Chapter 10: Factors which may influence cardiovascular disease – blood pressure and serum cholesterol

The majority of patients on renal replacement therapy will die of some form of cardiovascular disease, so factors which influence its development must be major targets for audit and intervention. This chapter considers two of the major determinants of cardiovascular disease in the general population, hypertension and serum cholesterol. The precise importance of these factors in patients on renal replacement therapy is uncertain, as there are other important influences in this situation which can cause vascular damage, and the vascular abnormalities are not necessarily the same as in people without renal failure. In particular, there is marked vascular calcification and vascular rigidity. The abnormalities of calcium and phosphate metabolism, and the measures taken to correct these, may play a dominant role in vascular disease in renal failure.

Blood pressure

Introduction

The current Renal Association Standards Document recommends similar blood pressure control for haemodialysis and peritoneal dialysis patients, although no standard is recommended for transplant patients. The standards for systolic and diastolic blood pressure vary in relation to age, although current available evidence does not support this differentiation. It has been shown in the general population that the absolute benefits of blood pressure reduction are greater in elderly than in younger patients, due to their higher baseline risk, and that hypertension in patients up to the age of 80 can be safely treated with good results[1].

The current standards for control of hypertension published in 1997 are:
Age <60: BP < 140/90 mmHg. (predialysis for haemodialysis patients).
Age ≥60: BP < 160/90 mmHg. (predialysis for haemodialysis patients).
(Korotkoff V if auscultation is used.)

In the proposals under discussion for the next standards document, the age variation is not maintained, and a lower standard of 130/80 mmHg is being considered for peritoneal dialysis patients.

Studies in renal replacement therapy do not show the relationship between achieved blood pressure control and outcome seen in the general population. In some studies apparently good blood pressure control is associated with poor outcome. There are factors in renal replacement therapy which may account for this:

- "Good" control groups include patients with established heart disease and poor myocardial function, either as a result of years of chronic renal failure and hypertension, or because vascular disease was the primary cause of renal failure. These patients do not have good blood pressure control, but poor cardiac function.

- The major factor driving hypertension in many dialysis patients is inadequate control of salt and water status. Patients will be hypertensive unless they already have impaired cardiac function.

- Those who can tolerate anti-hypertensive drugs without symptomatic hypotension during or between dialysis sessions have less severe cardiac disease.

The studies of the relationship between hypertension and outcome in renal replacement therapy have been short-term. It is probable that hypertension, often sustained over many years longer than the observation periods of the studies, is a major cause of cardiac damage and eventually of cardiac failure, low blood pressure, and death. A recent paper supports this interpretation: in a single centre study, early mortality was associated with low diastolic blood pressure, but late mortality was associated with high systolic blood pressure [2]. However, there have been no controlled trials examining the effect of blood pressure reduction, however achieved, on outcome in haemodialysis patients. In the light of this, the comparative results on blood pressure control presented here must be interpreted with extreme caution.

Perhaps the most remarkable observation in the results presented below, whatever the measured blood pressure indicates, is the enormous variation between renal units in blood pressure control achieved.

Achievement of combined systolic and diastolic standard

Haemodialysis

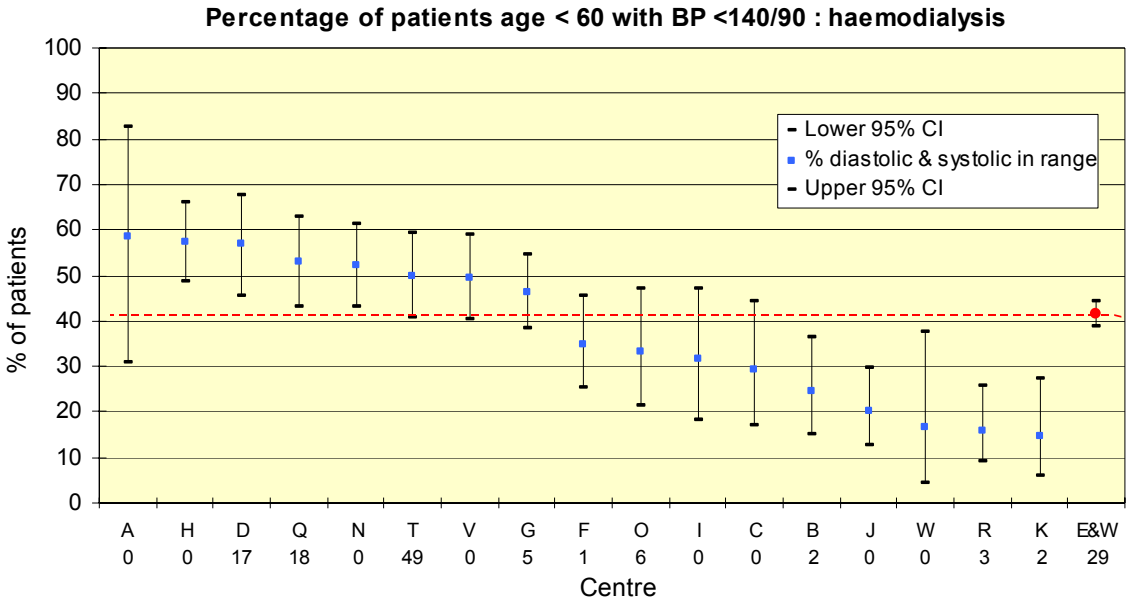

Figure 10.1 Percentage of patients age < 60 with BP ≤ 140/90 on haemodialysis

For patients on HD, the percentage of patients aged < 60 with a combined systolic blood pressure < 140 mm Hg and diastolic pressure < 90 mm Hg was found to differ significantly between centres (X^2 = 105.6, d.f. = 16, p<0.001). This was also significant in patients aged ≥60 with a combined systolic pressure < 160 mm Hg and diastolic pressure < 90 mm Hg (X^2 = 135.5, d.f. = 16, p<0.001).

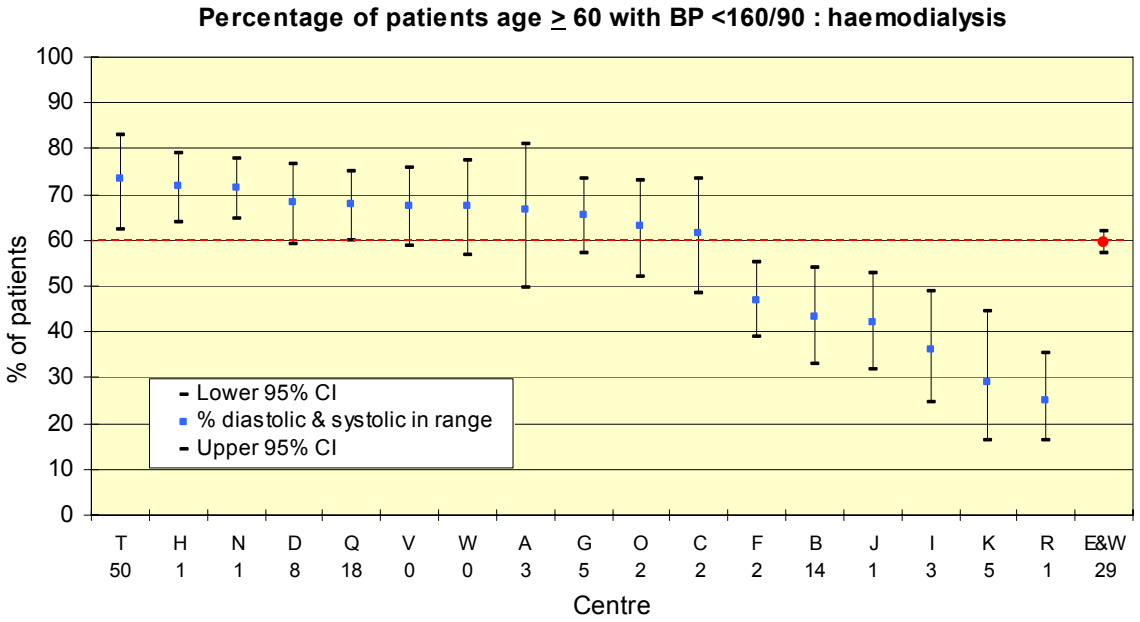

Figure 10.2 Percentage of patients age ≥ 60 with BP ≤ 160/90 on haemodialysis

Peritoneal dialysis

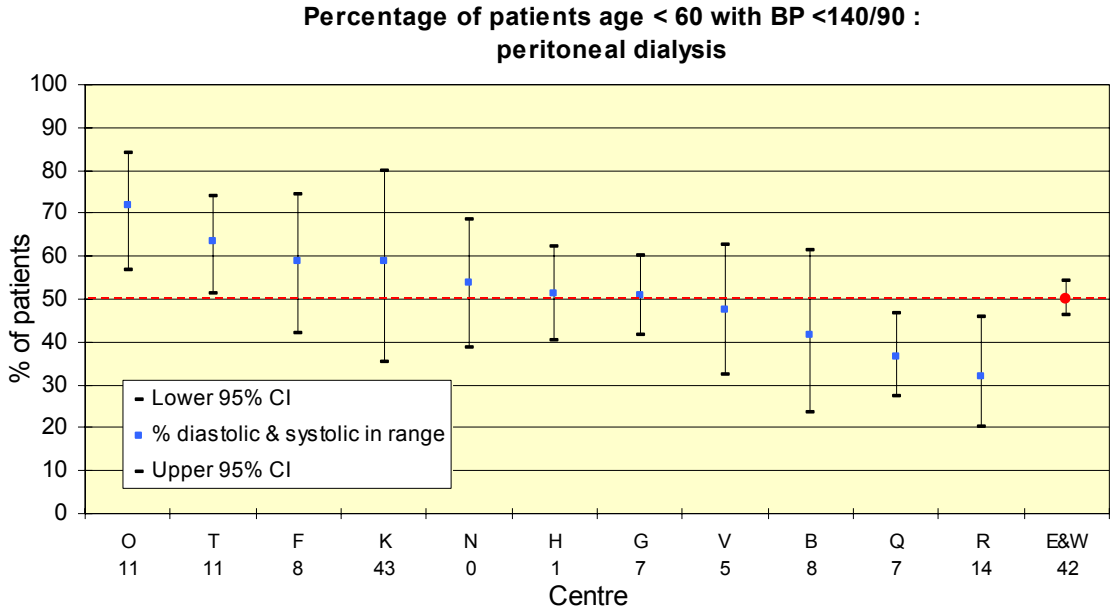

Figure 10.3 Percentage of patients age < 60 with BP < 140/90 on PD

For patients on peritoneal dialysis, the percentage of patients aged < 60 with a combined systolic blood pressure < 140 mm Hg and diastolic pressure < 90 mm Hg was found to differ significantly between centres ($X^2 = X^2 = 28.0$, d.f. = 10, $p<0.001$). This was also significant in patients aged ≥60 with a combined systolic pressure < 160 mm Hg and diastolic pressure < 90 mm Hg ($X^2 = 37.1$, d.f. = 10, $p=0.005$).

