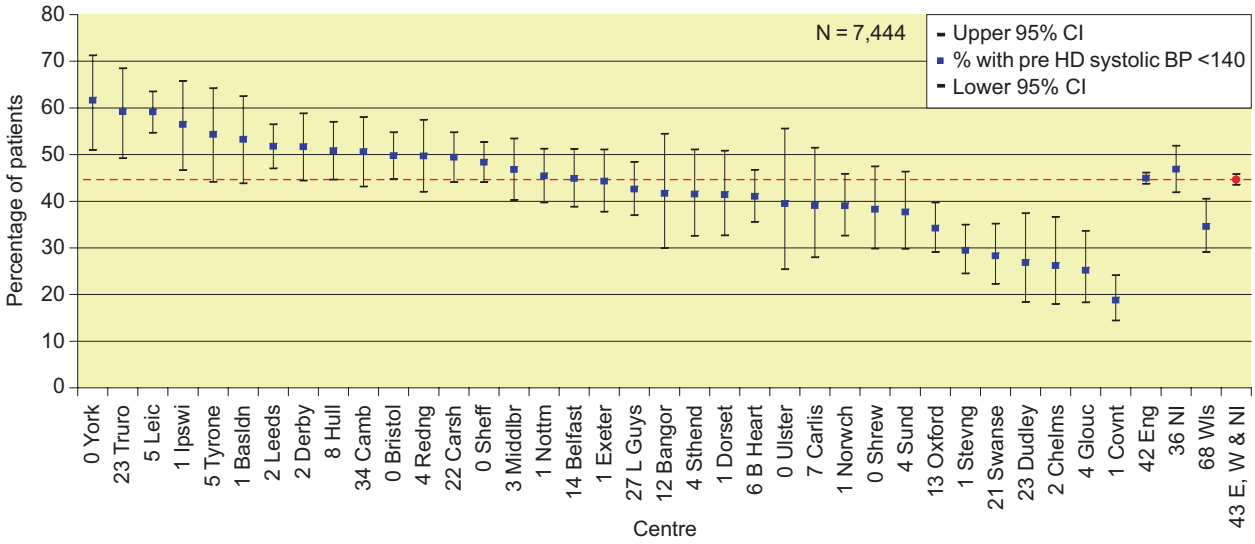

Figure 10.9: Percentage of patients with systolic BP <140 mmHg: pre-HD

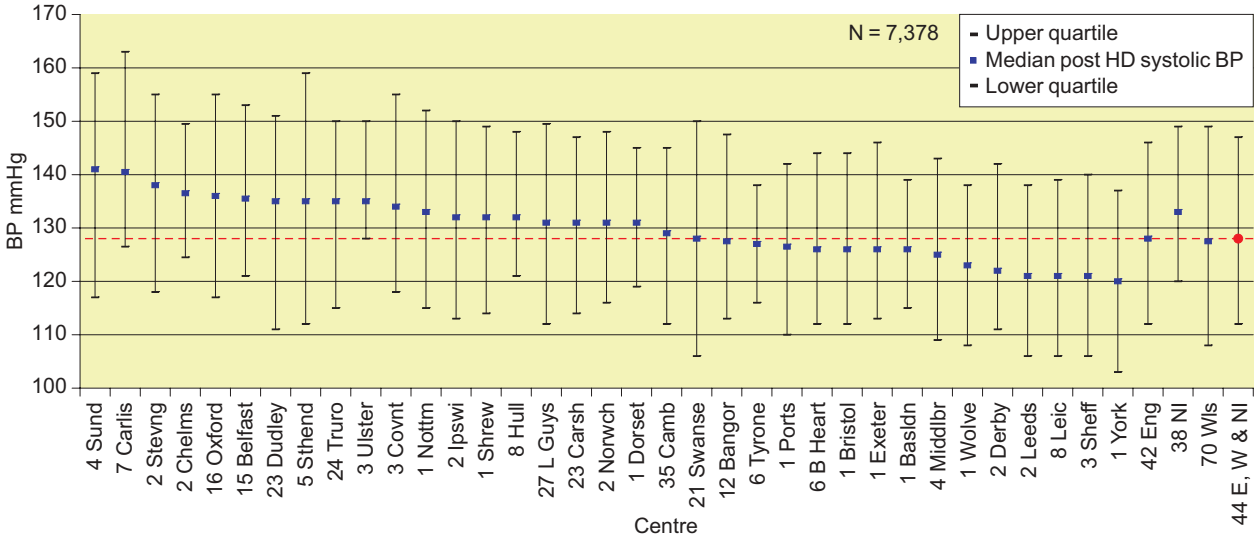

Figure 10.10: Median systolic BP <130 mmHg: post-HD

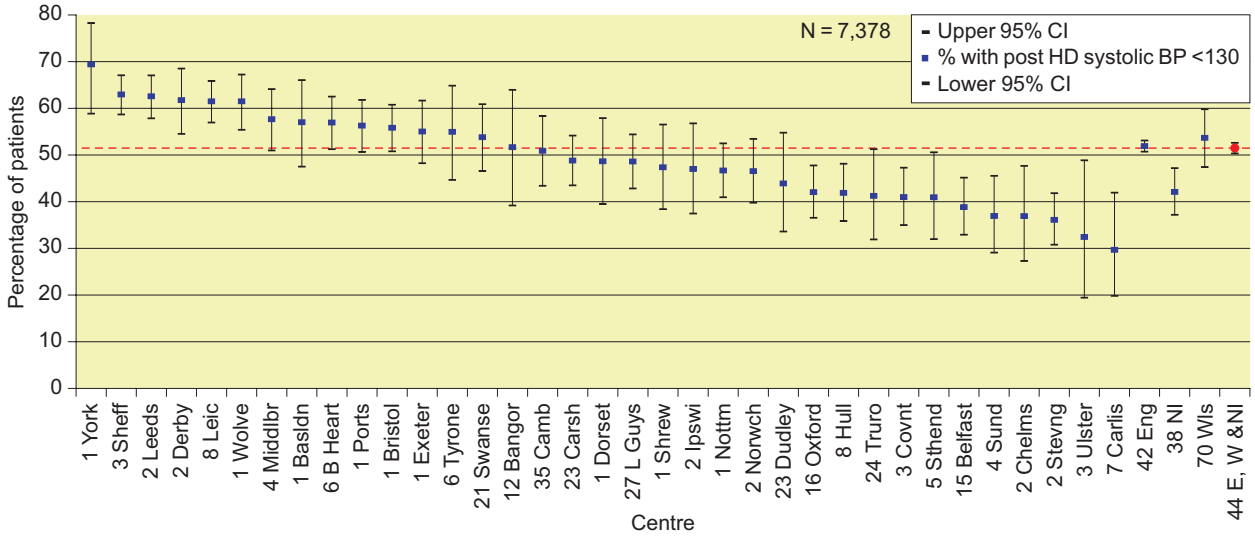

Figure 10.11: Percentage of patients with systolic BP <130 mmHg: post-HD

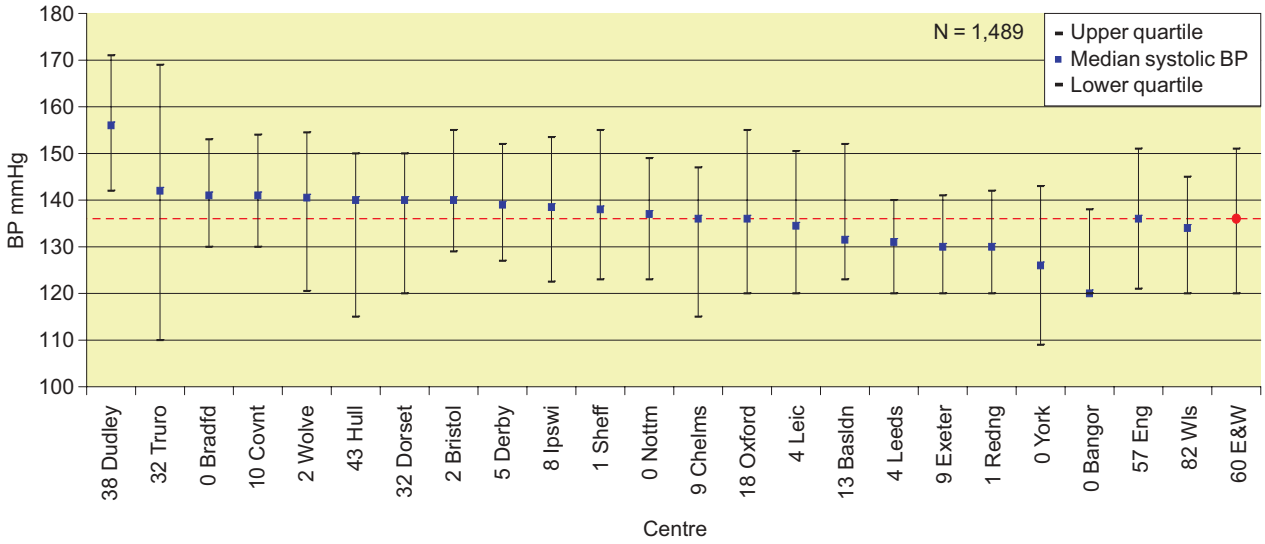

Figure 10.12: Median systolic BP: PD

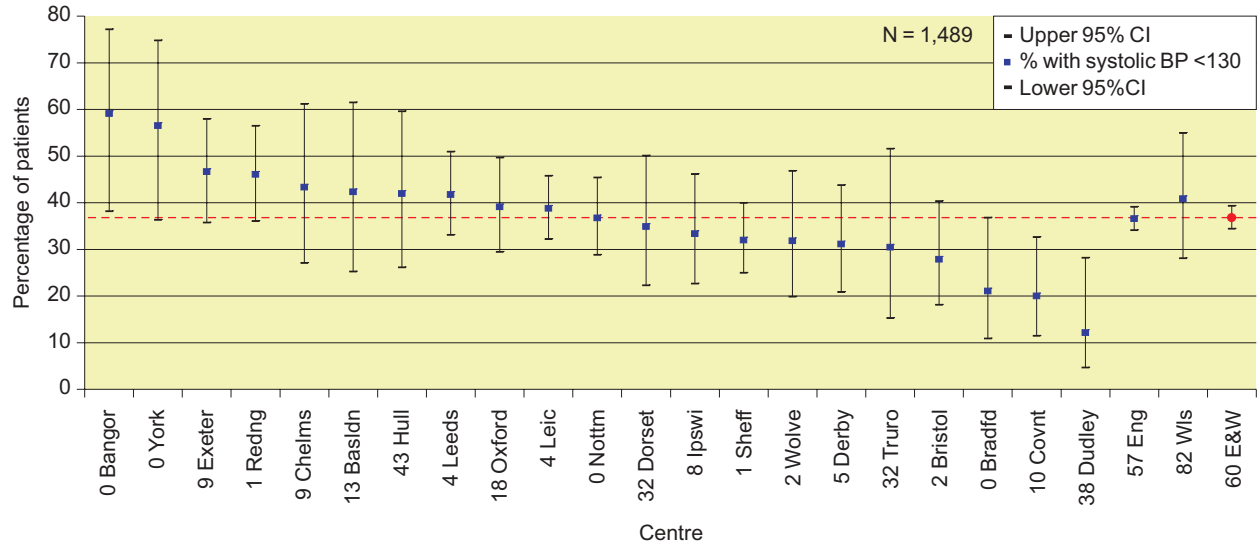

Figure 10.13: Percentage of patients with systolic BP <130 mmHg: PD

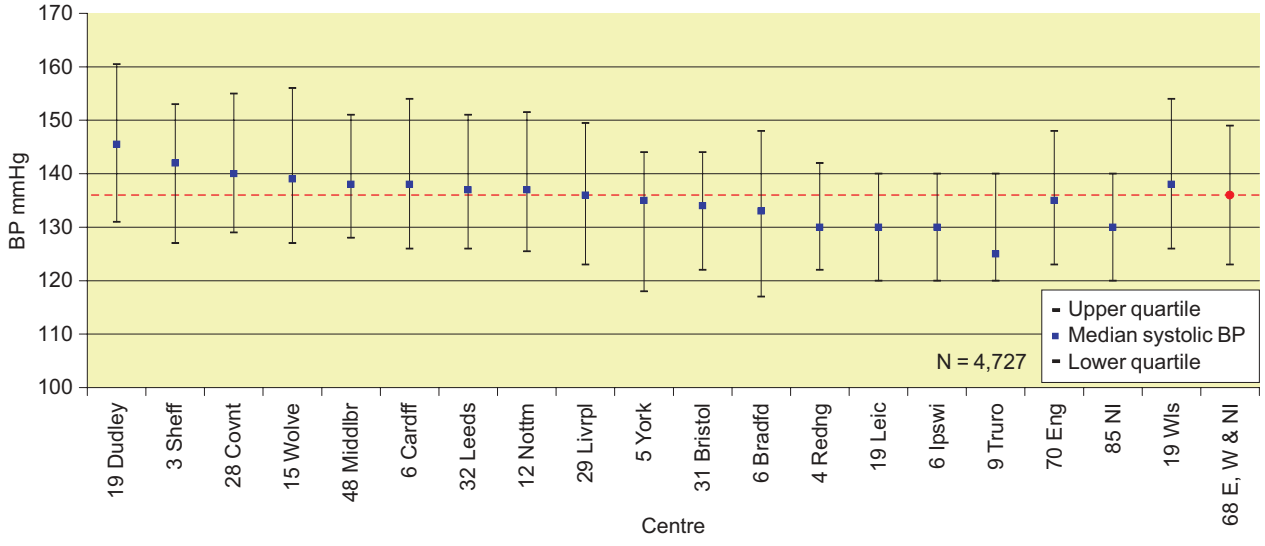

Figure 10.14: Median systolic BP: Transplant

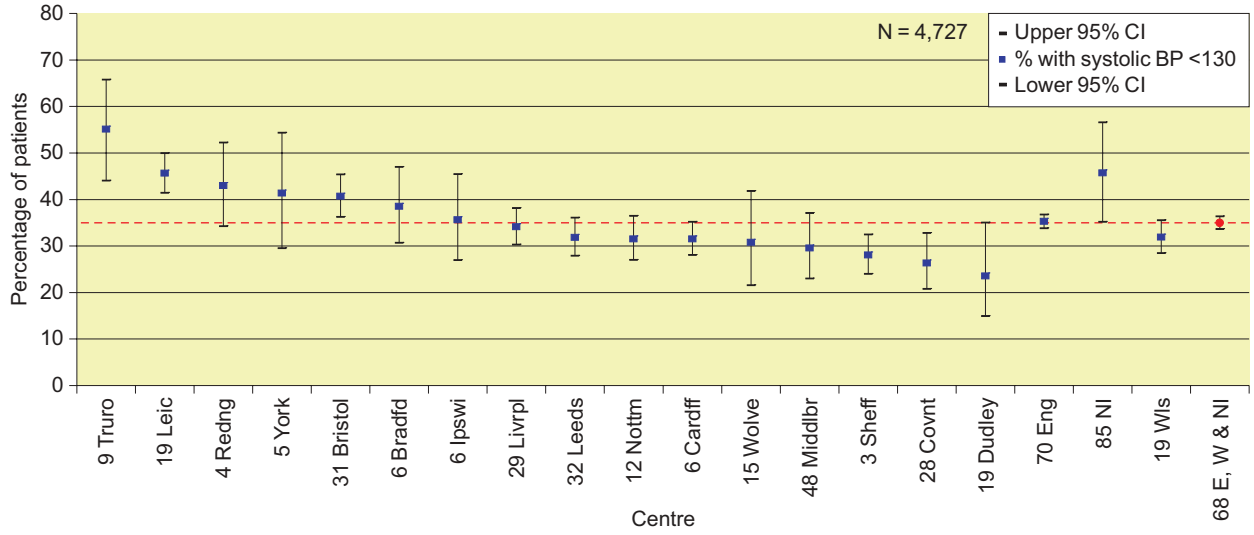

Figure 10.15: Percentage of patients with systolic BP <130 mmHg: Transplant

between centres is significant for each treatment modality ($p \leqslant 0.003$). The variation between nations is significant for HD ($p \leqslant 0.005$) and Tx ($p = 0.029$) but not for PD. Median SBP for pre-HD, post-HD, PD and Tx is 143, 128, 136 and 136 mmHg respectively.

Diastolic pressure alone

Figures 10.16–10.23 show wide variation between renal units achieving the diastolic blood pressure (DBP) standard. In England, Northern Ireland and Wales, the percentage of HD patients achieving the standard pre-dialysis averages 84% (range 69–96%) and post-dialysis averages 77% (range 59–90%). On average 47% of PD patients achieve the standard (range 27–61%) and 52% of Tx patients (range 30–74%). Chi squared testing indicates the variation between centres for HD and Tx is significant ($p < 0.001$) but not for PD. The variation between nations is significant for pre-HD and Tx ($p < 0.001$) but not for post-HD or PD.

The median DBP for pre-HD, post-HD, PD and Tx is 75, 69, 80 and 79 mmHg respectively. The median, and lower quartile for Tx DBP in Northern Ireland are both 70 mmHg. These values are the same because there are only 81 observations and there is evidence of digit bias. The data shows approximately half (50.6%) of the observations recorded as exactly 70 mmHg. It is not clear whether DBP is lowest post-HD