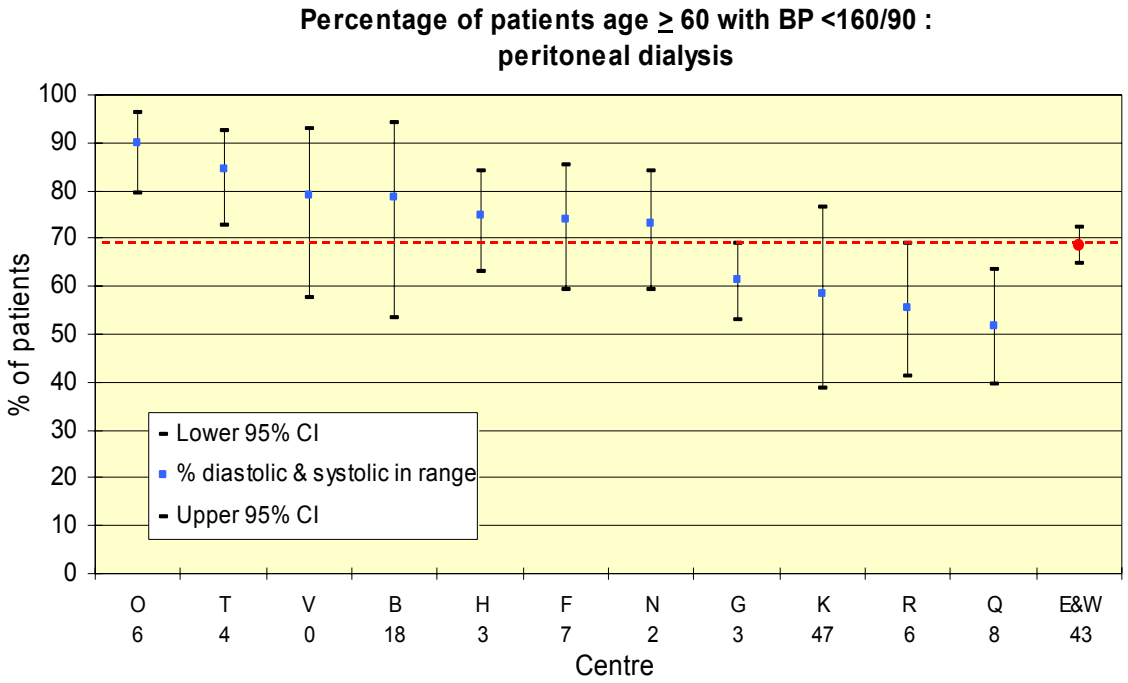

Figure 10.4 Percentage of patients age ≥ 60 with BP < 160/90 on PD

Figures 10.1-10.4 show wide variation between units in percentage of patients within the blood pressure standard.

The standard is achieved more frequently in peritoneal dialysis patients than in haemodialysis patients. The variation for younger haemodialysis patients is from 15% to 60% of patients in individual centres meeting the standard, average 41%: for older haemodialysis patients the corresponding figures are 25% to 73%, average 60%. For younger peritoneal dialysis patients the variation is from 32% to 71% of patients achieving the standard, average 60%: for older peritoneal dialysis patients the figures are from 52% to 90%, average 79%. More older patients achieve the standard than younger patients, because the standard for older patients is less rigorous.

Systolic pressure alone

In the general population systolic pressure is an indicator of vascular risk. Many elderly patients have isolated systolic hypertension. There is benefit from reducing systolic blood pressure in the elderly general population [3], but this has not been specifically examined in renal replacement therapy. The appropriate approach to systolic hypertension in the elderly dialysis patient is therefore unclear.

Haemodialysis

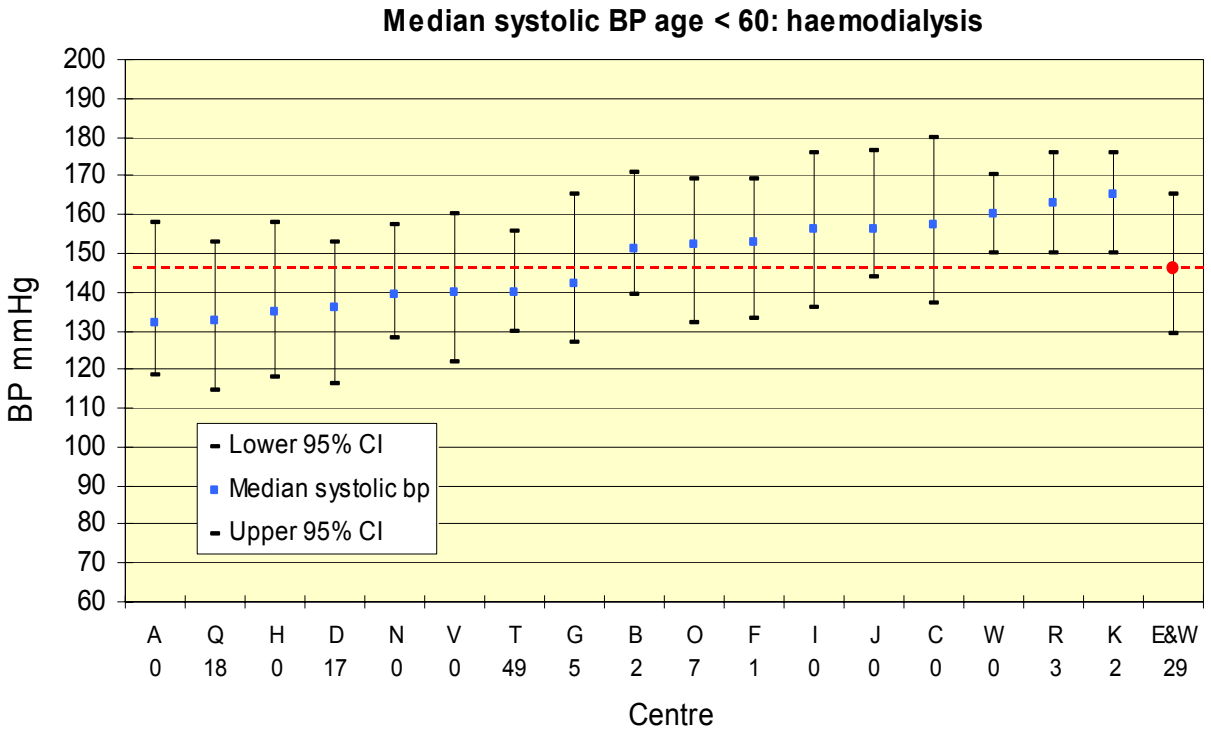

Figure 10.5 Median systolic blood pressure age < 60 on haemodialysis

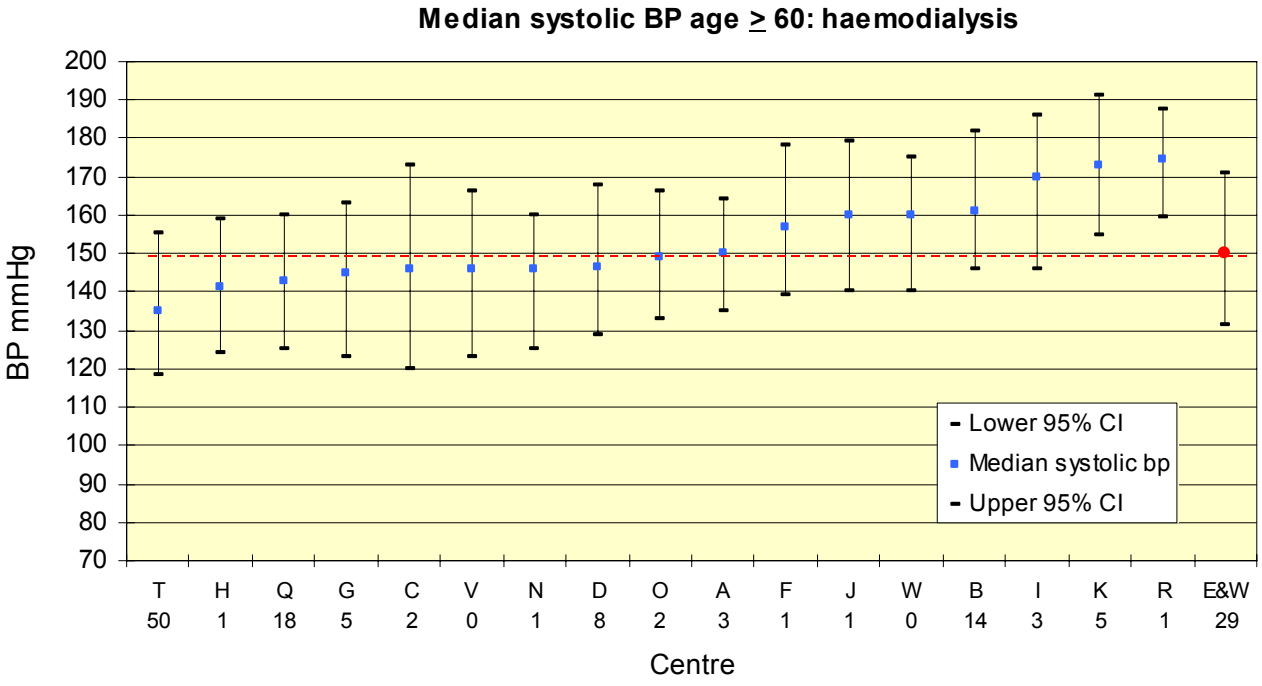

Figure 10.6 Median systolic blood pressure age ≥ 60 on haemodialysis

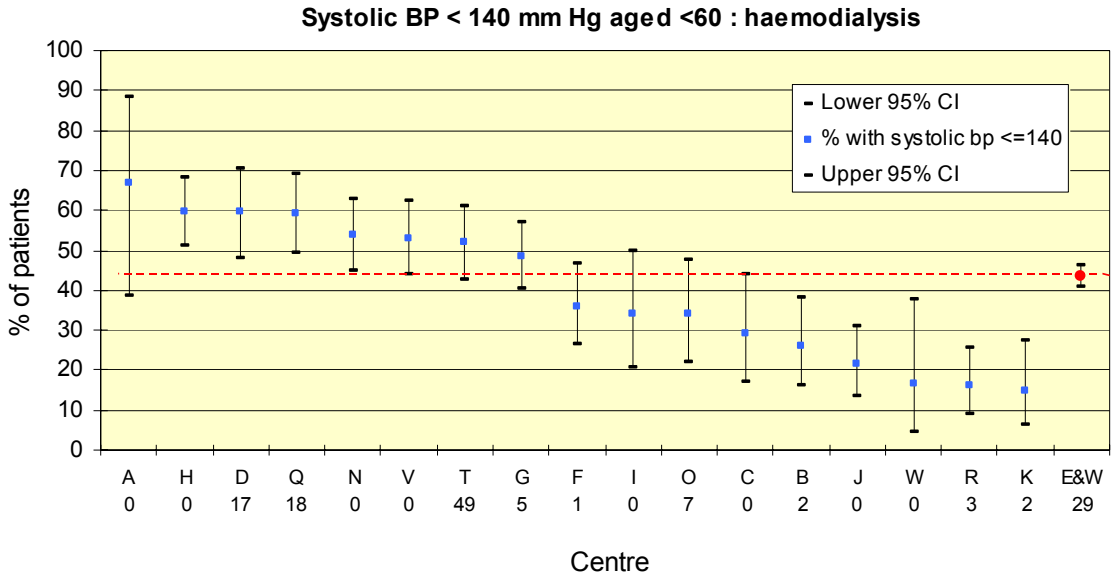

Figure 10.7 Percentage of patients with systolic BP ≤ 140 mm Hg aged < 60 on HD

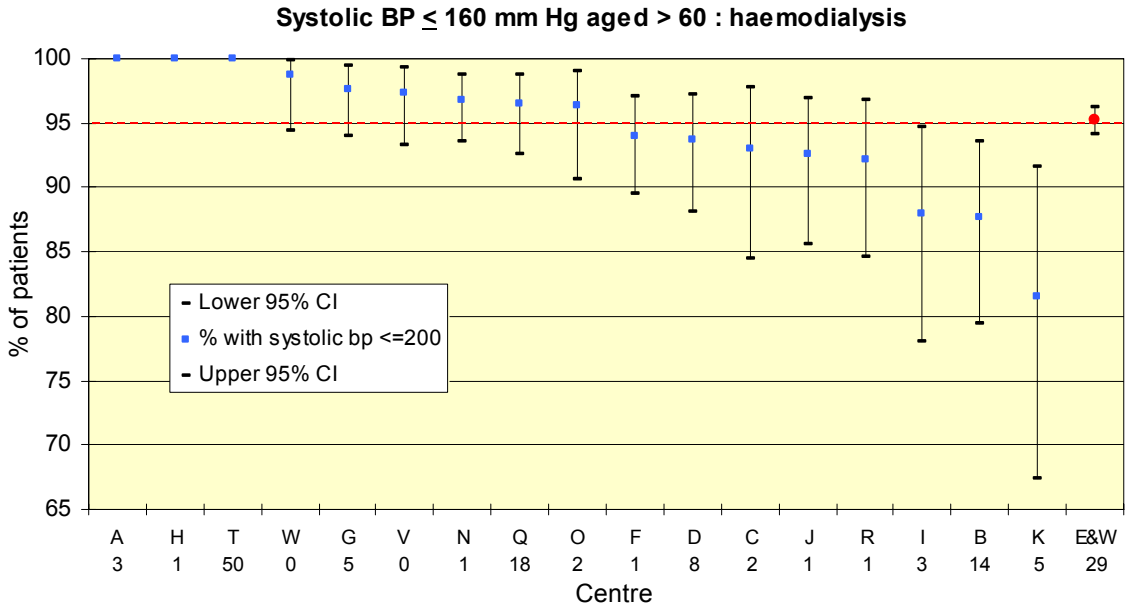

Figure 10.8 Percentage of patients with systolic BP ≤ 160 mm Hg aged ≥ 60 on HD

The percentage of elderly haemodialysis patients achieving the systolic standard is higher (centre variation from 83% to 100%, mean 95%) than younger patients (variation from 15% to 68%, mean 44%), as the standard is more liberal in this age group. The median blood pressure obtained in the two groups is similar (148 mm/Hg in the younger patients, 150 mm/Hg in the older patients) (figures 10.5 – 10.8).

For patients on HD, the percentage of patients aged < 60 with a systolic blood pressure < 140 mm Hg was found to differ significantly between centres (X^2 = 121, d.f. = 16, p<0.001).This was also significant in patients aged ≥60 (X^2 = 55.6, d.f. = 16, p<0.001).

Peritoneal dialysis

Similar relationships are seen in peritoneal dialysis patients (figures 10.9 - 10.12), but overall blood pressure control was better in patients on PD (median systolic pressure 140 mm/Hg in the younger patients, 143 mm/Hg in the older, with 55% and 98% patients achieving the standard in each age group).

A significance level of 0.01 has been used within the biochemistry and blood pressure chapters due to the large number of tests. At this significance level, the percentage of patients aged < 60 with a systolic blood pressure < 140 mm Hg was just found to differ significantly between centres (X^2 = 24, d.f. = 10, p<0.008).This was **NOT** significant in patients aged ≥60 (X^2 =17, d.f. = 10, p=0.07).