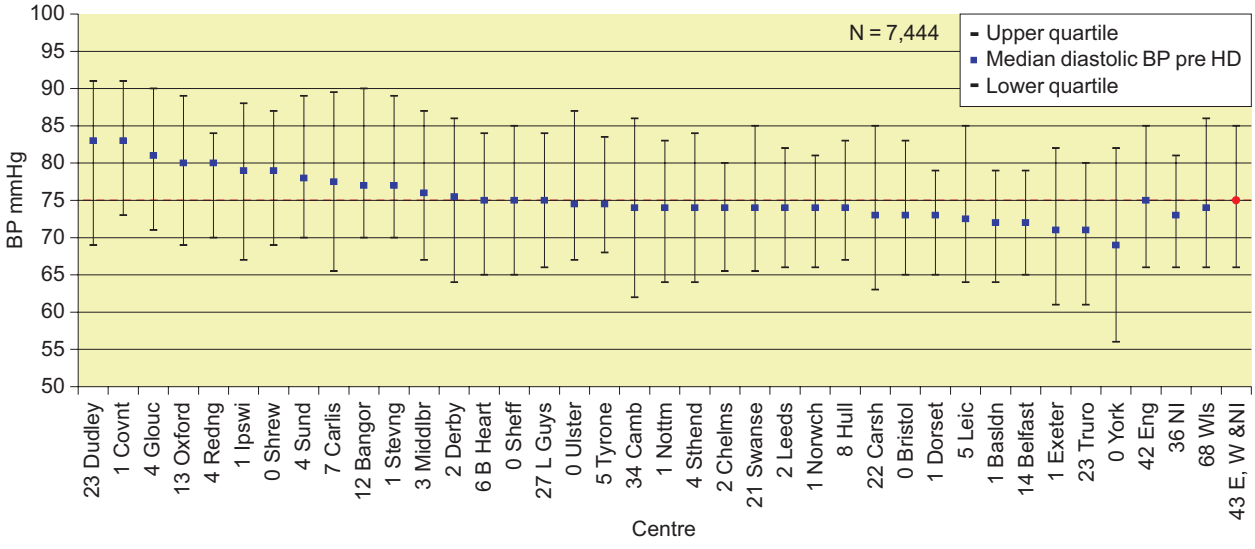

Figure 10.16: Median diastolic BP: pre-HD

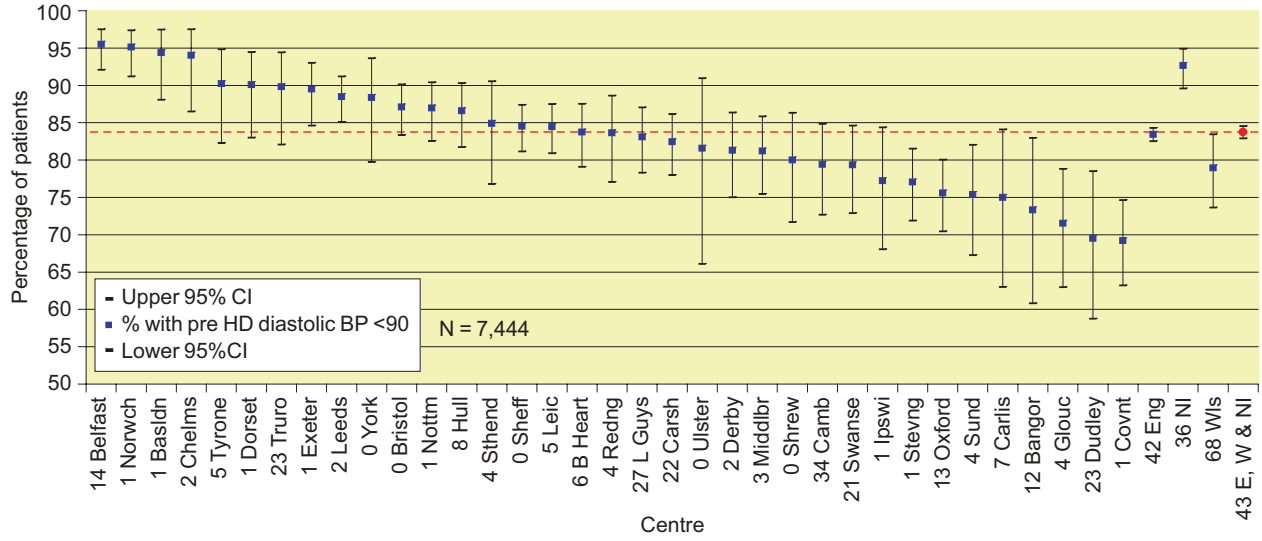

Figure 10.17: Percentage of patients with diastolic BP <90 mmHg: pre HD

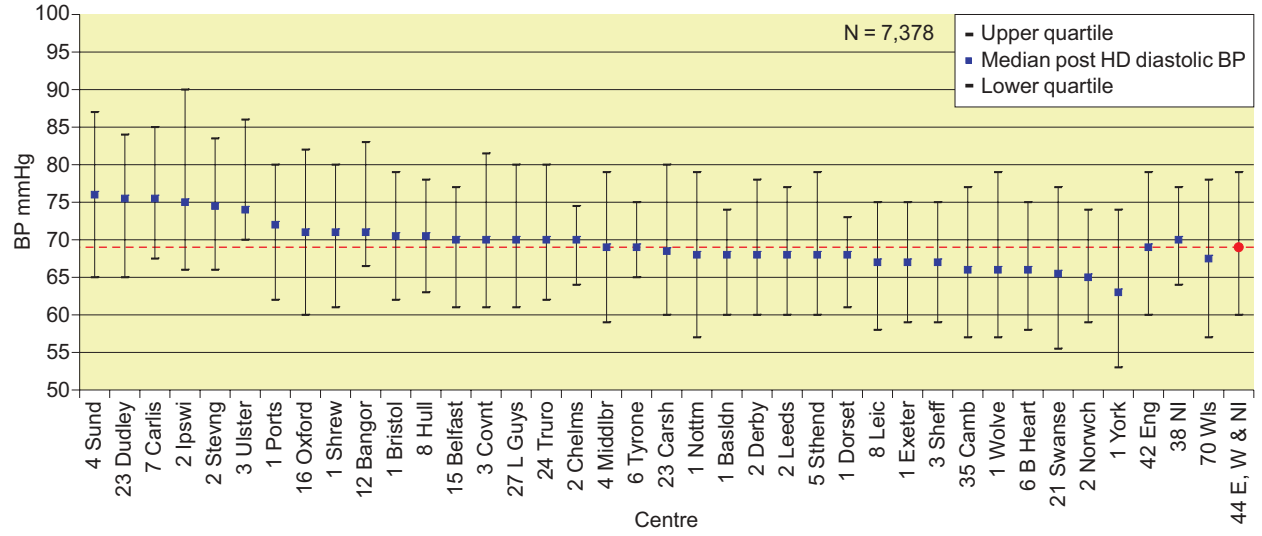

Figure 10.18: Median diastolic BP: post-HD

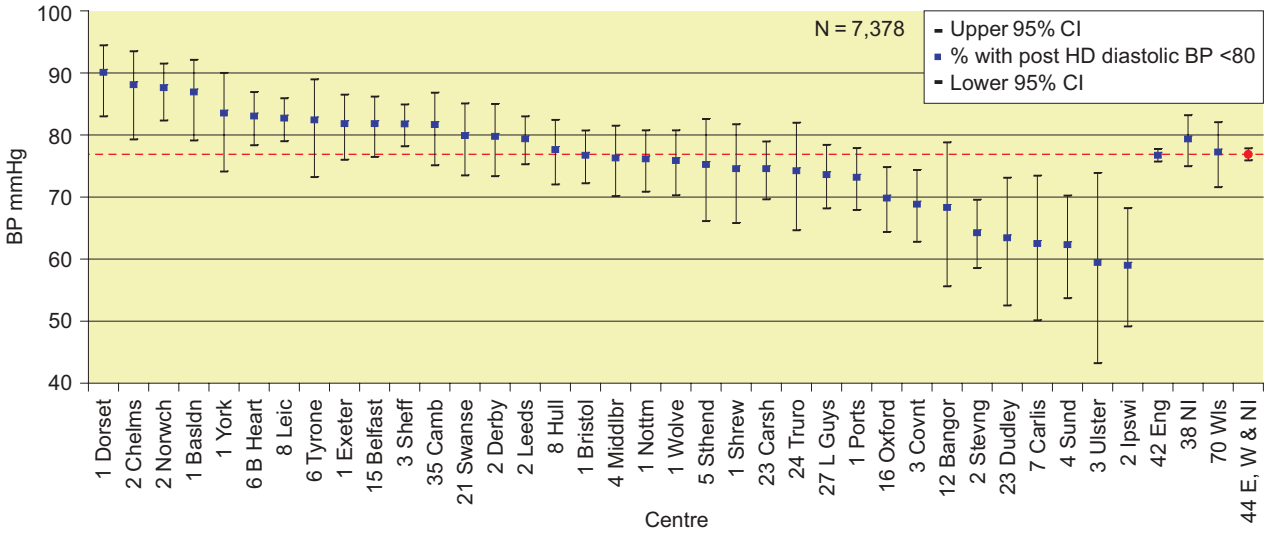

Figure 10.19: Percentage of patients with diastolic BP <80 mmHg: post-HD

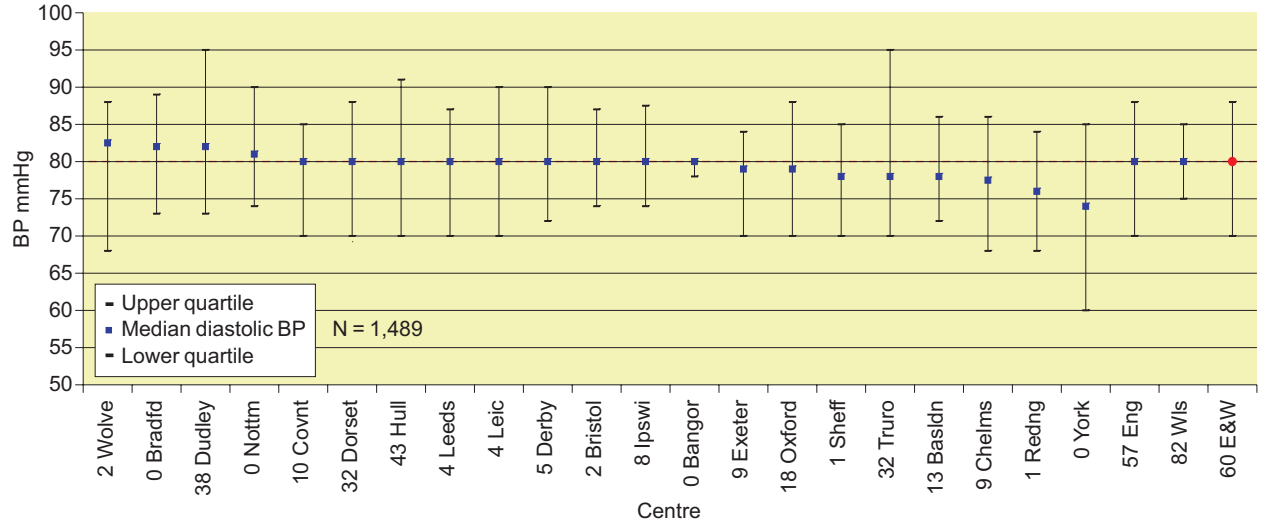

Figure 10.20: Median diastolic BP: PD

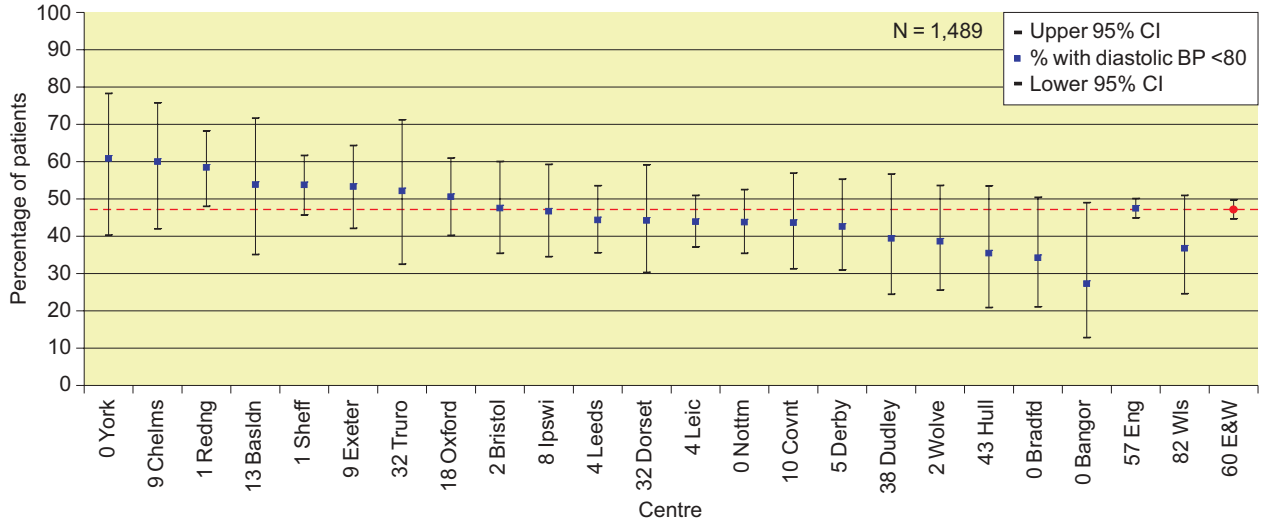

Figure 10.21: Percentage of patients with diastolic BP <80 mmHg: PD

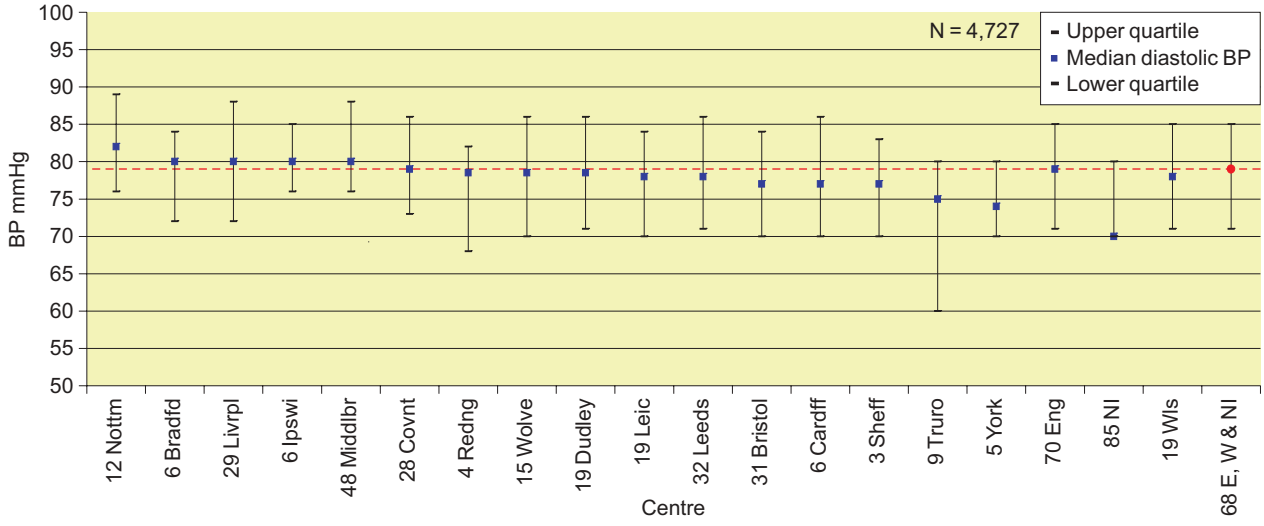

Figure 10.22: Median diastolic BP: Transplant

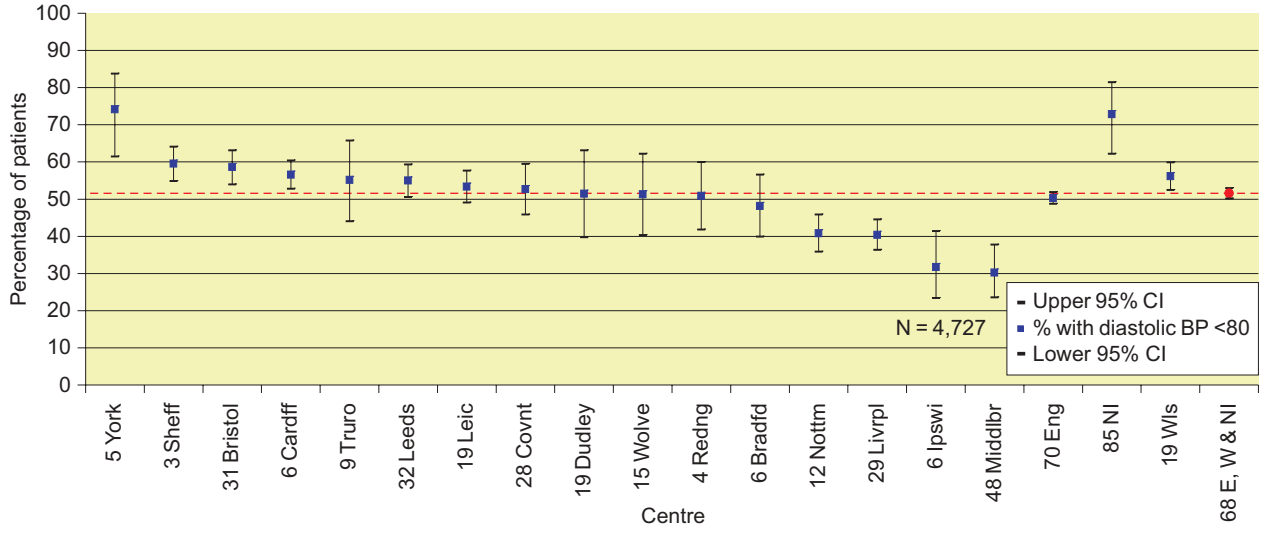

Figure 10.23: Percentage of patients with diastolic BP <80 mmHg: Transplant

because HD patients are older (DBP falls after 60 years of age in the general population due to increasing arterial stiffness) or because of the synergistic effect between ultrafiltration and antihypertensive medication.

Mean arterial pressure

Figures 10.24–10.31 show wide variation between renal units achieving the desired mean arterial pressure (MAP). MAP is calculated as DBP plus one third of the pulse pressure. In England, Northern Ireland and Wales, the percentage of HD patients achieving the standard pre-dialysis averages 72% (range 43–89%) and post-dialysis averages 69% (range 43–80%). On average 48% of PD patients achieve the standard (range 32–68%) and 48% of Tx patients (range 34–74%). Chi squared testing indicates that there is significant variation between centres for HD and Tx ($p < 0.001$). The variation is less marked for PD and is only of borderline significance ($p = 0.052$). The variation between nations is significant for pre-HD ($p = 0.001$) and Tx ($p < 0.001$) but not for post-HD or PD. The median MAP for pre-HD, post-HD, PD and Tx is 98, 89, 98 and 97 mmHg respectively.

Pulse pressure

Figures 10.32–10.35 show the variation between renal units for pulse pressure (PP). PP is calculated as SBP minus DBP. The median pulse pressure for pre-HD, post-HD, PD and Tx is 66, 59, 57 and 57 mmHg respectively. A high