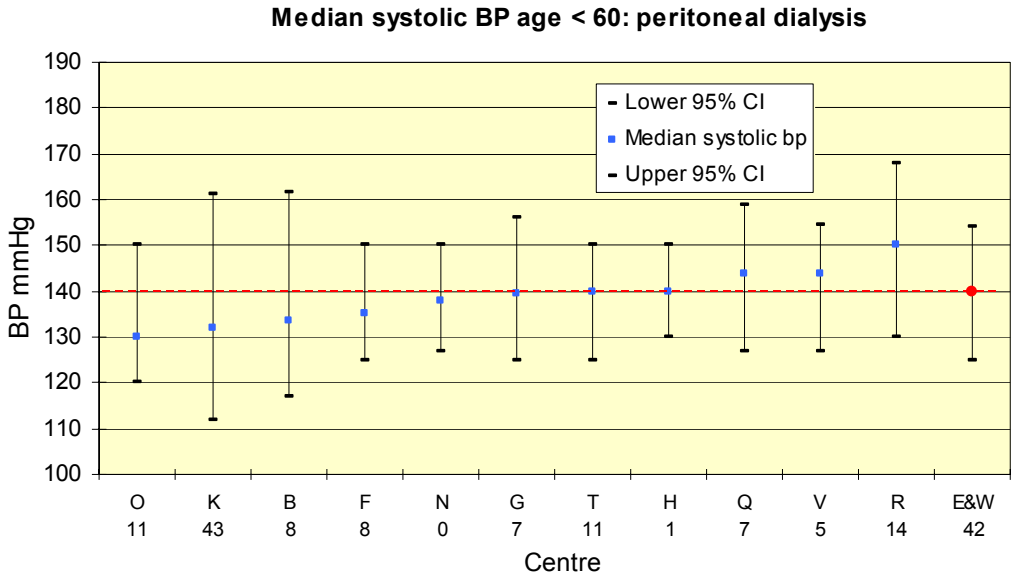

Figure 10.9 Median systolic blood pressure age < 60 on peritoneal dialysis

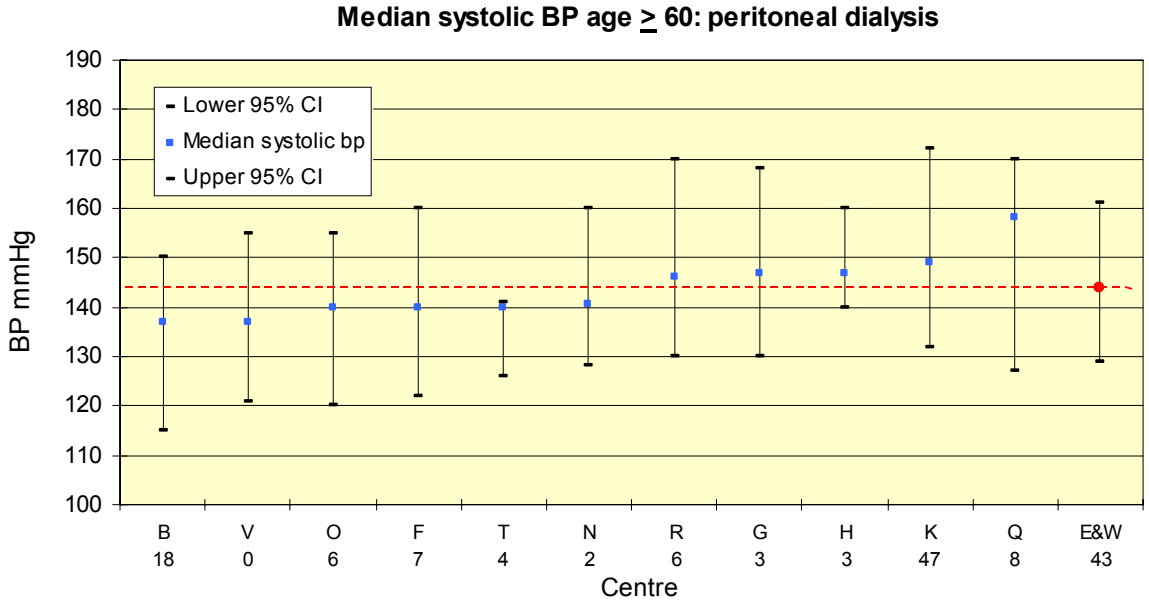

Figure 10.10 Median systolic blood pressure age ≥ 60 on peritoneal dialysis

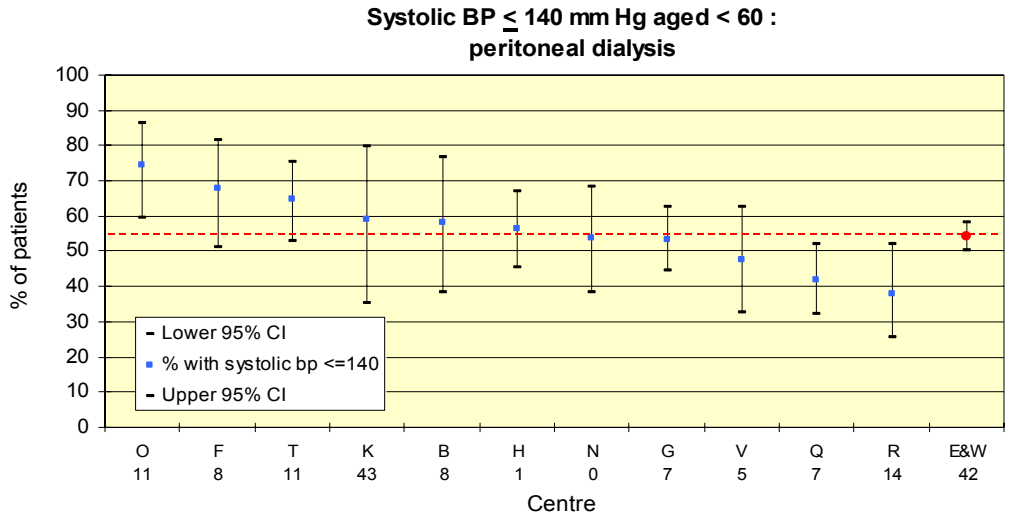

Figure 10.11 Percentage of patients with systolic BP < 140 mm Hg age < 60: PD

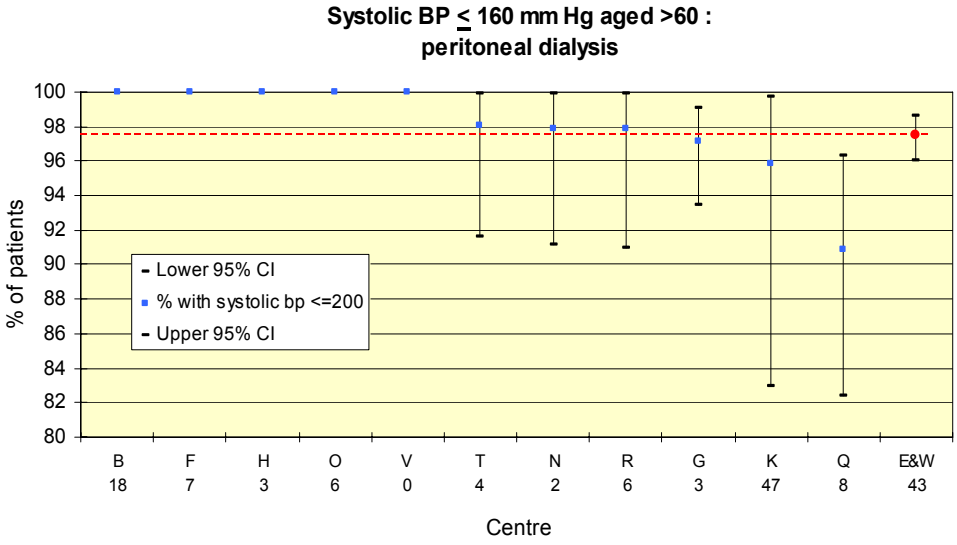

Figure 10.12 Percentage of patients with systolic BP < 160 mm HG age > 60: PD

Diastolic pressure alone

Haemodialysis

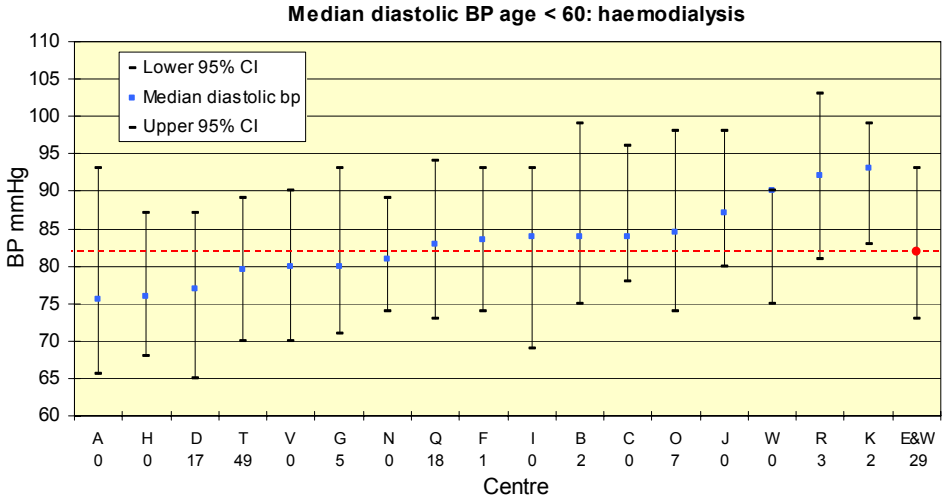

Figure 10.13 Median diastolic blood pressure age < 60 on haemodialysis

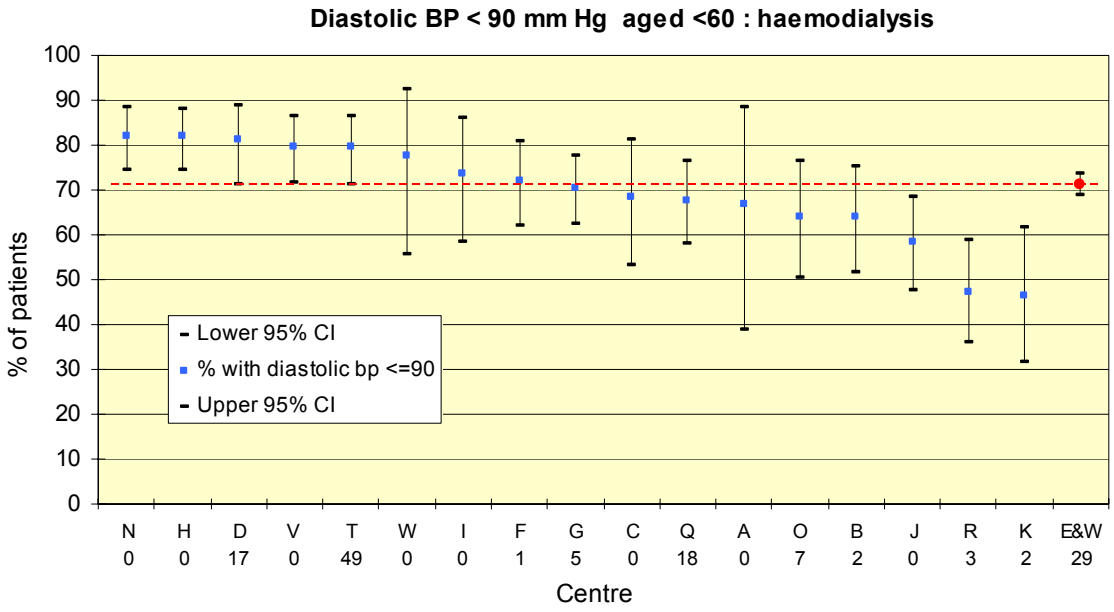

Figure 10.14 Percentage of patients age < 60 with diastolic BP ≤ 90 mmHg on HD

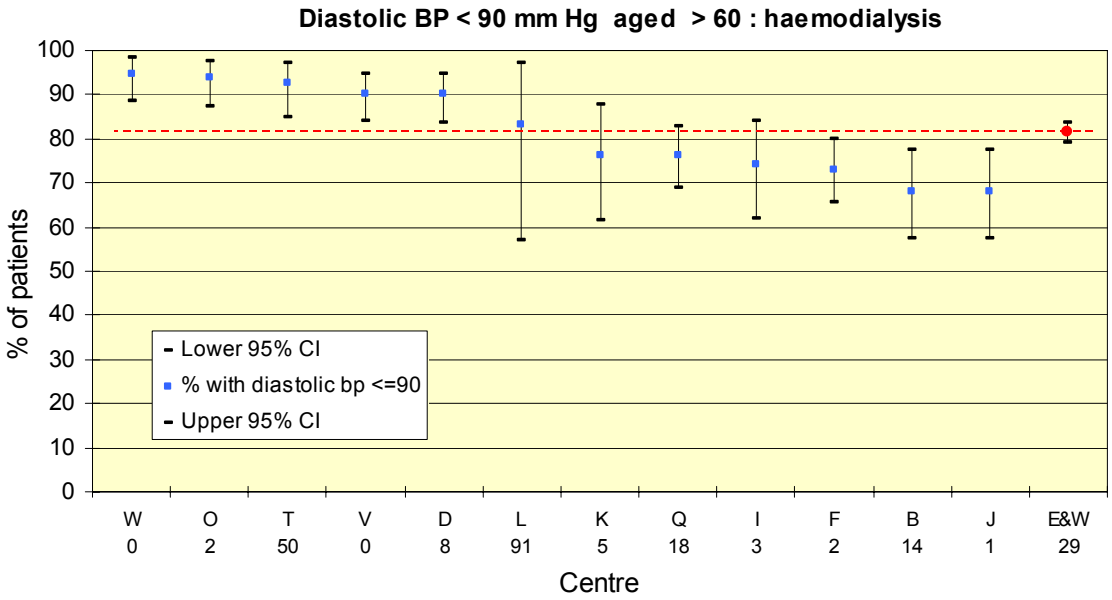

Figure 10.15 Percentage of patients age ≥ 60 with diastolic BP < 90 mmHg on HD

The median diastolic pressure of younger haemodialysis patients (84 mm/Hg) is higher than that of older haemodialysis patients (82 mm/Hg), (figures 10.13 – 10.15), and similar in peritoneal dialysis patients (figures 10.16 – 10.19). Thus fewer younger patients achieve the standard value (71% vs 81% in haemodialysis, 77% versus 82%in peritoneal dialysis). Overall results are again better in peritoneal dialysis patients.

For patients on HD, the percentage of patients aged < 60 with a diastolic blood pressure < 90 mm Hg was found to differ significantly between centres (X^2 = 69, d.f. = 16, p<0.001).This was also significant in patients aged ≥60 (X^2 = 68, d.f. = 11, p<0.001).

Peritoneal dialysis

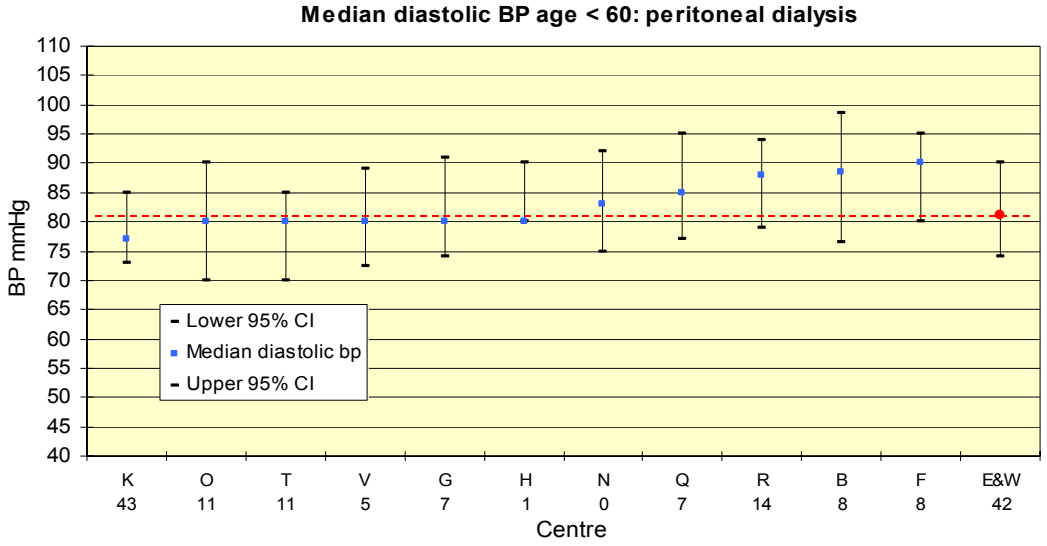

Figure 10.16 Median diastolic blood pressure age < 60 on PD

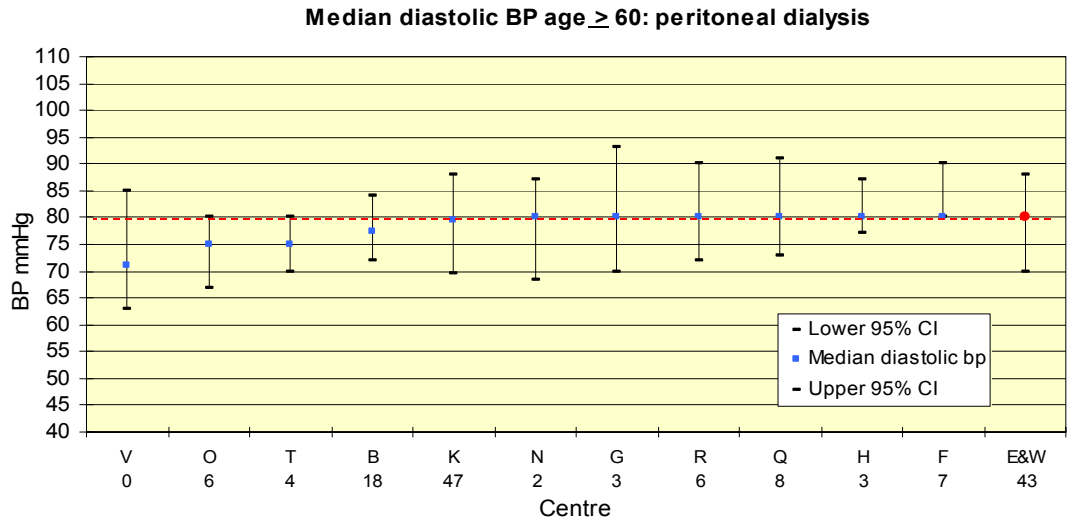

Figure 10.17 Median diastolic blood pressure age ≥ 60 on peritoneal dialysis

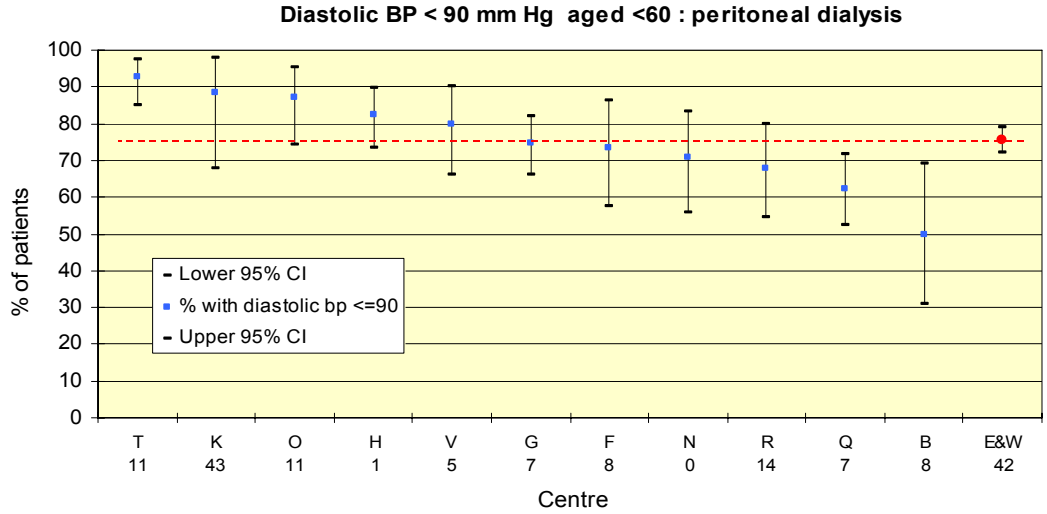

Figure 10.18 Percentage patients age < 60 with diastolic BP ≤ 90 mmHg on PD

For patients on PD, the percentage of patients aged < 60 with a diastolic blood pressure < 90 mm Hg was found to differ significantly between centres (X^2 = 37, d.f. = 10, p<0.001).This was also significant in patients aged ≥60 (X^2 = 26, d.f. = 11, p<0.003).

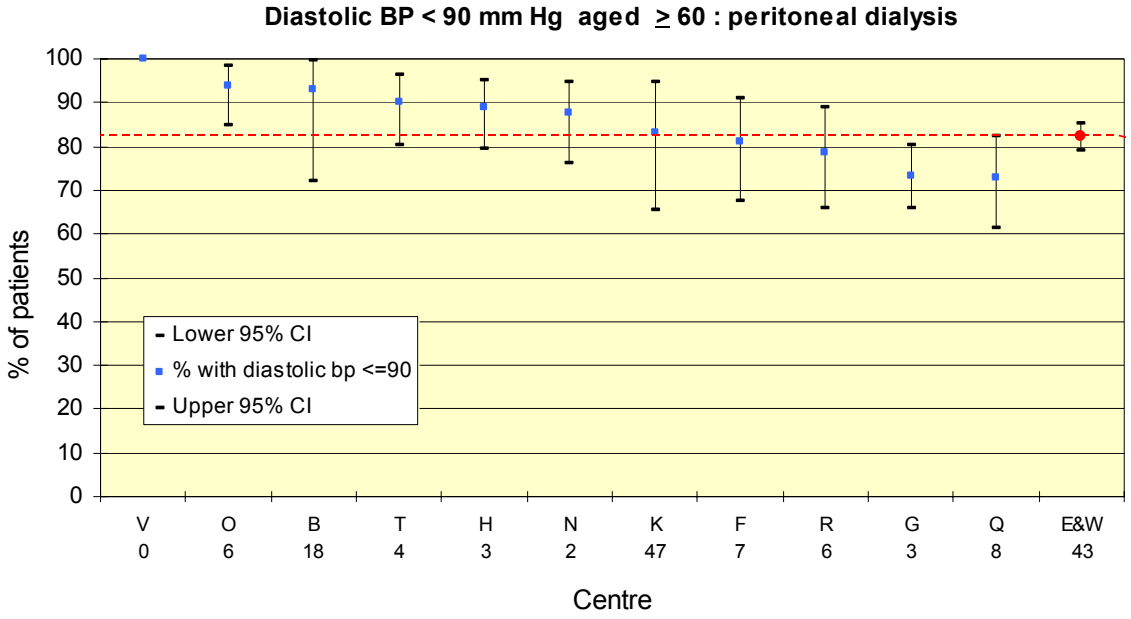

Figure 10.19 Percentage patients age ≥ 60 with diastolic BP < 90 mmHg on PD

Mean arterial pressure

Mean arterial pressure is calculated as diastolic pressure plus one-third the difference between systolic and diastolic pressures. The standards for systolic and diastolic blood pressure are equivalent to a mean arterial pressure of 106.7mmHg in those under 60 and 113.3mmHg in older patients.