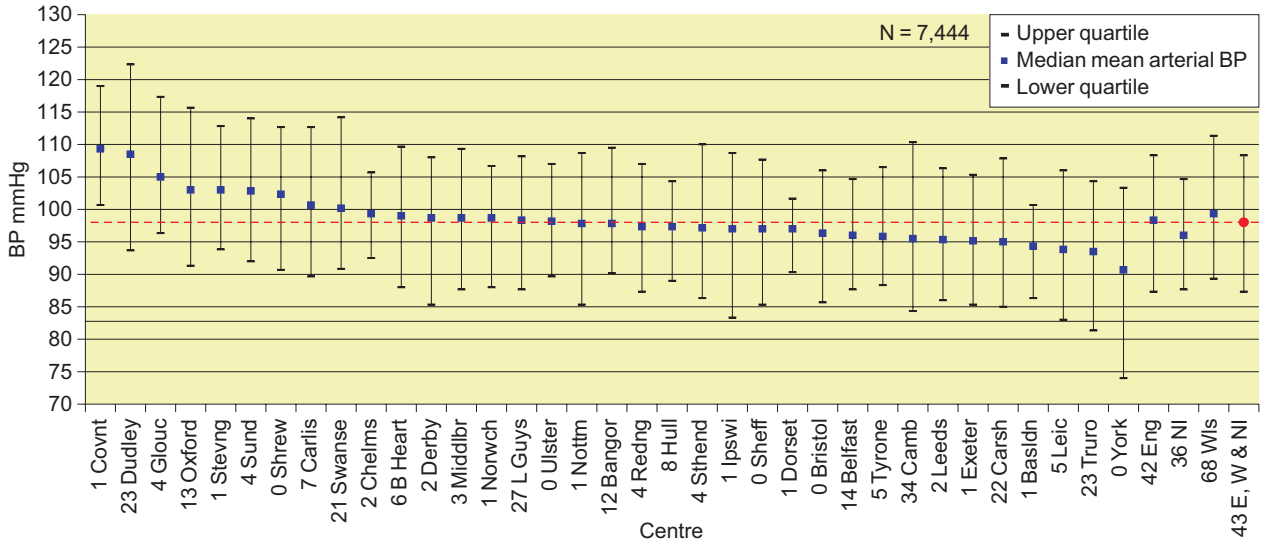

Figure 10.24: Median MAP: pre-HD

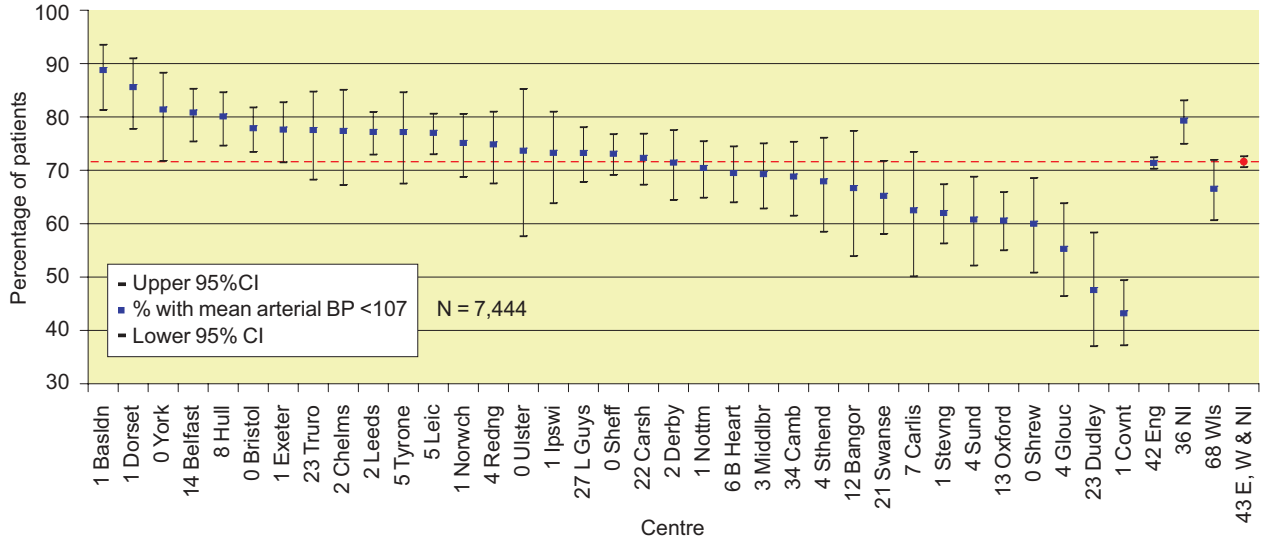

Figure 10.25: Percentage of patients with MAP <107 mmHg: pre-HD

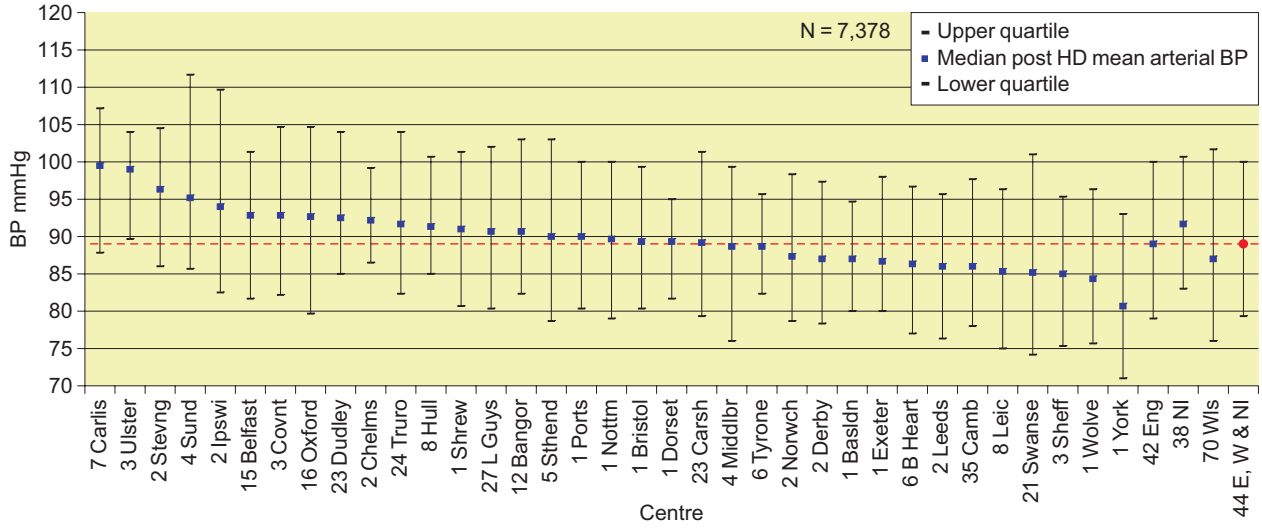

Figure 10.26: Median MAP: post-HD

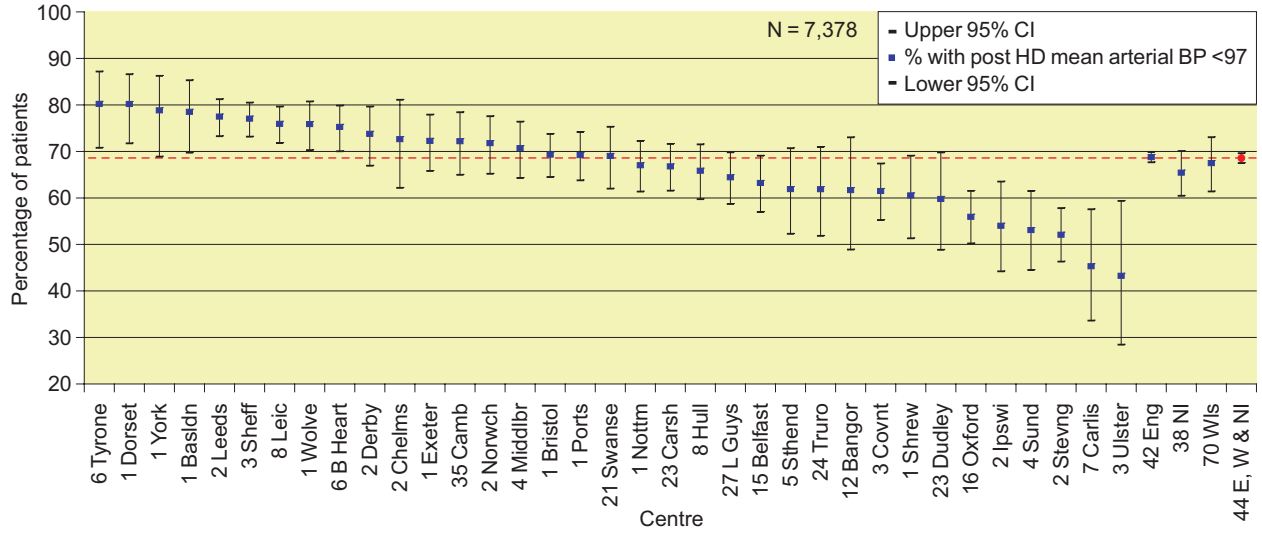

Figure 10.27: Percentage of patients with MAP <97 mmHg: post-HD

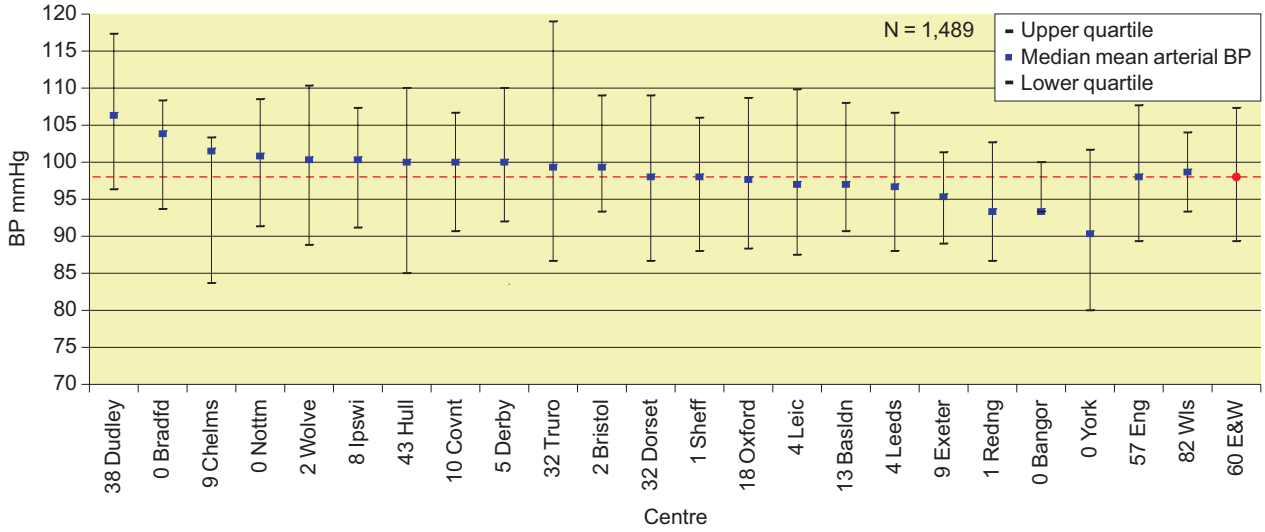

Figure 10.28: Median MAP: PD

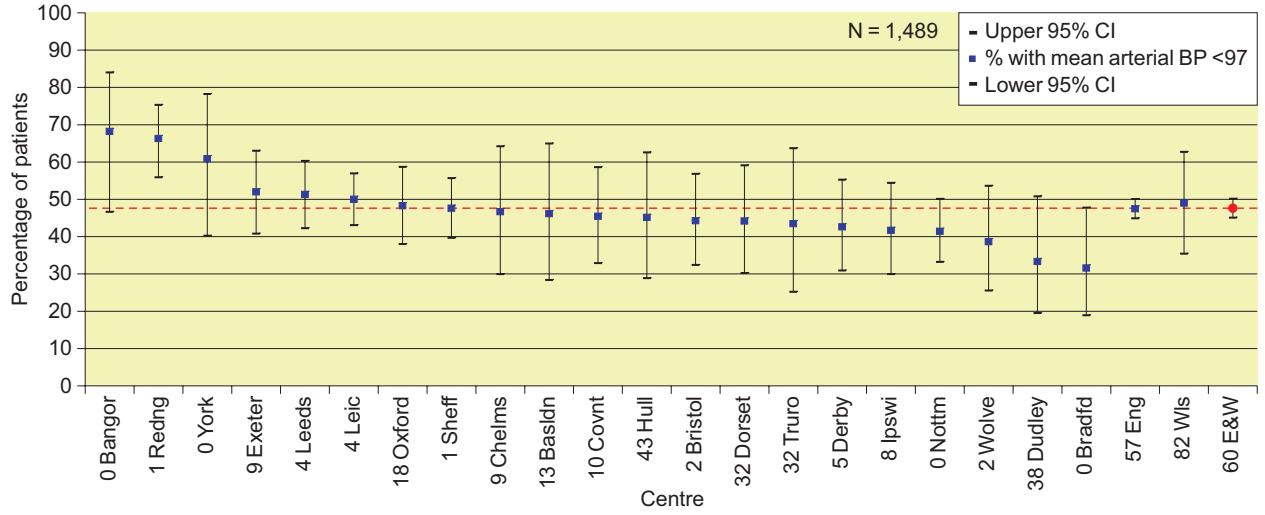

Figure 10.29: Percentage of patients with MAP <97 mmHg: PD

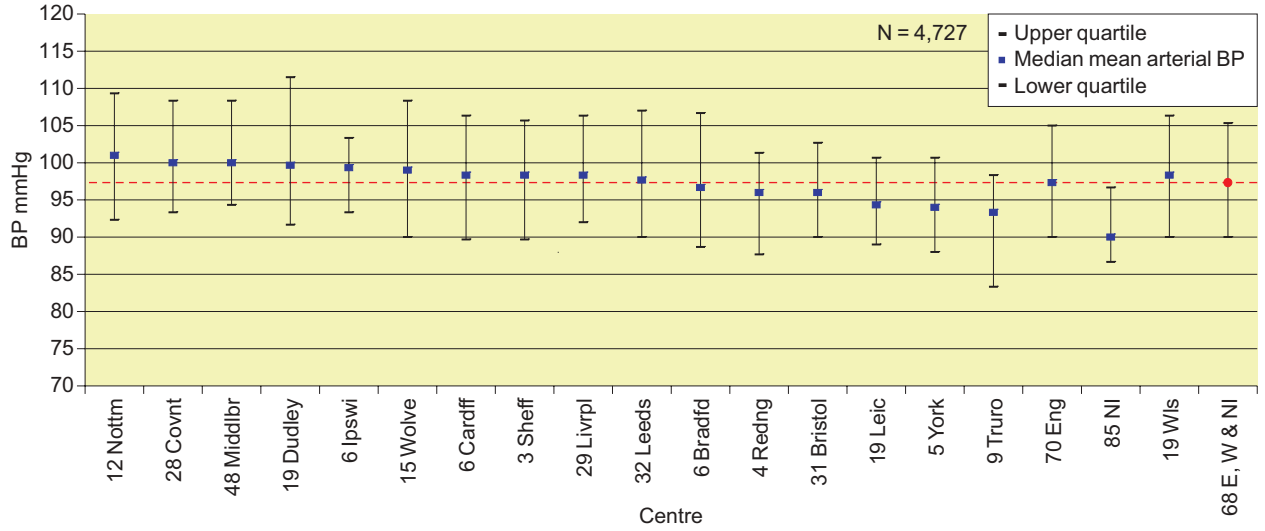

Figure 10.30: Median MAP: Transplant

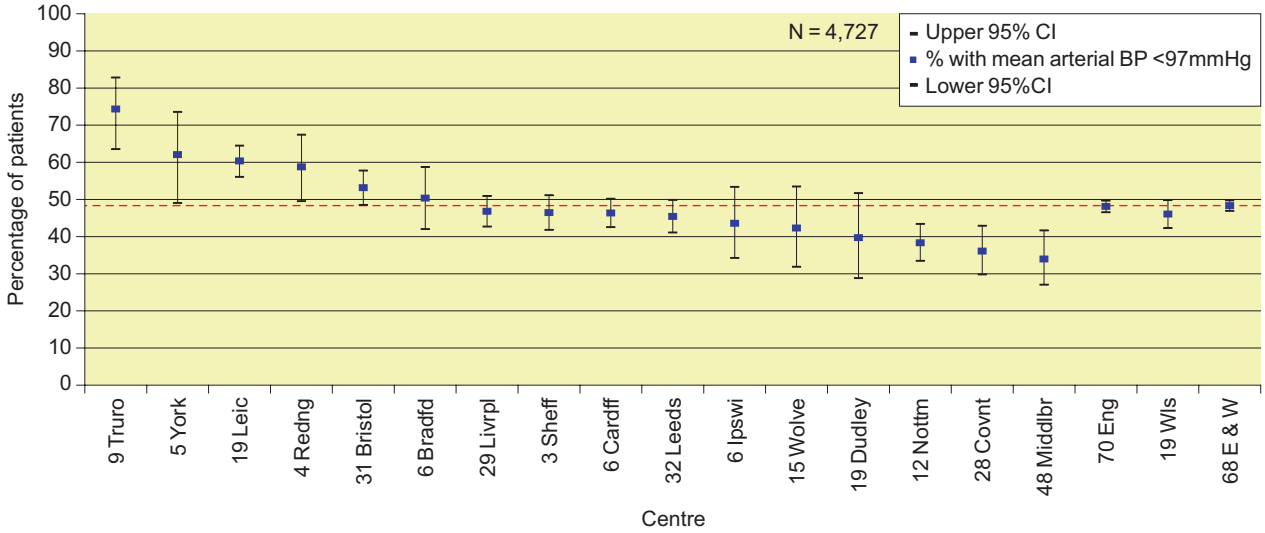

Figure 10.31: Percentage of patients with MAP <97 mmHg: Transplant

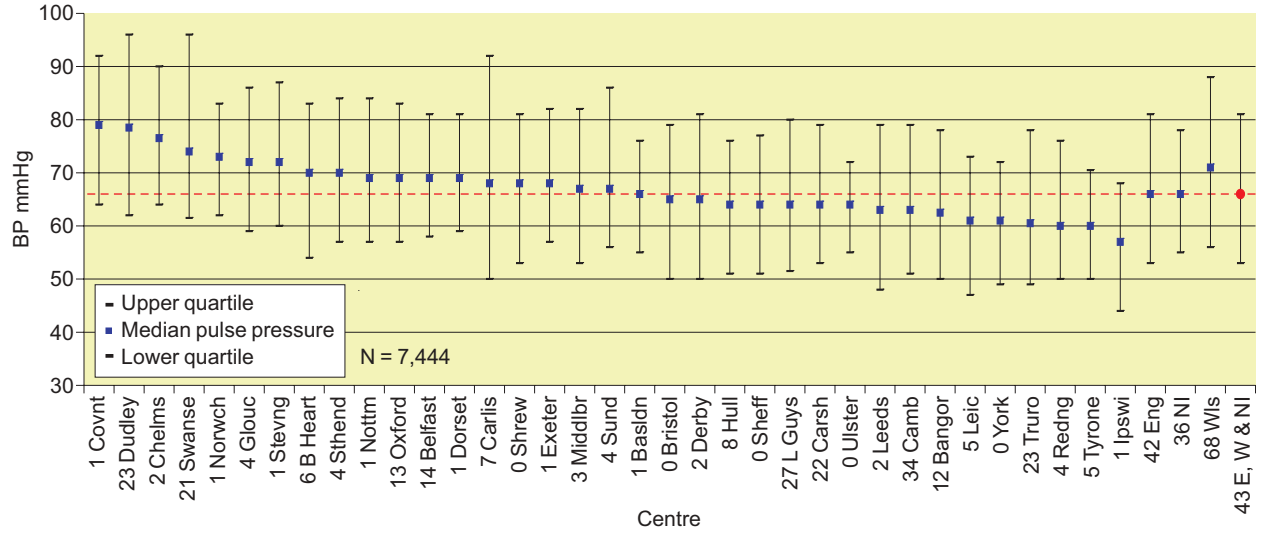

Figure 10.32: Median PP: pre-HD

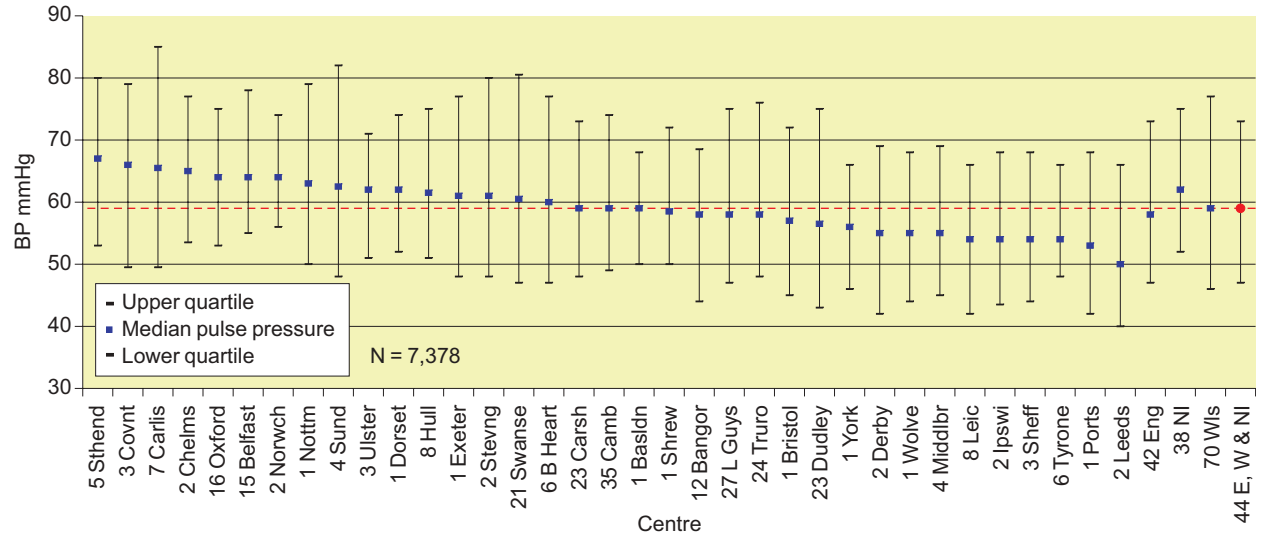

Figure 10.33: Median PP: post-HD

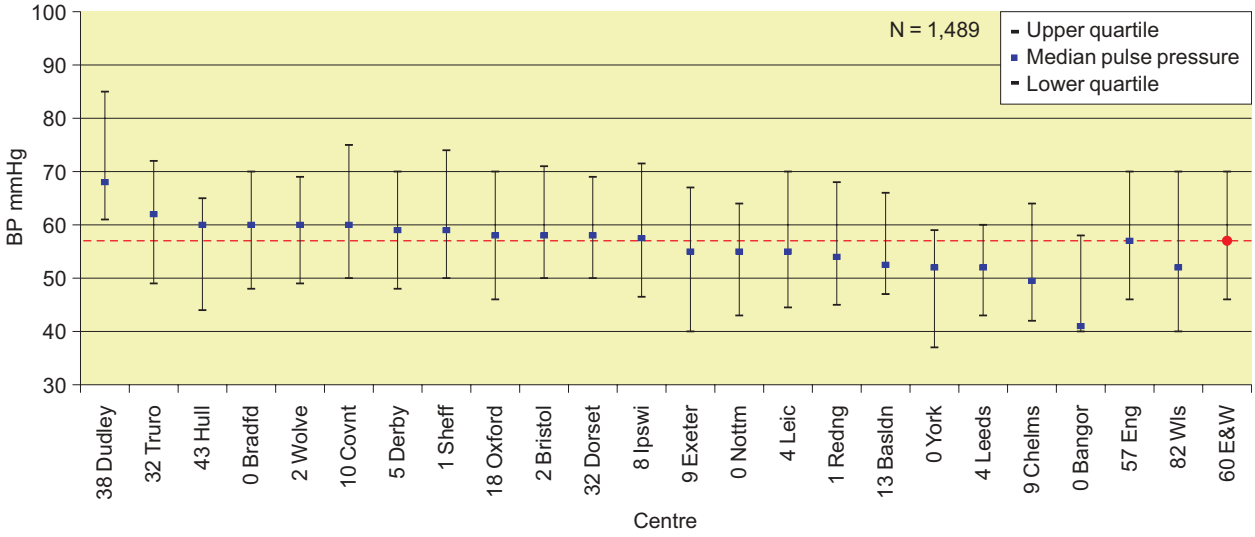

Figure 10.34: Median PP: PD

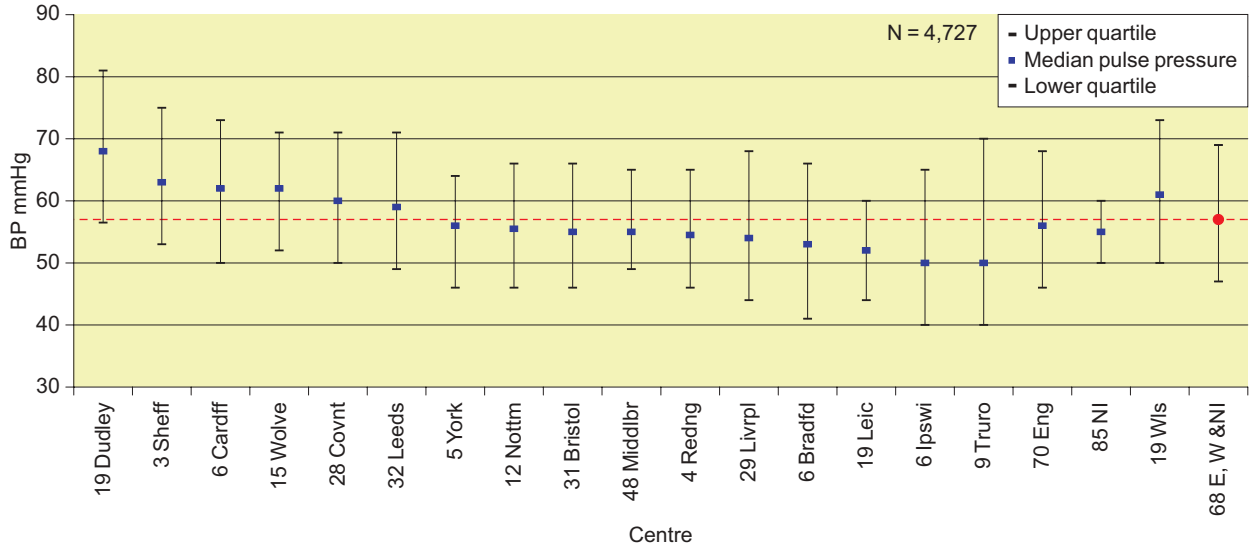

Figure 10.35: Median PP: Transplant

SBP accounts for the wider PP in HD patients pre-dialysis.