Haemodialysis

Results are shown in figures 10.20 – 10.23

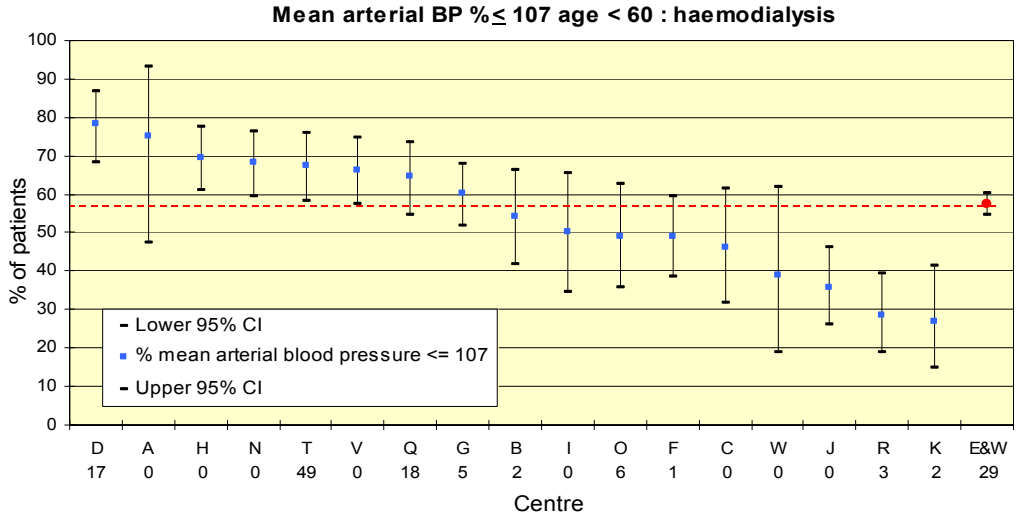

Figure 10.20 Percentage patients age < 60 with mean arterial BP < 107 on HD

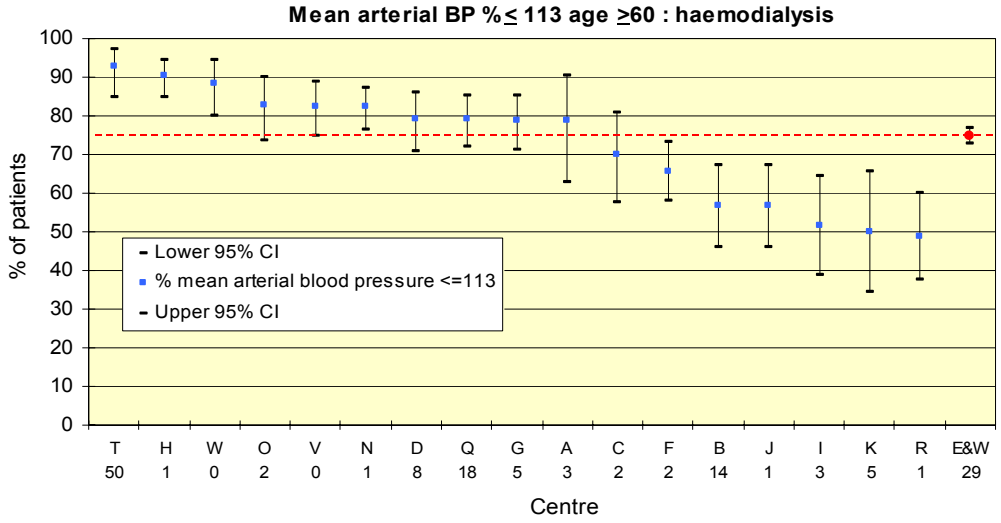

Figure 10.21 Percentage patients age ≥ 60 with mean arterial BP < 113 on HD

Peritoneal dialysis

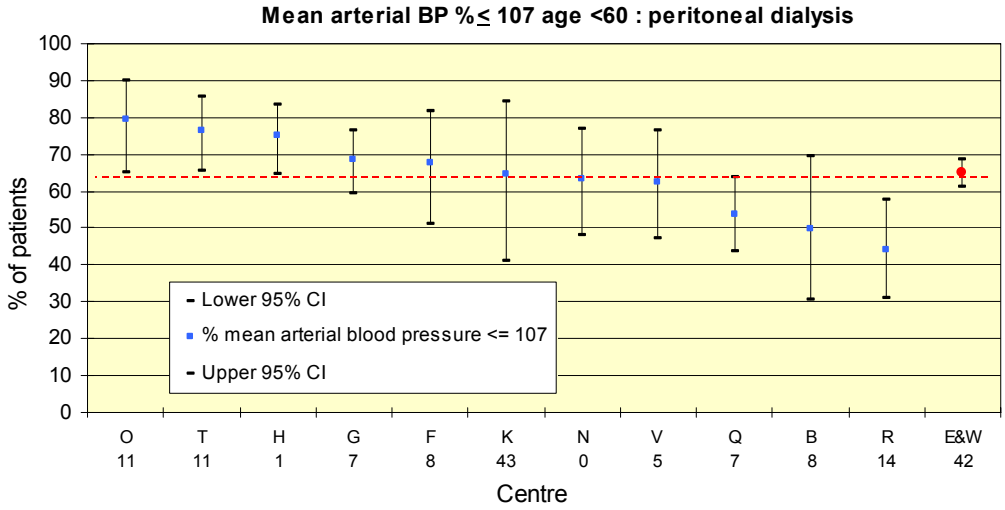

Figure 10.22 Percentage patients age < 60 with mean arterial BP < 107 PD

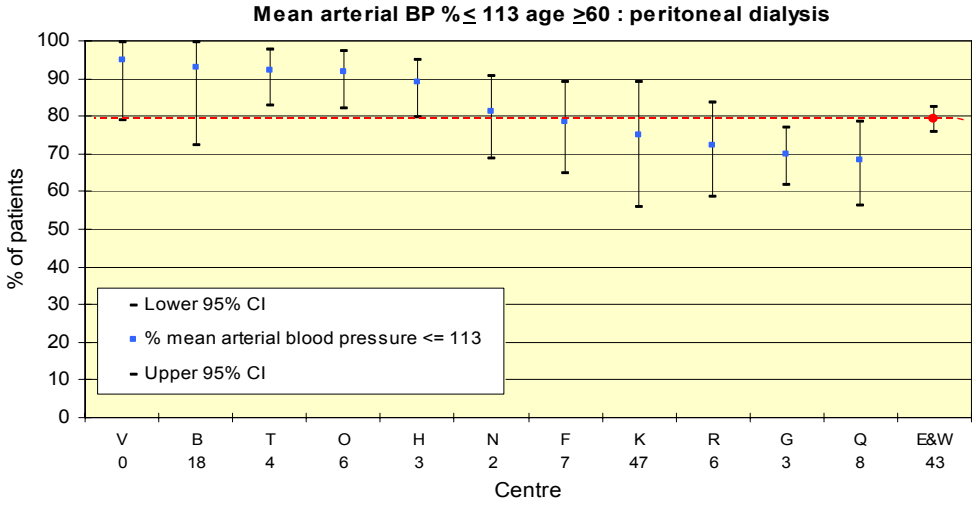

Figure 10.23 Percentage patients age ≥ 60 with mean arterial BP < 113 on PD

Of younger haemodialysis patients, 56% achieve this nominal standard compared with 75% of older patients. For peritoneal dialysis the figures are 66% and 80% respectively.

Patients aged ≥ 60 years had the same mean arterial pressure as those < 60 years (103 mm Hg for patients on haemodialysis and 101 mm Hg on peritoneal dialysis). The prognostic significance of mean arterial pressure is doubtful.

Recent studies have shown that increased pulse pressure, a result of decreased conduit artery compliance, is a much more powerful risk factor for death in the general population than systolic or diastolic blood pressure [4-9]. For patients with the same mean arterial pressure prognosis may be very different depending on the pulse pressure. Increased pulse pressure is common in dialysis patients [10], and increased pulse wave velocity, a more direct marker of decreased conduit artery compliance, has been associated with poor outcome in dialysis patients [11]. Studies examining the effects of anti-hypertensive strategies aimed at reducing pulse pressure, and the effects of such treatment strategies on outcome, are required both in the general population and in patients on dialysis [12].

Further problems

Pre-dialysis or post-dialysis measurements?

Most studies of blood pressure in haemodialysis patients have used pre-dialysis blood pressure measurements. This is what the Registry has analysed in haemodialysis patients, although post-dialysis blood pressure records have been collected from some renal units.