Blood pressure by primary diagnosis

Figures 10.36–10.43 show the variation in blood pressure control by primary diagnosis for each treatment modality (post-HD data is shown). Each year in the Registry Report, the data have shown a similar pattern. Systolic blood pressure is highest in patients with macrovascular disease (diabetes and renovascular disease), lower in patients with glomerulonephritis and lower still in patients with tubular disorders (PCKD and pyelonephritis).

Diabetics have the poorest blood pressure control of all the diagnostic groups. While salt intake correlates with water intake in non-diabetics, hyperglycaemia accounts for 50% of water intake by diabetics on HD[13] so may exacerbate hypertension. Blood pressure control is significantly better on HD for all diagnostic groups ($p < 0.0001$ for all groups). Combining groups, the percentage of patients achieving the BP standard on HD compared to PD or Tx are 42% vs 24% for macrovascular disease, 49% vs 26% for glomerulonephritis and 53% vs 26% for tubular disorders ($p < 0.0001$ for each comparison). This may be due to more frequent monitoring and intervention in the HD population. If so, nephrologists will need to devise

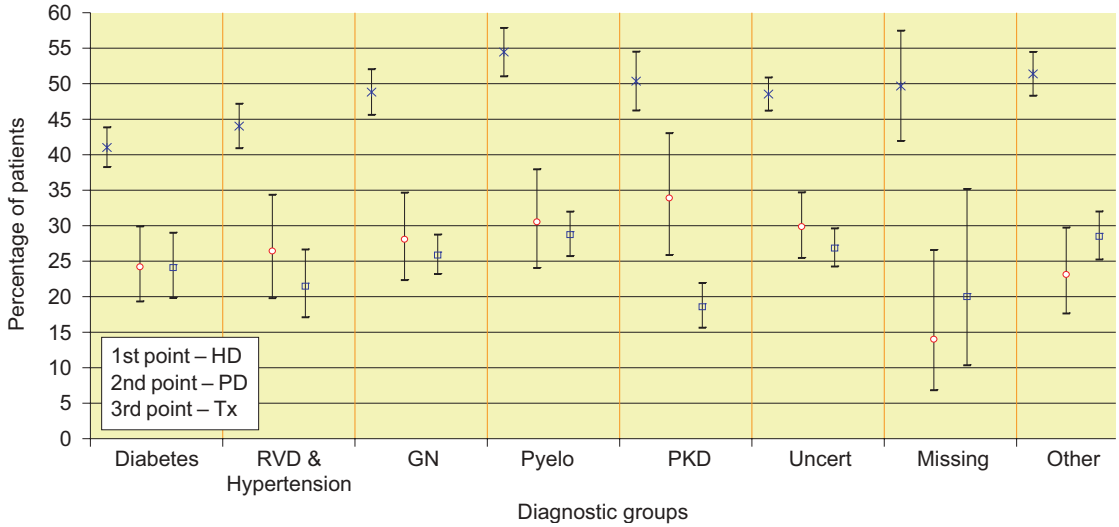

Figure 10.36: Percentage of patients with BP in standards by primary diagnosis

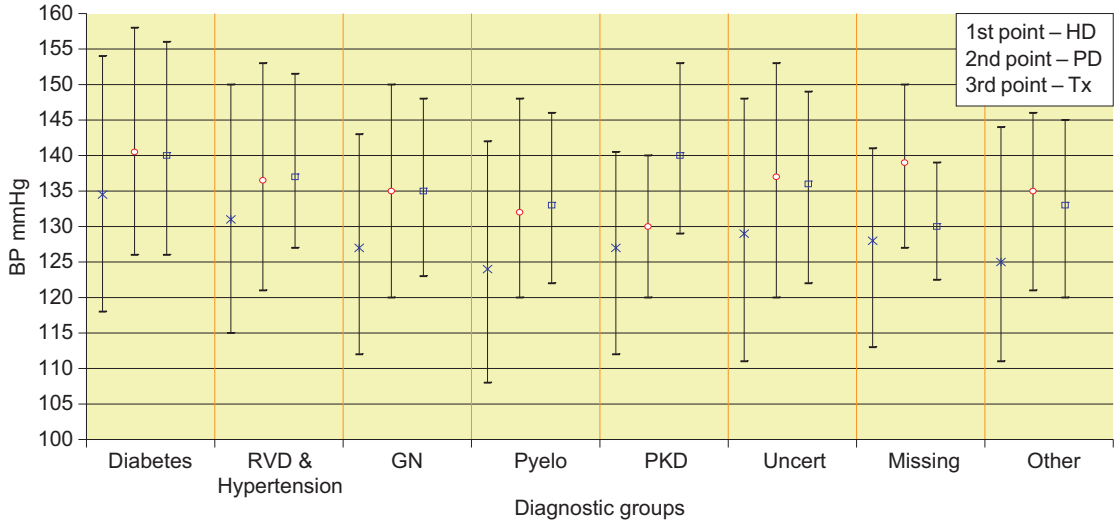

Figure 10.37: Median SBP by primary diagnosis

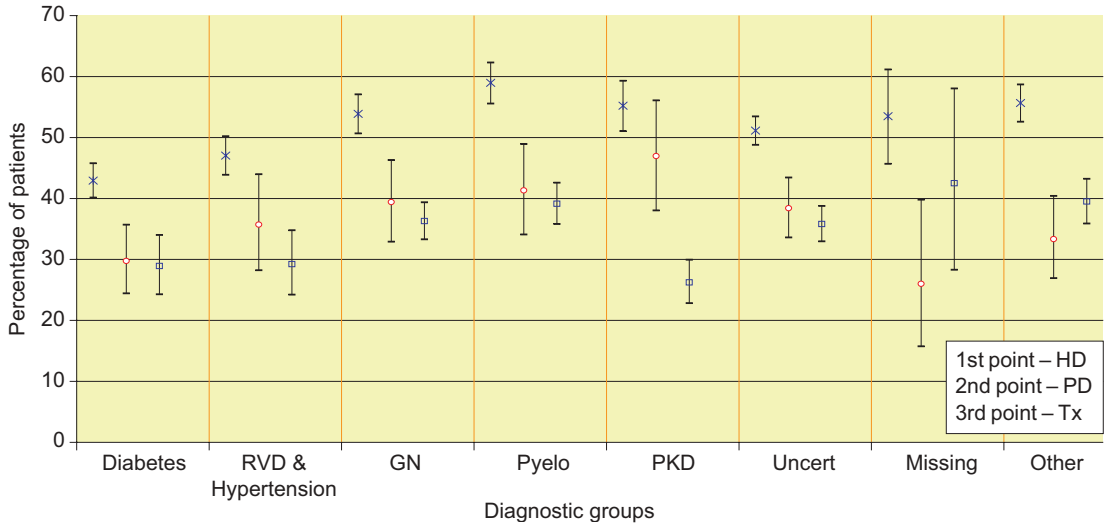

Figure 10.38: Percentage of patients with SBP in standards by primary diagnosis

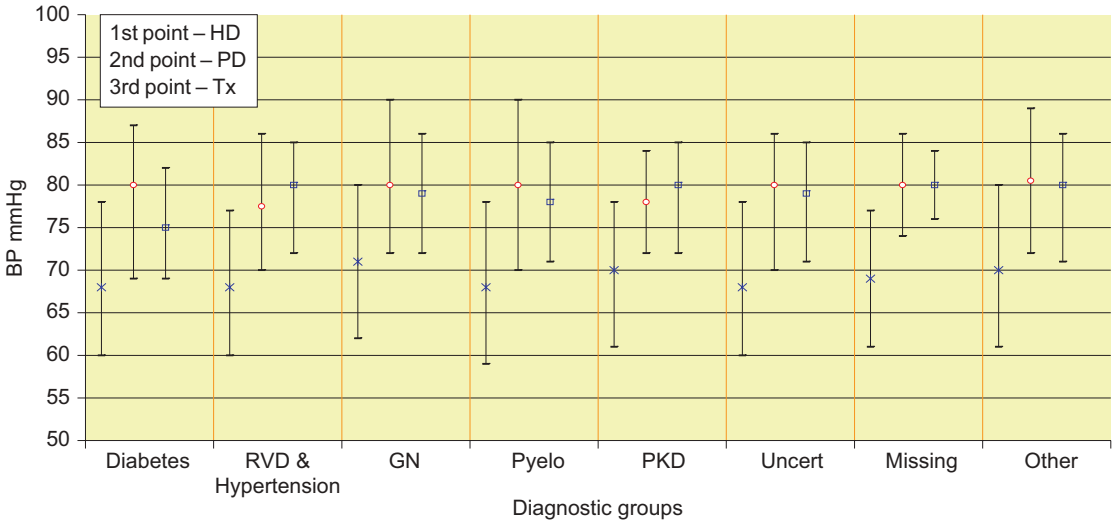

Figure 10.39: Median DBP by primary diagnosis

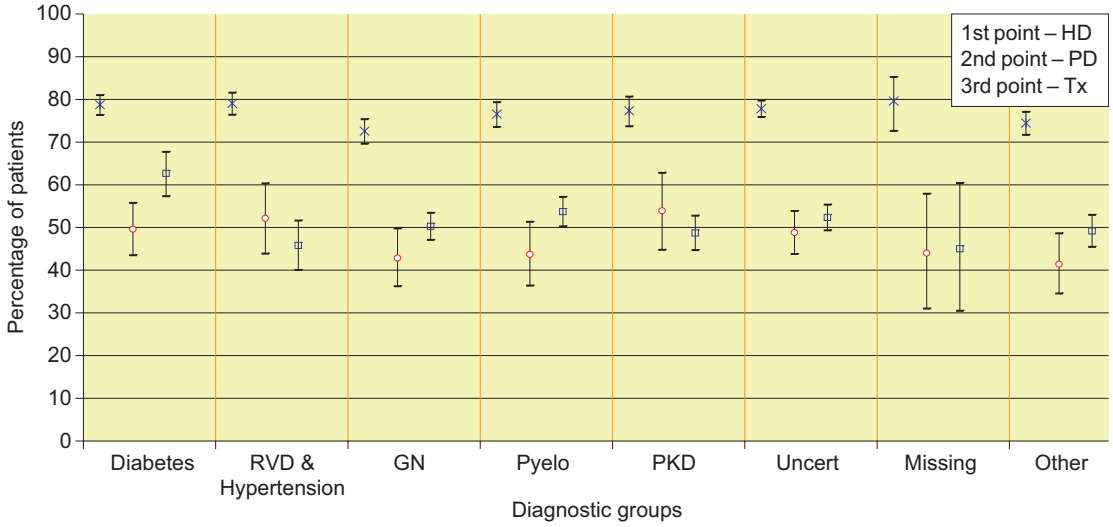

Figure 10.40: Percentage of patients with DBP in standards by primary diagnosis

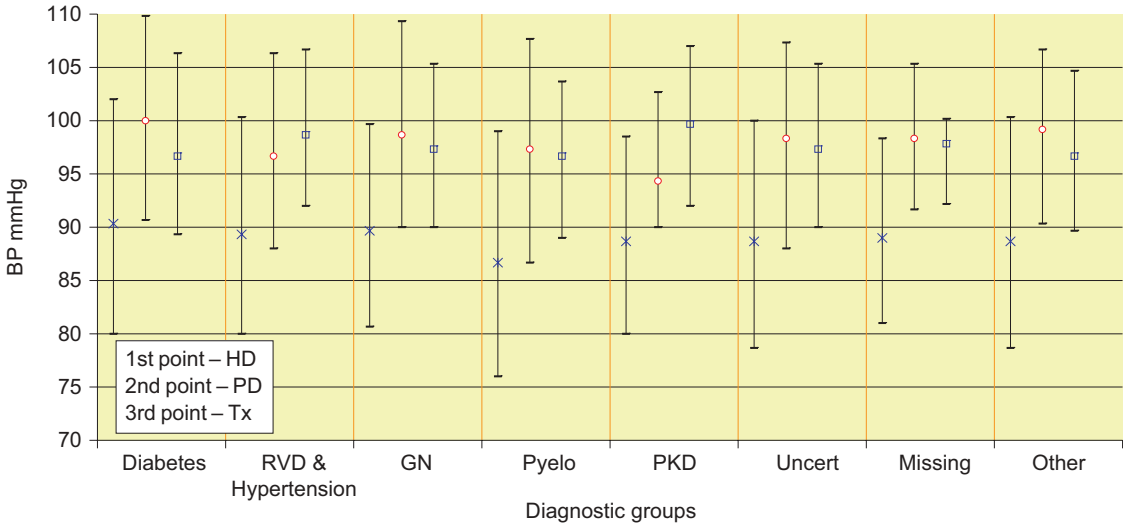

Figure 10.41: Median MAP by primary diagnosis

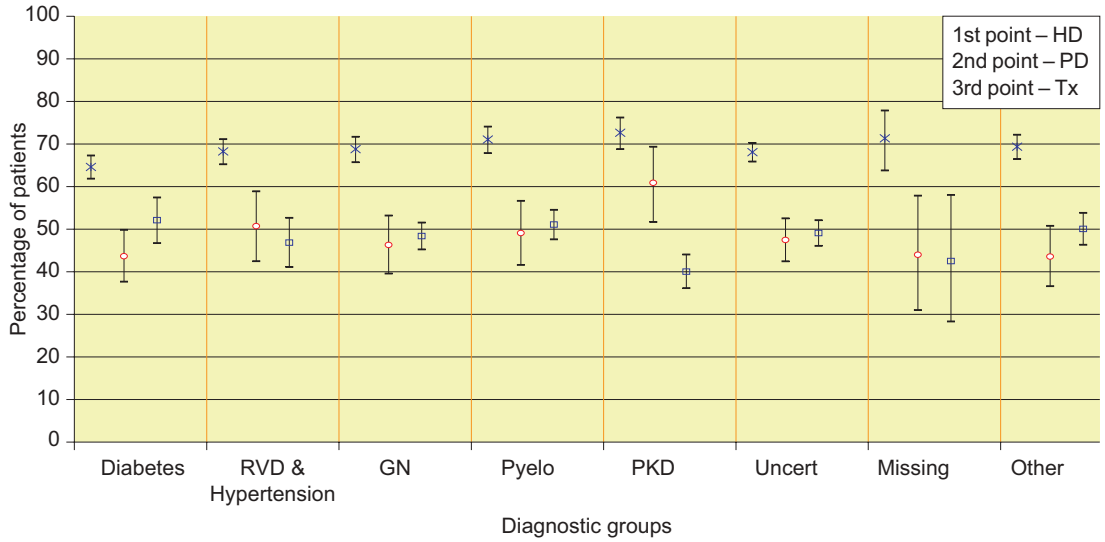

Figure 10.42: Percentage of patients with MAP in standards by primary diagnosis

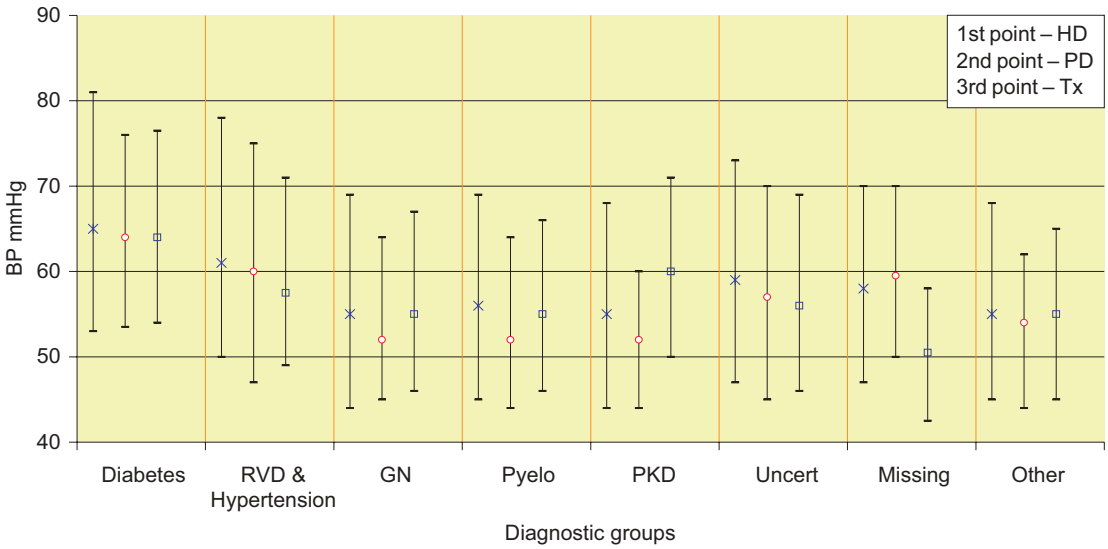

Figure 10.43: Median PP by primary diagnosis

more effective strategies for monitoring blood pressure control in outpatient populations.

Future Direction

The UK Renal Registry needs improved returns of comorbidity data for each patient to perform adjusted survival analyses. The question of whether achieving blood pressure standards are beneficial for all patients receiving RRT can then be addressed. The Registry requests that blood pressure data is logged every session for HD patients so it can assess blood pressure variability during the dialysis week.

References

1. Chobanian AV, Bakris GL, Black HR *et al.* The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA* 2003; 289:2560–2572.
2. National Kidney Foundation: K/DOQI clinical practice guidelines on hypertension and hypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004;43:S1–S290.
3. European Society of Hypertension – European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21(6):1011–1053.

4. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005;91 Suppl 5:v1–52.
5. Zager PG, Nikolic J, Brown RH *et al*. 'U' curve association of blood pressure and mortality in hemodialysis patients. *Kidney International* 1998;54: 561–569.
6. Port FK, Hulbert-Shearon TE, Wolfe RA *et al*. Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients. *Am J Kidney Dis* 1996;33:507–517.
7. UK Renal Registry Report 2003.
8. Li Z, Lacson E, Lowrie EG *et al*. The epidemiology of systolic blood pressure and death risk in hemodialysis patients. *Am J Kidney Dis* 2006;48:606–615.
9. Stidley CA, Hunt WC, Tentori F *et al*. Changing relationship of blood pressure with mortality over time among hemodialysis patients. *J Am Soc Nephrol* 2006;17:513–520.
10. Pohl MA, Blumenthal S, Cordonnier DJ *et al*. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the Irbesartan Diabetic Nephropathy Trial: clinical implications and limitations. *J Am Soc Nephrol* 2005;16:3027–3037.
11. Davenport A. Audit of the effect of dialysate sodium concentration on inter-dialytic weight gains and blood pressure control in chronic haemodialysis patients. *Nephron Clin Pract* 2006;104(3): c120–c125.
12. Asci G, Ozkahya M, Duman S *et al*. Volume control associated with better cardiac function in long-term peritoneal dialysis patients. *Perit Dial Int* 2006;26(1): 85–88.
13. Ramdeen G, Tzamaloukas AH, Malhotra D *et al*. Estimates of interdialytic sodium and water intake based on the balance principle: differences between non diabetic and diabetic subjects on hemodialysis. *ASAIO J* 1998;44:812–817.

Appendix – Definition of the cohort for blood pressure analyses

Defining the cohort

- Analysis of prevalent patients.
- Prevalent patients are defined as all patients (including the incident cohort for that year) alive on 31st December for that year.
- Dataset called **Qtreat**.

Qtreat

- Usual UKRR checking programs run on dataset.
- Exclusion criteria applied to create dataset **Qtemp**.

Exclusion criteria are:

- Patients who had died before the first day of the quarter.
- Patients on dialysis with a treatment centre of elsewhere (not identified).
- Patients receiving treatment at a non-Registry site.
- Patients with no date of starting ERF treatment.
- Patients who had been receiving treatment for a negative number of days ie incorrect starting dates or incorrect patient number on data sent in.
- Patients who had recovered before the start of the quarter.
- Where data on a patient are submitted from more than one centre, only data from the primary centre are used.

Qtemp

- Further exclusion criteria applied to Qtemp to create dataset called **Quarter**.

Exclusion criteria are:

- Patients who have transferred out of the centre (qhcent) by the end of the quarter.
- Patients who had not yet transferred in to the centre (qhcent) by the end of the quarter.
- Patients who had recovered by the end of the quarter.
- Patients who had stopped treatment by the end of the quarter.

- Patients who had died by the end of the quarter.
- Patients who were lost to follow up by the end of the quarter.

Quarter

- Further exclusion criteria applied to quarter to create dataset called **Bichem**.

Exclusion criteria are:

- Patients who had been on ERF treatment for $\leqslant 90$ days at the end of the quarter.
- Patients who changed treatment modality in the quarter.
- Patients who transferred into the centre (qhcent) at some time in the quarter.