Predialysis pressure may not be the most appropriate to study. Two recent large studies showed no increase in cardiovascular mortality with increasing pre-dialysis blood pressure, but did find increasing mortality at the higher levels of post-dialysis blood pressure [13,14]. There is a rapid rise in blood pressure a few hours before each haemodialysis session [15,16], and several ambulatory blood pressure monitoring studies [15-17] have shown a closer relationship between mean ambulatory blood pressure and post-dialysis blood pressure than with pre-dialysis blood pressure. The closest estimate of the ambulatory blood pressure may be obtained by measuring blood pressure 20 minutes after completion of dialysis [16], but this is impractical in routine practice, and a measurement shortly after completion of dialysis has to be acceptable, despite the concern that this may be influenced unduly by haemodynamic instability caused by continued equilibration between the blood volume and the interstitial compartment. Mean ambulatory systolic pressure may be more closely related to the predialysis measurement, and diastolic pressure to the post–dialysis measurement [18].

Measurement of blood pressure

In the management of essential hypertension, the need for care in the interpretation of blood pressure measurements, and the unreliability of casual measurements taken while the patient is stressed or anxious, are well recognised. In clinical practice, pre-dialysis blood pressure is often measured in conditions far removed from those recommended for the measurement of resting blood pressure. Pressures recorded are often from casual, hurried, measurements of

blood pressure in a stressed patient just prior to the commencement of dialysis (involving needling of the fistula). Such readings may be expected to give misleadingly high readings. Renal registry blood pressure records will be from a variety of techniques and conditions of blood pressure measurement.

Relationship of measured blood pressure to outcomes

The lack of the expected relationship between hypertension and outcome in renal replacement therapy has already been considered. This is not entirely surprising. Techniques and conditions of blood pressure measurement vary considerably. The vascular disease in renal failure differs significantly from that usually seen in the general population. The measured blood pressure reflects many things including myocardial function, arterial rigidity and resistance, fluid overload, and hypotensive treatment given. Treatment of hypertension may be by drugs (some of which are cardio-protective), salt and water control, and possibly by interventions which may have unknown benefits, such as long haemodialysis. Different interventions may not be of equivalent benefit. Given all these confounding factors it might be considered surprising if any relationships were found between registry blood pressure measurement and outcome. A preliminary analysis of the relationship between measured blood pressure and outcome is presented in chapter 18. As in several other studies higher blood pressures are associated with better outcomes over a short time scale. The relationship is strongest for diastolic pressures and weakest for mean arterial pressures.

Serum Cholesterol

Introduction

There are difficulties in making firm recommendations on desirable serum cholesterol in renal replacement therapy. Although cardiovascular disease is an important cause of premature mortality in patients on dialysis, the patterns of disease differ from the general population. There is less contribution from acute myocardial infarction and cerebrovascular disease, and a greater incidence of sudden cardiac death, hypertensive heart failure, altered myocardial capillary density, increased cellular susceptibility to ischaemia, and endocarditis. The risk factors for atherosclerosis in dialysis patients are different from those in the general population. The effects of peroxidation and carbamylation of lipoprotein particles, hyper-homocystinaemia, and many other "non-classical" risk factors may confound the contribution from traditional risk factors such as hypertension and hyperlipidaemia. Large-scale epidemiological studies in haemodialysis patients have, shown an inverse or U-shaped relationship between serum cholesterol and subsequent mortality [19-23]. This probably reflects the effects of malnutrition and/or a chronic inflammatory response in ill patients causing low serum cholesterol. Nevertheless some studies have, found an association between ischaemia heart disease and dyslipidaemia in dialysis patients, and in CAPD patients a direct correlation between total cholesterol or total: HDL cholesterol ratio and survival [24,25], has been observed.

The current renal standards document does not contain any recommendations on control of serum cholesterol.

The Standards committee is considering a revision which recommends that hyperlipidaemia in dialysis patients with a history of cardiac or vascular disease should be treated be along the lines of the published national guidelines for secondary prevention. This means aiming for a total:HDL cholesterol ratio of < 5.0, or serum cholesterol below 5.0 mmol/L. For effective audit of this, renal units will need to record on their databases symptoms of vascular disease and vascular events so that such patients can be identified.

Methods

The Renal Registry is able to harmonise cholesterol data to facilitate direct comparisons of measurements between centres. The Renal Registry has analysed the most recent cholesterol data over one year as many centres only measure this annually. Some centres may not regularly repeat measurement if a result is normal without use of a lipid-lowering agent. The treatment modality was defined on 31/12/99, although some patients may have changed modality over the course of the preceding year.

The analysis has been performed around levels of serum cholesterol $\leq$5.0 mmol/L for men and women, in accordance with the recommendations for primary prevention by the 'Joint British recommendations on prevention of coronary heart disease in clinical practice'[26]. These recommendations categorise renal failure patients to be high risk individuals.

Data on serum cholesterol in dialysis patients are presented below.

Results

All results are presented using laboratory harmonised serum cholesterol.

Haemodialysis

Serum cholesterol results for patients on haemodialysis are shown in figures 10.24 and 10.25.

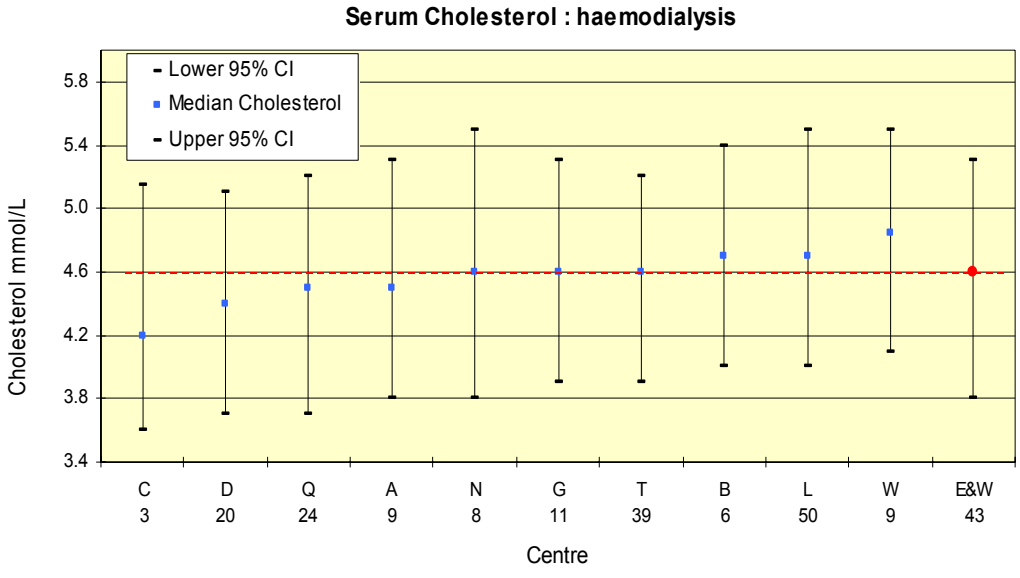

Figure 10.24 Median serum cholesterol (mmol/L) on haemodialysis

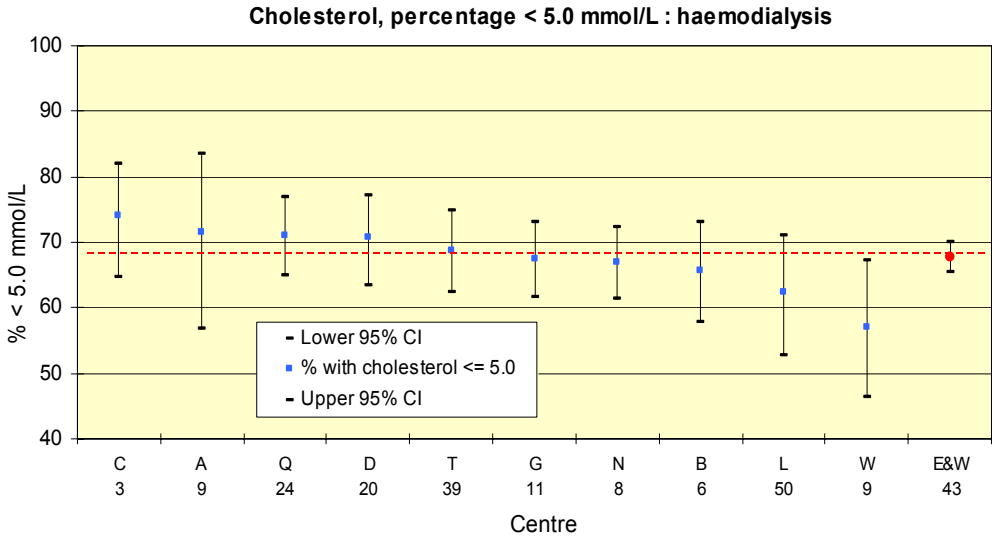

Figure 10.25 Percentage cholesterol ≤ 5.0 mmol/L on haemodialysis

A chi-squared test was used to determine whether the percentage of patients with cholesterol ≤ 5.0 differed between centres. For patients on haemodialysis, the percentage of patients with cholesterol ≤ 5.0 did **NOT** differ significantly between centres ($X^2 = 10.2$, d.f. = 9, p=0.337).

Peritoneal dialysis

Serum cholesterol results for patients on peritoneal dialysis are shown in figures 10.26 and 10.27.

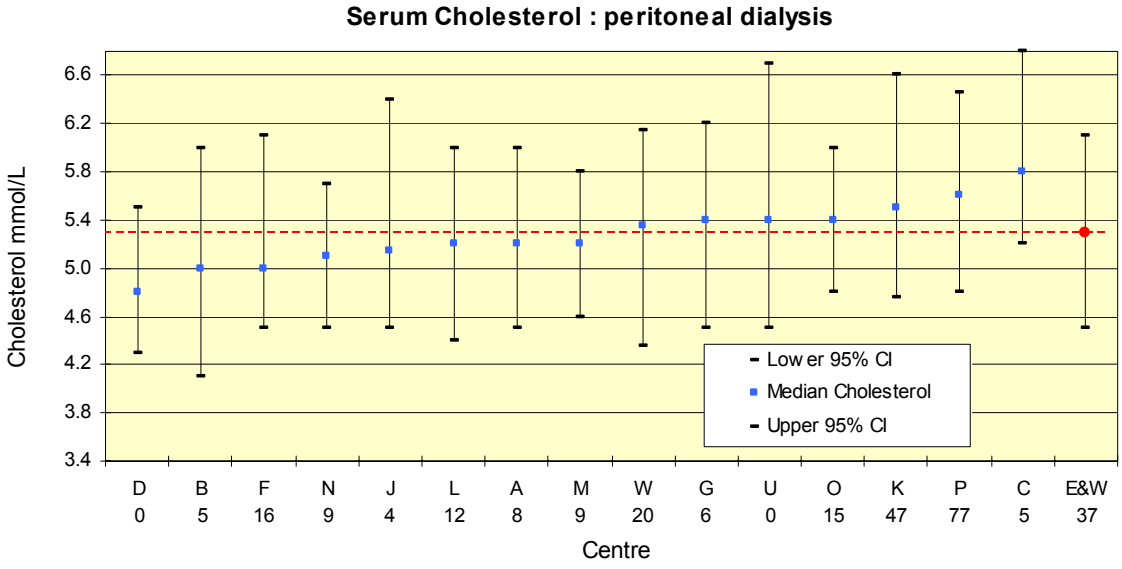

Figure 10.26 Serum cholesterol (mmol/L) on peritoneal dialysis

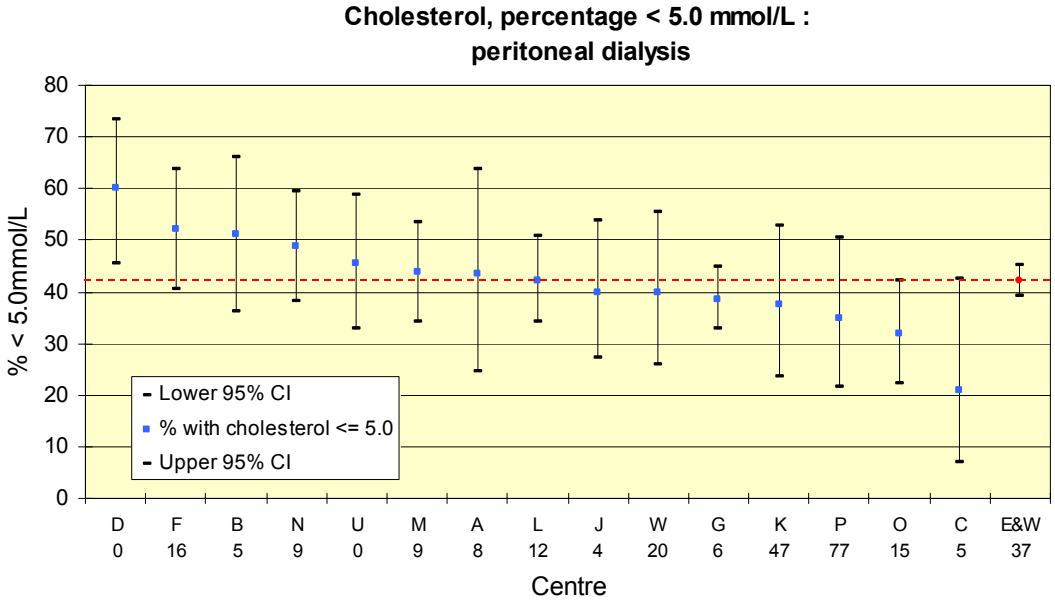

Figure 10.27 Percentage cholesterol ≤ 5.0 mmol/L on peritoneal dialysis

For patients on peritoneal dialysis, the percentage of patients with cholesterol ≤ 5.0 was **NOT** found to differ significantly between centres ($X^2 = 21.7$, d.f. = 14, p=0.085).

The dialysis population differed from the transplant population which did show a significant difference (p <0.001) in serum cholesterol between centres in these patients.

Change in cholesterol 1998–1999

Changes in percentage of patients with serum cholesterol below 5.0 mol/l from 1998 to 1999 are shown in figures 10.28 and 10.29 for the ten renal units from which results are available.

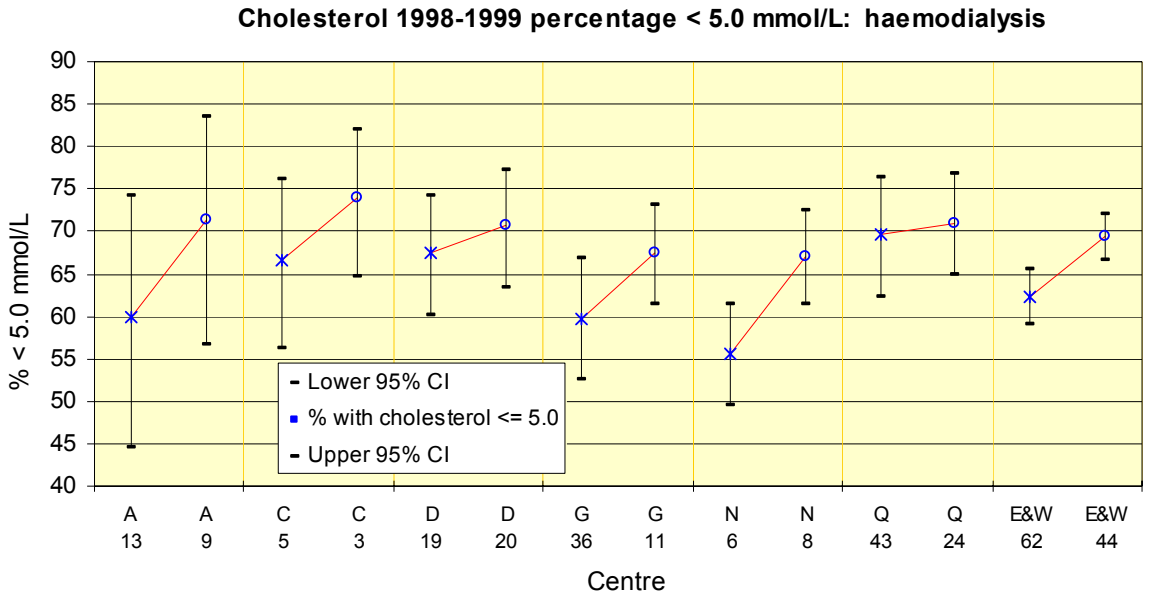

Figure 10.28 Percentage cholesterol ≤ 5.0 mmol/L on haemodialysis, 1998-1999

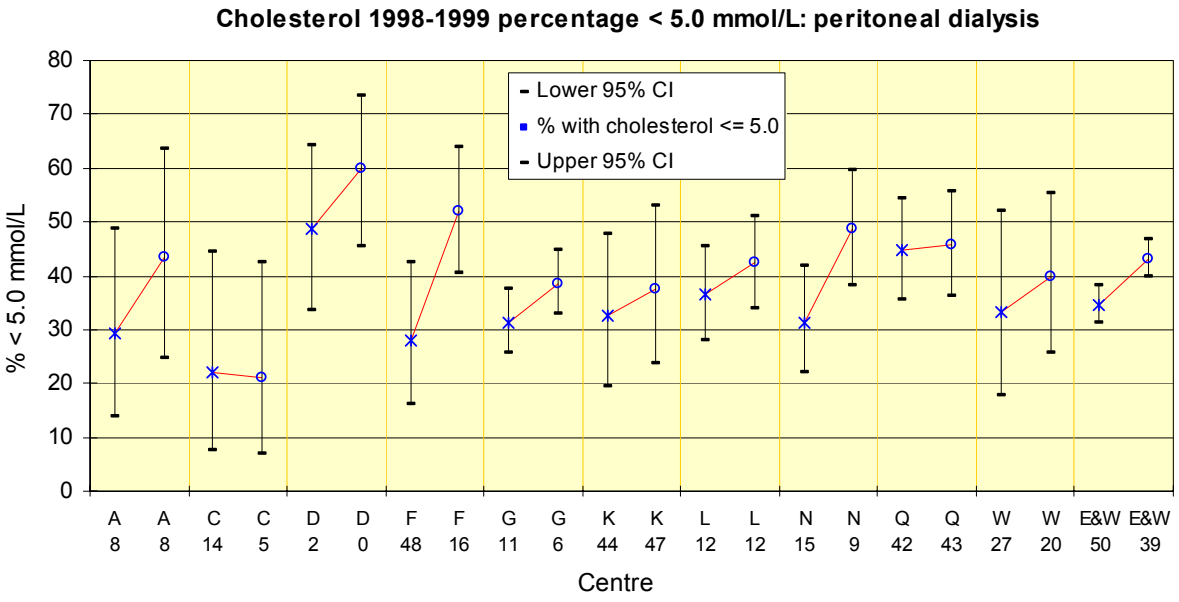

Figure 10.29 Percentage cholesterol ≤ 5.0 mmol/L on peritoneal dialysis, 1998-1999

It appears that serum cholesterol is maintained at a lower level in haemodialysis patients than in peritoneal dialysis patients. Serum cholesterol control in all ten units appears to have improved except for peritoneal dialysis patients in unit C.

Clinical trial of cholesterol lowering in CRF

To answer some these questions on the importance of serum cholesterol in patients with renal failure, the clinical trials committee of the Renal Association has set up a trial on the use of statins in chronic renal failure. The Heart and Renal Protection pilot study (HARP), assessing the safety and efficacy of a statin + aspirin in these patients, has just completed enrolment. Towards the middle of 2001 the pilot study will be extended to a full-scale trial. Interested centres wanting further information should contact the Clinical Trials Support Unit in Oxford on 0800-585323 (Freefone) or 01865 240972

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